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The Surprising Reach of FDA Regulation of Cannabis Even after Rescheduling

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THE SURPRISING REACH OF FDA REGULATION OF CANNABIS, EVEN AFTER DESCHEDULING

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As more states legalize cannabis, the push to “deschedule” it from the Controlled Substances Act is gaining momentum. At the same time, the Food and Drug Administration (FDA) recently approved the first conventional drug containing a cannabinoid derived from cannabis—cannabidiol (CBD) for two rare seizure disorders. This would all seem to bode well for proponents of full federal legalization of medical cannabis. But some traditional providers are wary of drug companies pulling medical cannabis into the regular small molecule drug development system. The FDA’s focus on precise analytical characterization and on individual active and inactive ingredients may be fundamentally inconsistent with the “entourage effects” theory of medical cannabis. Traditional providers may believe that descheduling cannabis would free them to promote and distribute their products free of federal intervention, both locally and nationally. Other producers appear to assume that descheduling would facilitate a robust market in cannabis-based edibles and dietary supplements. In fact, neither of these things is true. If cannabis were descheduled, the FDA’s complex and comprehensive regulatory framework governing foods,

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drugs, and dietary supplements would preclude much of this anticipated commerce. For example, any medical claims about cannabis would require the seller to complete the rigorous new drug approval process, the cost of which will be prohibitive for most current traditional providers. Likely also unexpected to some, there is no pathway forward for conventional foods containing cannabis constituents, with the (probably exclusive) exception of certain hemp seed ingredients, if those foods cross state lines. And it will certainly come as a shock to many that federal law already prohibits the sale of dietary supplements containing CBD—including those already on the market as well as those made from “hemp,” which has recently been descheduled under the 2018 Farm Bill. This Article describes in detail the surprising reach of the FDA and then outlines three modest, but legal, pathways forward for cannabis-based products in a world where cannabis has been descheduled.

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INTRODUCTION

As a number of states have legalized cannabis—at least for state law purposes—a quasi-licit above-ground industry has emerged.¹ This industry is enormous, with estimates into the billions of dollars of annual revenues.² Along with this economic opportunity, one of the selling points of legalization for voters is that an illicit and often dangerous underground industry will be transformed into a safe and well-regulated one.³

Yet, “marihuana”—defined to include much of what is derived from the plant *Cannabis sativa L.*⁴—is still illegal under the federal Controlled Substances Act (CSA).⁵ “Marihuana” is expressly listed in Schedule I of the CSA,⁶ which means there were government findings, credible or not,⁷ that: (1) it “has a high potential for abuse”; (2) it “has

1. *State Medical Marijuana Laws*, NAT’L CONF. ST. LEGISLATURES (Oct. 17, 2018), <http://www.ncsl.org/research/health/state-medical-marijuana-laws>.

2. See, e.g., Thomas Pellechia, *Legal Cannabis Industry Poised for Big Growth, in North America and Around the World*, FORBES (Mar. 1, 2018), <https://www.forbes.com/sites/thomaspellechia/2018/03/01/double-digit-billions-puts-north-america-in-the-worldwide-cannabis-market-lead> (estimating North American industry revenues in 2017 at \$9.2 billion).

3. See, e.g., 2013 Wash. Legis. Serv. Ch. 3 § 1 (West) (“The people intend to stop treating adult marijuana use as a crime and try a new approach that: . . . (3) Takes marijuana out of the hands of illegal drug organizations and brings it under a tightly regulated, state-licensed system similar to that for controlling hard alcohol.”).

4. 21 U.S.C. § 802(16) (2012). For further details on the origin and exact scope of this definition, see *infra* Part II.

5. 21 U.S.C. §§ 801–904.

6. See § 812(c), Schedule I(c)(10).

7. Am. Coll. Physicians, *Supporting Research into the Therapeutic Role of Marijuana: An Addendum by the Health and Public Policy Committee 17* (2008) (“Considering the evidence available today about the potential therapeutic benefits

no currently accepted medical use in treatment in the United States”; and (3) “[t]here is a lack of accepted safety” for use of the drug or other substance under medical supervision.⁸ Tetrahydrocannabinols (THC) and cannabimimetic agents (compounds that mimic the effects of cannabinoids) are also listed in Schedule I.⁹ Manufacturing, distributing, dispensing, or possessing with the intent to do any of the foregoing is allowed under the CSA only for individuals who have been issued a so-called “Schedule I license.”¹⁰ These licenses are rare and hard to come by.¹¹

The Department of Justice (DOJ), and more specifically, the Drug Enforcement Agency (DEA) generally enforce the CSA.¹² Their actions with regard to illicit trade in drugs are usually perceived to be straightforward criminal prosecutions: “*Miami Vice*”- or “*Cops*”-style drug busts.¹³ There is a misperception that such enforcement is not available in states with recreational or medical marijuana laws, at least with regard to state law-compliant cannabis enterprises.¹⁴ The reality

and risks associated with marijuana and its cannabinoids, ACP believes that it is time to review the evidence to determine whether reclassification is appropriate.”).

8. § 812(b)(1)(A)–(C); *see also infra* Part II.

9. *See* § 812(c); § 812(d)(2)(A).

10. §§ 821–823; Synthetic Drugs, Real Danger: Hearing Before the Subcomm. on Crime, Terrorism, Homeland Sec. & Investigations of the H. Comm. on the Judiciary, 114th Cong. 4 (2016) (statement of David Earl Nichols, Ph.D., Adjunct Professor of Chemical Biology and Medicinal Chemistry at the University of North Carolina at Chapel Hill, NC) (“Obtaining a Schedule I license is not a trivial matter . . . [T]he investigator must have a strong personal belief that something useful will be discovered by their research that is of sufficient importance to justify the regulatory demands of a Schedule I license. To wit, a researcher must submit an application to the DEA that includes the investigator’s scientific credentials, the description of the laboratory, a precise description of the work to be carried out, listing the specific substance to be used, and a calculation of how much substance will be needed and for how long. If the DEA determines that the . . . license is justified, there is then an inspection of the storage facility . . . to ensure that the controlled substance cannot be easily diverted Inventory and use must be documented, and there is a license fee for most non-public institutions.”).

11. *See* NAT’L ACADS. SCIS. ENG’G & MED., THE HEALTH EFFECTS OF CANNABIS AND CANNABINOIDS: THE CURRENT STATE OF EVIDENCE AND RECOMMENDATIONS FOR RESEARCH 378–84 (2017) [hereinafter THE HEALTH EFFECTS OF CANNABIS].

12. BRIAN YEH, CONG. RESEARCH SERV., RL34635, THE CONTROLLED SUBSTANCES ACT: REGULATORY REQUIREMENTS I (2012).

13. *See* Sean M. O’Connor & Jason Liu, *The Risks of Clouded Property Title for Cannabis Business Owners, Investors, and Creditors*, 3 TEX. A&M J. PROP. L. 67, 68 (2016).

14. *See id.* (“[B]ecause federal law does not distinguish between shadowy underworld drug deals and the clean, well-lit places licensed and regulated under the new state-legal regimes, all of the forfeiture rules apply equally to both. Accordingly,

here again is further complicated by current DOJ policy and by an annual congressional appropriations rider prohibiting the use of funds for cannabis prosecution.¹⁵ Aside from cannabis drugs approved by the Food and Drug Administration (FDA), and cannabis production and research licensed by the National Institute of Drug Abuse (NIDA), *all* cannabis production, distribution, or sale violate federal criminal law under the CSA.

State decriminalization of medical marijuana (MMJ) in the 1990s began flipping this dynamic.¹⁶ At the same time, even the federal government was forced to provide cannabis to some patients under “compassionate use” programs.¹⁷ Accordingly, the DOJ and the DEA did not act as aggressively as they could have in relation to cooperatives and dispensaries operating under first California’s, and then other states’, MMJ quasi-legal frameworks.¹⁸ An uneasy partial truce was established for patients who grew their own MMJ for personal use because this was a grey area under the CSA as it did not involve distributing or dispensing the substance to others, and the “manufacturing” and possession was not for the purpose of distributing or dispensing to others either.

This was the opening for cooperatives, and ultimately, dispensaries: if a patient can grow cannabis for her own personal use, then she should also be able to share resources for growing with other MMJ patients. Accepting this premise, courts also had difficulty settling on anything like a uniform minimum level of patient-member participation, and so soon, effectively non-working members were allowed.¹⁹ All that was needed was the minor formality of a member card showing one had joined the co-op, perhaps with a doctor’s note recommending cannabis to alleviate some symptoms.²⁰

the façade of legitimacy and regularity rapidly attaching to the most well-intentioned state-legal cannabis businesses is, of course, quite illusory.”).

15. *See infra* Part II.

16. *See id.* at 71–72.

17. *See infra* Part III.

18. *See infra* Part II.

19. *See* Alex Kreit, *Reflections on Medical Marijuana Prosecutions and the Duty to Seek Justice*, 89 DENV. U. L. REV. 1027, 1041–44 (2012) (discussing various court decisions on how much participation is required of a member of a marijuana cooperative).

20. *See* Gerald Caplan, *Medical Marijuana: A Study of Unintended Consequences*, 43 MCGEORGE L. REV. 127, 144 (“Routinely identifying individuals who are growing more than the number of plants legally allowed, who purchased a fake recommendation or forged one themselves . . . is impossible, except by happenstance.”). Thus, case law soon established a free-speech right for doctors to recommend, but not necessarily

With state MMJ laws enabling these quasi-licit cannabis enterprises—effectively commercial businesses—and DOJ and DEA restraining their enforcement efforts under the CSA, other federal regulatory agencies began treating these operations as any other (licit) businesses. Nevertheless, cannabis and illicit drug operations can violate a host of other federal laws and regulations beyond the CSA—e.g., dumping pollutants, dangerous work environments (to put it mildly), using banned or improper pesticides, and discriminatory employment and business practices.²¹ However, the respective federal agencies enforcing these laws traditionally have not been on the front lines with the DEA, busting down doors of derelict warehouses.²² To be clear, many MMJ co-ops and dispensaries appear to be well-run and compliant with laws and regulations. And some that were not fully

“prescribe,” cannabis to clients. *E.g.*, *Conant v. Walters*, 309 F.3d 629, 639 (9th Cir. 2002) (“[W]hether a doctor-patient discussion of medical marijuana constitutes a ‘recommendation’ depends largely on the meaning the patient attributes to the doctor’s words. This is not permissible under the First Amendment.”). Excellent summaries of this history can be found elsewhere. *See generally* DOUGLAS A. BERMAN & ALEX KREIT, *MARIJUANA LAW AND POLICY* (forthcoming 2019); ROBERT A. MIKOS, *MARIJUANA LAW, POLICY, AND AUTHORITY* (2017); Kathleen Ferraiolo, *From Killer Weed to Popular Medicine: The Evolution of American Drug Control Policy, 1937–2000*, 19 J. POL’Y. HIST. 147 (2007).

21. Stephen Lee, *Workplace Violations Found in Marijuana Sector*, BLOOMBERG L.: OCCUPATIONAL SAFETY (Aug. 27, 2015), <https://www.bloomberglaw.com/document/X60LREIK000000> (reporting on workplace hazards associated with the marijuana industry); Bart Schaneman, *Costly Employment-Related Lawsuits on the Rise in Cannabis Industry as MJ Workforce Grows*, MARIJUANA BUS. DAILY (Oct. 18, 2017), <https://mjbizdaily.com/costly-employment-related-lawsuits-rise-cannabis-industry-mj-workforce-grows> (reporting on “an increasing number of lawsuits over everything from wrongful termination and discrimination to sexual harassment”); Shannon Service, *Pot: Not so Green After All?*, PBS: NEED TO KNOW (May 21, 2010), <http://www.pbs.org/wnet/need-to-know/environment/pot-not-so-green-after-all> (discussing the marijuana industry’s environmental impact, including diesel spills and toxic pesticides that wash into rivers).

22. *See* Lee, *supra* note 21 (explaining that “because marijuana remains an illegal narcotic at the federal level, the EPA hasn’t taken action, leaving growers in murky legal terrain,” and reporting that the Occupational Safety and Health Administration is collaborating with Colorado’s health department on “advisory efforts”). The exception might be the Internal Revenue Service (IRS), which has had a surprisingly prominent role taking down gangsters and criminals for tax evasion since the early twentieth century. *See, e.g.*, *United States v. Hurley*, 957 F.2d 1, 2, 7–8 (1st Cir. 1992) (upholding a jury verdict that found two lawyers guilty of conspiracy to defraud the Internal Revenue Service because they had helped a drug smuggler hide millions of dollars earned from distributing marijuana and hashish).

compliant may have been the result of good faith lack of knowledge, especially given their largely unregulated status.

At the same time, MMJ regime enterprises were fairly restrained affairs with little open advertising or public promotion. The physical sites of dispensaries were generally nondescript, with little to indicate what was going on inside other than the ubiquitous green crosses seen in robust MMJ states like California, Oregon, and Washington. Accordingly, federal agencies of all kinds took a hands-off approach to these ventures, leaving regulation to the states.

Our focus here is on the FDA. Under MMJ regimes, whatever medical or health claims were being made occurred either in semi-private conversations in dispensaries, among users in person, or in chat-room-type environments on the internet. With little evident interstate activity—mandated, in fact, by the state MMJ laws themselves—the FDA’s jurisdiction under the Federal Food, Drug, and Cosmetic Act (FDCA)²³ was limited. Enacted under the Commerce Clause,²⁴ the FDCA permits the FDA to regulate only products that travel or have traveled in interstate commerce, as discussed in more detail in Part III. However, with both recreational and medical cannabis businesses emboldened by state legalization, overt marketing and sales activities in interstate commerce prompted the FDA to take enforcement action, also as reviewed in Part III. One of the Authors has had significant discussions with the state-legal recreational and medical industries and can report that FDA regulation is poorly understood and largely ignored for the time being.²⁵

At the same time, this grey market for medical cannabis under state MMJ regimes was highly advantageous for those who wished “to do good and do well” in the industry.²⁶ While recent state regimes for legal recreational cannabis have heavily taxed various levels of the production value chain, state MMJ regimes generally did not tax

23. 21 U.S.C. §§ 301–399h (2012).

24. U.S. CONST. art. I, § 8, cl. 3 (“The Congress shall have Power . . . [t]o regulate Commerce with foreign Nations, and among the several States, and with the Indian Tribes . . .”).

25. See Lee, *supra* note 21 (“Because growers, processors and sellers in states where marijuana is now legal have operated outside the law for so long, they have learned to ignore federal and state regulations . . .”).

26. See Terra Carver, *Executive Director, Humboldt County Growers Alliance*, INFOCAST (Oct. 3, 2018), <https://infocastinc.com/market-insights/cannabis/terra-carver-humboldt-county-growers-alliance> (commenting that “the combined medical and adult-use [marijuana] market may be worth \$5 billion by 2019 in California alone,” and mentioning that cannabis use appears to displace opioid use to some extent).

medical cannabis.²⁷ Part of this was because no sales of goods were supposed to be occurring: again, the idea was that all patients would participate in a co-op-type structure to produce communally the product they all used, or patients would produce solely for their personal medical cannabis use.²⁸ Nonetheless, with low tax, little to no regulations that regular commercial businesses are subject to, and a growing influx of essentially recreational users, the dispensaries did quite well.²⁹ Further, long-standing loyalty to producers and dispensaries that provided consistent strains with perceived or quantifiable effects—for both medical and recreational purposes—ensured stable customer bases.³⁰

Unsurprisingly then, many of these enterprises were wary of—or actively opposed—legalization efforts for recreational use.³¹ Correctly, they sensed that legalization would bring full regulation and taxation,³² not to mention broad free-market competition and a commoditized vice approach to cannabis (in which cannabis would be regulated and

27. See, e.g., *Taxes Due on Marijuana*, WASH. DEP'T OF REVENUE, <https://dor.wa.gov/print/46568> (last visited Feb. 5, 2019). But see Lisa Rough, *Cannabis Tax Rates: A State by State Guide*, LEAFLY, <https://www.leafly.com/news/industry/marijuana-tax-rates-by-state> (listing Alaska, California, Delaware, District of Columbia, Maine, Massachusetts, New Hampshire, New Mexico, North Dakota, Oregon, Vermont, and West Virginia among the states that did not tax medical cannabis as of late 2017).

28. See, e.g., WASH. REV. CODE § 69.51A.085 (2011) (repealed 2016) (providing that “qualifying patients” could participate in collective gardens for growing cannabis, but prohibiting more than ten qualifying patients per garden along with the delivery of cannabis to anyone other than the collective garden’s qualifying patients).

29. *From Less than \$100K to Millions of Dollars, Annual Marijuana Dispensary Revenues Run the Gamut*, MARIJUANA BUS. DAILY (Apr. 10, 2013), <https://mjbizdaily.com/from-less-than-100k-to-millions-of-dollars-annual-marijuana-dispensary-revenues-run-the-gamut> (discussing the self-reported annual revenues of MMJ dispensaries, with 15% reporting less than \$100,000; 27% reporting between \$100,000 and \$250,000; 18% reporting between \$250,000 and \$500,000; 15% reporting between \$500,000 and \$1 million; and 25% reporting over \$1 million).

30. See, e.g., *What Do Marijuana Strain Names Mean? Does it make a Difference?*, GROWNROGUE, <https://www.grownrogue.com/meaning-marijuana-strain-names> (last visited Feb. 5, 2019) (describing how customers look for quality and consistency when checking their preferred strains and dispensaries, often relying on characteristics such as flower, aroma, taste, and how the strains make them feel).

31. Evan Puschak, *Why the Medical Marijuana Industry Opposes Full Legalization*, MSNBC: THE LAST WORD WITH LAWRENCE O'DONNELL (July 29, 2013, 11:07 PM), <http://www.msnbc.com/the-last-word/why-the-medical-marijuana-industry-opposes>.

32. See, e.g., 2013 Wash. Legis. Serv. Ch. 3 (I.M. 502) §§ 26–27 (West).

sold similar to alcohol and tobacco).³³ None of this would have been particularly helpful to medical cannabis enterprises, although one could argue that legalization at the federal level would remove the ongoing threat of prosecution under the CSA. Some medical cannabis proponents thus focused on rescheduling cannabis so that it would be treated like a prescription drug, rather than a narcotic with “no currently accepted medical use.”³⁴ Rescheduling theoretically could have kept it from becoming a commoditized vice substance, while also opening a path to federally-compliant prescriptions under FDA and DEA regulations.

State legalization for recreational purposes has indeed not been great for medical cannabis businesses. First, there has been a flood of commercial cannabis businesses into states that have legalized cannabis, which has been tempered only by limits on the number of grower, processor, and retailer licenses that these states are willing to grant.³⁵ Second, in some states, medical cannabis businesses have had to become licensed for the new regulated and taxed recreational systems.³⁶ Third, and most challengingly, the FDA has increased its enforcement in light of widespread public advertisements and promotions, including medical claims, by commercial medical cannabis outfits.³⁷ Unlike these commercial medical cannabis outfits, the dispensaries had been very low-key and discrete in their public advertising and promotions, largely because this was also a grey area under state MMJ laws.³⁸ With general legalization in various states allowing for a higher and more explicit level of branding, advertising, marketing, and promotion than was allowed in the medical cannabis

33. *Vice Wars: Tobacco, Alcohol and the Rise of Big Marijuana*, NBC NEWS (Nov. 22, 2014, 1:46 PM), <https://www.nbcnews.com/storyline/legal-pot/vice-wars-tobacco-alcohol-rise-big-marijuana-n253801>.

34. 21 U.S.C. § 812(b)(1)(B) (2012); see also Grace Wallack & John Hudak, *Marijuana Rescheduling: A Partial Prescription for Policy Change*, 14 OHIO ST. J. CRIM. L. 207, 208 (2016) (noting arguments that a Schedule change for marijuana might “better reflect[] the medical, safety, chemical, and pharmacological realities of the substance”).

35. See, e.g., *Marijuana Licensing*, WASH. STATE LIQUOR & CANNABIS BD., <https://lcb.wa.gov/mjlicense/marijuana-licensing> (last visited Feb. 5, 2019).

36. See, e.g., *id.*

37. See *infra* Part III.

38. See THE HEALTH EFFECTS OF CANNABIS, *supra* note 11, at 68–69, 72–73 (“Medical cannabis law and policies vary greatly in terms of the regulations governing supply and use Some states protect and regulate the operation of storefronts known as dispensaries Some dispensaries openly advertise their wares and services to patients at point of sale, with others aggressively promoting their business to the general public.”).

regimes, the race is now on to sell one's expertise, services, and product attributes in whatever way one can.

The end result may be the FDA cracking down hard—perhaps in conjunction with state governments—on medical claims and any positioning of cannabis products as medical without successful completion of the arduous and expensive new drug application (NDA) process.³⁹ Further, given the high degree of reproductive variability of cannabis, as indicated by new genetic tests being done on a range of samples,⁴⁰ it is unlikely that the psychoactive part of cannabis in its natural state, and the way in which it is traditionally rolled and smoked, would give anywhere near the predictable and quantifiable product and clinical test results needed to satisfy the FDA under the NDA process.⁴¹ While proponents of medical cannabis may assume that the flower could simply be marketed as a dietary supplement outside the new drug framework, dietary supplement options are quite limited.⁴² Nor is marketing of medical cannabis in food an easy alternative, given the FDA's complex framework for food regulation and its interaction with the new drug framework.⁴³

After all, there were very good reasons why Congress passed the Pure Food and Drugs Act in 1906,⁴⁴ and its successor, the FDCA, in 1938.⁴⁵ Reformers at the turn of the last century and in the early decades of the twenty-first century sought to protect consumers from tainted, adulterated, toxic, mislabeled, or ineffective “patent medicines” and proverbial snake oils.⁴⁶ This is not to disparage or discredit medical cannabis as a general matter, but rather to say that there is good reason to require clinical proof that any particular product or process has the actual therapeutic benefits that are claimed (i.e., that the product or process is effective), and that it is safe enough for the indicated use. The question of federal regulation of medical cannabis is thus complex.

This Article focuses only on regulation under the FDCA, in the event that cannabis is descheduled from the CSA, and for certain products

39. See *infra* Section III.A.

40. See *infra* Part II.

41. See *infra* Section III.A.

42. See *infra* Section III.C.

43. See *infra* Section III.B.

44. Pub. L. No. 59-384, 34 Stat. 768 (1906).

45. Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. §§ 301–399h (2012)).

46. See Erika Lietzan, *The Drug Innovation Paradox*, 83 MO. L. REV. 39, 46–50 (2018) (cautioning that “patent medicines’ . . . should not be confused with ‘patented’ drugs”).

derived from the newly descheduled “hemp.”⁴⁷ While some might suspect that a Congress willing to deschedule cannabis would be willing to amend the FDCA to allow the free-form expansion of medical cannabis production, marketing, and sale that some proponents and commentators advocate,⁴⁸ this does not necessarily follow. Indeed, FDA Commissioner Scott Gottlieb laid out the compelling reasons why FDA should continue to regulate not only hemp products, but any product containing substances classified as a drug by the FDA—which includes THC and cannabidiol (CBD)—or for which medical claims are made, regardless of their CSA status.⁴⁹ The Article chooses descheduling over rescheduling because it calls the relevant questions of FDA regulation into starker relief and because it may be more politically feasible than conventional wisdom holds—especially with both Democrats and Republicans now espousing states’ rights.⁵⁰ Further, the analysis for rescheduling is effectively contained within that for descheduling. In particular, many Democrats and progressives would like to see the federal government allow state legal cannabis systems to expand with no threat of intervention, even as President Trump has signaled a willingness to allow the states to decide for themselves (with states’ rights long a plank in Republican party politics).⁵¹

47. See *supra* notes 225–28, 406.

48. Frank Robison, *Going Green: Legal Considerations for Marijuana Investors and Entrepreneurs*, 6 AM. U. BUS. L. REV. 57, 79–80 (2016) (“[T]he marijuana industry’s best, perhaps only, hope to achieve commercial parity with other industries is for the federal government to eliminate marijuana as a Schedule I controlled substance. This, however, will alter the legal and commercial landscape altogether . . .”).

49. Statement from FDA Commissioner Scott Gottlieb, M.D., on Signing of the Agriculture Improvement Act and the agency’s regulation of products containing cannabis and cannabis-derived compounds (Dec. 20, 2018) [hereinafter Statement on Signing of the Agriculture Improvement Act], <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm628988.htm?utm;> see also *infra* Part III.

50. Tom Angell, *Democrats Forming Marijuana Legalization Consensus*, FORBES, Feb. 15, 2018, <https://www.forbes.com/sites/tomangell/2018/02/15/democrats-forming-consensus-on-marijuana-legalization> (noting support for marijuana legalization among Democratic and Republican members of Congress and quoting Senate Democratic Leader Chuck Schumer’s statement that “the States should continue to be the labs of democracy when it comes to recreational & medical marijuana”).

51. See *id.*; Evan Halper, *Trump Administration Abandons Crackdown on Legal Marijuana*, L.A. TIMES (Apr. 13, 2018), <http://www.latimes.com/politics/la-na-pol-marijuana-trump-20180413-story.html> (reporting that “[t]he Trump administration [wa]s abandoning a Justice Department threat to crack down on recreational marijuana in states where it is legal,” and that Republican Senator Cory Gardner of Colorado, who had been “incensed” by the Department’s threat, “said he was assured

Some notes on terminology are warranted. First, this Article uses “cannabis” to cover the plant and its products except where referring to the defined legal category of “marihuana” under the CSA.⁵² “Marijuana” has unfortunate discriminatory and racial undertones to many and is seen by some as imposed by anti-immigrant and, pointedly, anti-Mexican activists in the early twentieth century.⁵³ “Cannabis,” by contrast, is the older and more widely accepted name of the plant, and indeed forms the basis of the scientific names of the two major strains or species (speciation is contested): *Cannabis sativa* L. and *Cannabis indica* Lam.⁵⁴ Further, states, like Washington, with advanced medical and recreational cannabis regimes have switched over to “cannabis” as well.⁵⁵

that the federal government would not interfere with his state’s marijuana industry and that Trump would champion a new law that gives states the authority to set their own pot policies”).

52. 21 U.S.C. § 802(16).

53. See Matt Thompson, *The Mysterious History of ‘Marijuana,’* NAT’L PUB. RADIO: CODE SWITCH (July 22, 2013, 11:46 AM), <https://www.npr.org/sections/codeswitch/2013/07/14/201981025/the-mysterious-history-of-marijuana> (“Numerous accounts say that ‘marijuana’ came into popular usage in the U.S. in the early 20th century because anti-cannabis factions wanted to underscore the drug’s ‘Mexican-ness.’ It was meant to play off of anti-immigrant sentiments.”); see also Alex Halperin, *Marijuana: Is it Time to Stop using a Word with Racist Roots?*, GUARDIAN, (Jan. 29, 2018), <https://www.theguardian.com/society/2018/jan/29/marijuana-name-cannabis-racism> (“For the prohibitionists of nearly a century ago, the exotic-sounding word emphasized the drug’s foreignness to white Americans and appealed to the xenophobia of the time. As with other racist memes, a common refrain was that marijuana would lead to miscegenation. Harry Anslinger, the bureaucrat who led the prohibition effort, is credited as saying back then: ‘There are 100,000 total marijuana smokers in the US, and most are Negroes, Hispanics, Filipinos and entertainers. Their Satanic music, jazz and swing result from marijuana use. This marijuana causes white women to seek sexual relations with Negroes, entertainers and any others.’”).

54. See Ethan B. Russo, Review, *History of Cannabis and Its Preparations in Saga, Science, and Sobriquet*, 4 CHEMISTRY & BIODIVERSITY 1614, 1616–19 (2007) (discussing the taxonomy of cannabis); Thompson, *supra* note 53 (“Throughout the 19th century, news reports and medical journal articles almost always use the plant’s formal name, cannabis.”).

55. For example, in 2011, the Washington legislature amended its MMJ statute, renaming the section “The Washington state medical use of cannabis act,” and replacing the word *marijuana* with *cannabis* throughout the statute. See 2011 Wash. Legis. Serv. Ch. 181 (West) (including amendments to Wash. Rev. Code § 69.51A.005 and § 69.51A.900). However, although the legislature has retained the statute’s title—the Washington state medical use of cannabis act—in 2015, an amendment switched *cannabis* back to *marijuana* throughout the statute. See WASH. REV. CODE §§ 69.51A.005–69.51A.900 (2015); 2015 Wash. Legis. Serv. Ch. 70 (West).

Second, this Article uses “medical cannabis” to refer to growth, production, processing, sale, and use of cannabis or its derivatives for health or medical benefits. Similar to “cannabis,” we use “medical marijuana” or “MMJ” only when referring to the legal, statutory categories created under state laws.

Third, “descheduling” means congressional amendment of the CSA to remove “marihuana”—or at least some parts of that broad statutory term—from any of the restricted Schedules of controlled substances. Descheduling should also include DEA action to remove medically relevant components of cannabis, such as THC and CBD, as well as synthetically-produced analogues, that it has placed in any of the controlled substances Schedules under its statutory authority granted under the CSA. Full descheduling would mean that (medical) cannabis is no longer a controlled substance at any level.

Fourth, “rescheduling” means that Congress amends the CSA to place “marihuana” into a less restrictive Schedule. Likewise, for full rescheduling, the DEA would also move any medically relevant natural or synthetic cannabis components that it has placed on Schedule I down to the same or lower Schedule as “marihuana” would now occupy. Rescheduling means that (medical) cannabis would still be a controlled substance, but it would be easier to pursue clinical trials and new drug approvals with compounds derived from the plant. Further, over-the-counter (non-prescription) status for those drugs would at least be theoretically possible (although unlikely).

Fifth, “traditional medical cannabis” means use of the plant in more or less natural form with minimal processing. This includes not only the familiar rolling and smoking of resinous flower or buds of the plant, but also simple processes such as making butter, oils, or tinctures. It can be contrasted with what might be called the pharmaceutical approach in which a particular molecule is identified and then purified or isolated, often through more sophisticated means.

Ultimately, we find only three pathways for “federal-legal” medical cannabis after descheduling, should that occur. Importantly, this includes CBD products that contain little to no THC and even those derived from “hemp.” Many traditional medical cannabis practitioners will be surprised and likely caught off guard by this. It will not be a free-for-all wherein providers can say or do anything they want. At the same time, these pathways are likely sound and provide a useful roadmap for medical cannabis researchers and practitioners of all stripes. The first pathway is “intrastate” product produced and marketed or sold exclusively within a single state’s borders, which will

be regulated primarily by state law. The second is small-molecule-drug product following completion of a conventional new drug research and development program and FDA approval of an NDA. The third is to test and market, after a premarket submission to the FDA, an herbal dietary supplement that does not include any ingredient or substance currently approved as a drug or even in drug clinical trials—which rules out any products containing THC or CBD. The relative distribution among these pathways will turn on factors, such as perceived or clinically measured efficacy, price, time to market, side effects, and preferences within the patient and healthcare communities.⁵⁶

This Article proceeds by giving a basic overview of the medical cannabis industry and its products in Part I. The CSA's treatment of "marihuana," including the mechanisms and effects of descheduling and rescheduling, are covered in Part II. The FDA and the FDCA regulations relevant to medical cannabis—and especially possible pathways to compliant production, marketing, and distribution—are covered in Part III. Finally, this Article sets out the pathways and discusses ways forward for medical cannabis under full descheduling in Part IV.

I. HISTORY AND OVERVIEW OF THE MEDICAL CANNABIS INDUSTRY

Claims are made for medical applications of cannabis plants and their parts going back thousands of years in different parts of the world.⁵⁷ The *Cannabis sativa* L. strain may have been one of the first wild plants cultivated by humans.⁵⁸ Early uses were through the raw seeds, oils, and fibers,⁵⁹ with other preparations following. There is controversy over whether the various suspected cannabis uses and references are to the same plant, however, or to different strains.⁶⁰ Ailments treated included pain, migraine, fungal infections,

56. For instance, for less regulated herbal products that seem more "natural" to consumers, or for finished pharmaceutical products known to have been tested in randomized controlled clinical trials. *See infra* Conclusion.

57. *See* Russo, *supra* note 54, at 1621–41.

58. *See id.* at 1616 (noting that "sativa" was added to the name cannabis to designate its status as "cultivated" as early as the 1500s).

59. *See id.* at 1626–27, 1630, 1636.

60. *See id.* at 1627, 1631 (endnotes omitted) ("Cannabis has over 50 synonyms in India, and has been discussed in detail, along with its attendant controversy. Some authorities have questioned whether *bhang* was a psychoactive at all, and others have questioned whether references to cannabis in Indian literature are reliable prior to the 11th century C.E. . . . Nyberg noted that the word *bang*, while still signifying cannabis in contemporary Iran, has also been applied to other plants throughout history." (citations omitted)).

psychological distress, anxiety or grief, ear infections, tumors, abscesses, and more.⁶¹ There is debate over the constituent active-ingredient components of the plants used in these ancient times, but as a general matter, the selective breeding for cannabis containing high levels of THC—the substance that produces the “high” from cannabis use—is of a recent nature.⁶² Thus, older plants likely had a more balanced profile across the various substances explained below and would have produced different experiences from much of the recreational cannabis sold today.⁶³

Cannabis’s medical use is better documented in the Middle Ages and up into the modern era in different parts of the world, than it was for ancient use claims.⁶⁴ However, with no knowledge of the constituent molecules, physicians had little way of precisely developing and administering cannabis-based remedies other than in the same manner as all other *materia medica* herbal remedies of the time.⁶⁵ Over time, the intoxicating properties of cannabis also began creating some concerns for particular social or religious groups, such as under Muslim *sharia* law.⁶⁶ There often seemed to be less focus on the intoxicating aspects of cannabis in ancient and medieval use references and more focus on the nutritive or medical properties of its seeds and oil, than we might expect today when the focus is primarily on the THC high.⁶⁷ However, the Scythians and other Central Asian groups seemed to have already been burning or heating leaves, flowers, or seeds in open fires or on heated dishes to release vapors that were intoxicating.⁶⁸ We now know that heating is necessary

61. *See id.* at 1624–26.

62. *See id.* at 1619–20, 1627, 1631.

63. *Id.* at 1628–37.

64. *See id.*; Antonio Zuardi, *History of Cannabis as Medicine: A Review*, 28 BRAZ. J. PSYCHIATRY 153, 153–55 (2006).

65. *See* Russo, *supra* note 54, at 1628; Zuardi, *supra* note 64, at 153, 156; *see also* *Materia medica*, OXFORD ENGLISH DICTIONARY (3d ed. 2001) (defining *materia medica* as “[t]he remedial substances and preparations used in the practice of medicine”).

66. *See* Russo, *supra* note 54, at 1627 (“[B]y this time, Egyptian medicine had become Islamic medicine [W]hile many derided its psychoactive effects on the basis of a ban on intoxicants in Muslim *sharia* law, a begrudging acknowledgement was frequently made of its abundant medical attributes.”).

67. *See generally id.*

68. *See* Zuardi, *supra* note 64, at 154.

to transform the relevant precursor chemicals from their natural state in the plant into the form that induces a high in humans.⁶⁹

Not surprisingly, substantial lore built up around medical, recreational, and spiritual uses of cannabis.⁷⁰ This lore continues to provide some of the basis for today's natural or herbal medical cannabis industry.⁷¹ In part, this segment of the industry has been bolstered by the continued interest in ancient and non-Western holistic medicine that began in earnest in the late twentieth century.⁷²

The benefits of this lore-based, medical cannabis attracted the attention of Western-trained physicians and scientists as early as the nineteenth century. For example, an Irish doctor working in Calcutta in 1840 utilized the anti-convulsant properties of cannabis to treat tetanus.⁷³ Additionally, a French physician treated mental disorders with cannabis by 1845.⁷⁴ In 1851, the third edition of the *United States Pharmacopoeia*⁷⁵ (USP)—then simply a compendium of recognized drugs—listed “extractum cannabis,” which it described as “[a]n alcoholic extract of the dried tops of *Cannabis sativa*—variety *Indica*.”⁷⁶ Subsequent editions explained how to prepare extracts and tinctures of dried cannabis flowers.⁷⁷ However, as mentioned above, anti-Mexican sentiment in the early twentieth century led to a

69. The scientific process is “decarboxylation,” during which a carboxyl group (-COOH) is removed and replaced by a hydrogen atom (H). In the process, the plant sheds CO₂. In addition to heating, decarboxylation can be accomplished by other means, including through premature aging by exposure to ultraviolet light. See, e.g., Stacie Carrier, *The Process of Decarboxylation*, CANABO MED. CLINIC (Oct. 20, 2017), <https://www.canabomedicalclinic.com/the-process-of-decarboxylation>.

70. See Zuardi, *supra* note 64, at 154–55 (describing the medical and spiritual uses of cannabis by various cultures).

71. See, e.g., Ethan Russo, *Cannabis in India: Ancient Lore and Modern Medicine*, in CANNABINOIDS AS THERAPEUTICS 1, 11–12 (R. Mechoulam ed., 2005).

72. Sneha Mantri, *History of Medicine: Holistic Medicine and the Western Medical Tradition*, 10 AM. MED. ASS'N J. ETHICS 177, 179 (2008).

73. See W.B. O'Shaughnessy, *New Remedy for Tetanus and Other Convulsive Disorders*, 23 BOS. MED. SURGICAL J. 153 (1840).

74. See Ethan Russo, *Cognoscenti of Cannabis I: Jacques-Joseph Moreau*, 1 CANNABIS THERAPEUTICS 85, 86 (2001) (discussing the work of Moreau, including his 1845 book, *DU HACHISCH ET DE L'ALIENATION MENTALE: ETUDES PSYCHOLOGIQUES*, which documented his use of cannabis to treat mental illness).

75. NAT'L MED. CONVENTION, *THE PHARMACOPOEIA OF THE UNITED STATES OF AMERICA* (Philadelphia, Lippincot, Grambo, & Co. 1851).

76. *Id.* at 50.

77. E.g., NAT'L CONVENTION FOR REVISING THE PHARMACOPOEIA, *THE PHARMACOPOEIA OF THE UNITED STATES OF AMERICA* 145, 318 (Philadelphia, J.B. Lippincott & Co. 1864).

demonization of “marihuana,” as the immigrants referred to it.⁷⁸ This story is complicated by the facts that the Mexican government was already working to control it through criminal statutes and that the peasants most likely to be fleeing to the United States following upheaval caused by the Mexican Revolution of 1910 seemed the most terrified by what the drug could do.⁷⁹ Thus, while there is evidence of news stories of the time focusing on “crazed” Mexicans committing violent crimes and debauchery under the influence of substances using terms we believe to correspond to strains or species of cannabis, there were also stories of other minorities, suspect groups such as “jazz musicians,” and other “undesirables,” engaged in such actions too. Whatever the actual mix of motives, it is clear that “marihuana” became a focal point of social, political, and legal concern in this period, which led to legislation.

At the federal level, medical cannabis was regulated under the minimalist provisions of the Pure Food and Drugs Act of 1906.⁸⁰ Notably, Eli Lilly & Co. marketed a regulated cannabis formulation as an antispasmodic, sedative, and narcotic.⁸¹ But it was not until the Marihuana Tax Act of 1937⁸² that cannabis was singled out as something more pernicious than other herbal remedies of the time.⁸³ Rapidly disappearing was media coverage of the medical benefits of cannabis. Some individual states in fact were banning cannabis outright, and most made it available under prescription only.⁸⁴

78. See, e.g., Eric Schlosser, *Reefer Madness*, ATLANTIC (Aug. 1994), <https://www.theatlantic.com/magazine/archive/1994/08/reefer-madness/303476> (describing how Texas police officers claimed that marijuana caused a lust for blood and incited violent crime while rumors also spread that Mexicans were distributing “killer weed” to American schoolchildren).

79. See ERIC SCHLOSSER, REEFER MADNESS: SEX, DRUGS, AND CHEAP LABOR IN THE AMERICAN BLACK MARKET 19 (2003); Schlosser, *supra* note 78.

80. Pure Food and Drugs Act, Pub. L. No. 59-384, § 8, 34 Stat. 768, 770 (1906) (repealed by 21 U.S.C. § 1-5 (1940)) (deeming an article “misbranded” if the label does not include the “quantity or proportion of any . . . cannabis indica, . . . or any derivative or preparation of any such substances contained therein”), *repealed by* Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (codified as amended at 21 U.S.C. §§ 301–399h (2012)).

81. See, e.g., ALISON MACK & JANET JOY, MARIJUANA AS MEDICINE?: THE SCIENCE BEYOND THE CONTROVERSY 18 (2001) (reproducing images from 1913 Eli Lilly product labels).

82. Pub. L. No. 75-238, ch. 553, 50 Stat. 551 (1937).

83. Ferraiolo, *supra* note 20, at 148.

84. See *id.* at 153 (describing the Federal Bureau of Narcotics support for the Uniform Narcotic Act, which made marijuana available only by prescription); see also,

Nonetheless, cannabis research continued and major advances towards identifying and isolating important constituents of the plant took place in the 1930s and 1940s.⁸⁵ Two key substances were isolated from hemp oil: cannabidiol (CBD) and THC.⁸⁶ The latter was present in a mixture of two THC variants that induced “marihuana-like” physiological results in dogs.⁸⁷ The exact molecular structure of these variants remained elusive, however. A single THC variant was soon isolated from cannabis resin.⁸⁸ But in many ways, THC was still a predicted, and not fully realized, molecular construct.

By the 1940s, significant segments of the population had hardened against “marihuana” for any use.⁸⁹ Much of this resulted from the work of the Federal Bureau of Narcotics, which, among other things, released the low budget propaganda film, *Reefer Madness*,⁹⁰ and publicized the “marijuana menace” through allies in the newspaper industry.⁹¹ In 1942, the United States Pharmacopeia Convention removed cannabis from the twelfth edition of the USP, a compendium now formally recognized under the FDCA of 1938.⁹² With this, the medical cannabis industry moved underground.⁹³ Few mainstream researchers pursued it anymore. Unfortunately, this also sent the traditional medical cannabis community back to the largely lore-based trial and error practices it had used before the nineteenth century.⁹⁴

e.g., 1913 Cal. Stat. 692, 697 §§ 8a–b (1913) (amending the California Poison Act of 1907 and making the possession of hemp or its derivatives a misdemeanor).

85. See Roger G. Pertwee, *Cannabinoid Pharmacology: The First 66 Years*, 147 *BRIT. J. PHARMACOLOGY* S163, S163 (2006).

86. *Id.*

87. THE HEALTH EFFECTS OF CANNABIS, *supra* note 11, at 46 (citing R. Adams et al., *Structure of Cannabidiol, a Product Isolated from the Marihuana Extract of Minnesota Wild Hemp*, 62 *J. AM. CHEM. SOC'Y* 196 (1940); R. Adams et al., *Conversion of Cannabidiol to a Product with Marihuana Activity*, 62 *J. AM. CHEM. SOC'Y* 2245 (1940)).

88. *Id.* (citing H.J. Wollner, *Isolation of a Physiologically Active Tetrahydrocannabinol from Cannabis sativa Resin*, 64 *J. AM. CHEM. SOC'Y* 26 (1942)).

89. See Ferraiolo, *supra* note 20, at 153–54 (describing the public shift in perceptions of drugs and marijuana, spearheaded by Anslinger, and the lack of marijuana defenders).

90. REEFER MADNESS (George A. Hirliman Productions 1938) (also screened under different titles across the United States in the 1940s–1950s).

91. Ferraiolo, *supra* note 20, at 156.

92. NAT'L ACAD. SCI., MARIJUANA AND MEDICINE: ASSESSING THE SCIENCE BASE 16 (Janet E. Joy et al. eds., 1999) [hereinafter MARIJUANA AND MEDICINE]; THE HEALTH EFFECTS OF CANNABIS, *supra* note 11, at 43.

93. Ferraiolo, *supra* note 20, at 154–55.

94. See *supra* notes 70–71 and accompanying text.

The next set of major advances in cannabis research came in the 1960s and 1970s. Overshadowing them all was the discovery of the elusive structure of the THC variant in cannabis that generates its intoxicating effect.⁹⁵ The development of nuclear magnetic resonance imaging had enabled researchers to conclusively identify what became known as Δ^9 -THC.⁹⁶ But such new tools also led to the discovery of exact molecular structures of other key cannabis substances including CBD,⁹⁷ cannabigerol (CBG),⁹⁸ cannabichromene,⁹⁹ cannabidivarin,¹⁰⁰ tetrahydrocannabivarin,¹⁰¹ and CBN.¹⁰² The enactment of the CSA in 1970—with its placement of “marihuana,” THC, and “cannabimimetic agents” in Schedule I—erected serious barriers to research on cannabis.

Nonetheless, in the 1980s and 1990s, the mammalian cannabinoid system came into view. The idea of cannabinoid receptors on cells was postulated based on demonstrations of the selective binding to brain membranes of synthetic molecules designed to mimic the actions of Δ^9 -THC.¹⁰³ A “receptor” is a protein, typically on the surface of a cell.¹⁰⁴ Binding to a receptor triggers changes in the cell’s activity and, in this case, causes psychological changes such as euphoria and shifts in sensory perception.¹⁰⁵ The actual existence of this first receptor, CB₁, was

95. Pertwee, *supra* note 85, at S164.

96. THE HEALTH EFFECTS OF CANNABIS, *supra* note 11, at 46 (citing Y. Gaoni and R. Mechoulam, *Isolation, Structure and Partial Synthesis of an Active Constituent of Hashish*, 86 J. AM. CHEM. SOC’Y 1646 (1964)).

97. See Ethan B. Russo, *Taming THC: Potential Cannabis Synergy and Phytocannabinoid-terpenoid Entourage Effects*, 163 BRIT. J. PHARMACOLOGY 1344, 1345 (2011) (citing R. Mechoulam & Y. Shvo, *Hashish—I: The Structure of Cannabidiol*, 19 TETRAHEDRON 2073 (1963)).

98. *Id.* (citing Y. Gaoni & R. Mechoulam, *The Structure and Function of Cannabigerol, a New Hashish Constituent*, 1 PROC. CHEMISTRY SOC’Y 82 (1964)).

99. *Id.* (citing Y. Gaoni & R. Mechoulam, *Cannabichromene, a New Active Principle in Hashish*, 1 CHEMICAL COMM. 20 (1966)).

100. *Id.* (citing L. Vollner et al., *Hashish. XX. Cannabidivarin, a New Hashish Constituent*, 3 TETRAHEDRON LETT. 145 (1969)).

101. *Id.* (citing E.W. Gill et al., *Preliminary Experiments on the Chemistry and Pharmacology of Cannabis*, 228 NATURE 134 (1970)).

102. R.E. Musty et al., *Interactions of Δ^9 -Tetrahydrocannabinol and Cannabinol in Man*, in 2 THE PHARMACOLOGY OF MARIHUANA 559, 559–63 (M.C. Braude and S. Sarza, eds., 1976).

103. THE HEALTH EFFECTS OF CANNABIS, *supra* note 11, at 46 (citing William A. Devane et al., *Determination and Characterization of a Cannabinoid Receptor in Rat Brain*, 34 MOLECULAR PHARMACOLOGY 605 (1988)).

104. See *Receptor*, TABER’S CYCLOPEDIA MEDICAL DICTIONARY 1760 (19th ed. 2001).

105. See, e.g., MACK & JOY, *supra* note 81, at 58–59 (discussing potential psychological changes and effects due to marijuana).

corroborated in 1990.¹⁰⁶ In 1993, a second receptor, CB₂, was cloned and identified.¹⁰⁷ Endocannabinoids—cannabinoids produced by a mammal’s own body—were also discovered, suggesting that endocannabinoid systems are inherent to at least some mammals, and not merely a response to external triggers such as Δ⁹-THC or CBD.¹⁰⁸ This discovery also led to one bold hypothesis that humans and cannabis co-evolved.¹⁰⁹

The fascination with the dramatic effects of THC unfortunately led to a near-exclusive research focus on that set of substances, and particularly Δ⁹-THC.¹¹⁰ This may have also stemmed from the dominant Western small molecule pharmaceutical approach in which “active ingredients” are identified, isolated, purified, and concentrated for therapeutic delivery, as other substances in source plants and other natural materials are largely ignored.¹¹¹ This approach has led to many notable successes where modified concentrations of substances, or new chemicals synthesized from them, provide much greater therapeutic benefit than available from the naturally-occurring versions. For example, acetylsalicylic acid, or aspirin, was synthesized in the mid-nineteenth century from substances that had been identified in willow leaves and bark.¹¹² The latter had been used therapeutically for thousands of years.¹¹³ But this success can crowd out research on the interactions and effects of the full range of chemicals—whether known or considered “active” or “inactive” ingredients—in herbal remedies

106. THE HEALTH EFFECTS OF CANNABIS, *supra* note 11, at 46 (citing Miles Herkenham et al., *Cannabinoid Receptor Localization in Brain*, 87 PROC. NAT’L ACAD. SCI. U.S. 1932 (1990); Lisa A. Matsudo et al., *Structure of a Cannabinoid Receptor and Functional Expression of the Cloned cDNA*, 346 NATURE 561 (1990)).

107. *Id.* (citing Sean Munro et al., *Molecular Characterization of a Peripheral Receptor for Cannabinoids*, 365 NATURE 61 (1993)).

108. See Russo, *supra* note 97, at 1354 (citing William A. Devane et al., *Isolation and Structure of a Brain Constituent that Binds to the Cannabinoid Receptor*, 258 SCIENCE 1946 (1992); Raphael Mechoulam et al., *Identification of an Endogenous 2-Monoglyceride, Present in Canine Gut, that Binds to Cannabinoid Receptors*, 50 BIOCHEMICAL PHARMACOLOGY 83 (1995); Takayuki Sugiura, *2-Arachidonoylglycerol: A Possible Endogenous Cannabinoid Receptor Ligand in Brain*, 215 BIOCHEMICAL BIOPHYSICAL RES. COMM. 89 (1995)).

109. See Russo, *supra* note 54, at 1614 (citing J.M. McPartland & G.W. Guy, *The Evolution of Cannabis and Coevolution with the Cannabinoid Receptor—A Hypothesis*, in THE MEDICAL USE OF CANNABIS AND CANNABINOIDS 71–101 (G.W. Guy, B.A. Whittle & P.J. Robson, eds., 2004)).

110. See Russo, *supra* note 97, at 1345.

111. See Si-Yuan Pan et al., *New Perspectives on How to Discover Drugs from Herbal Medicines: CAM’s Outstanding Contribution to Modern Therapeutics*, 2013 EVIDENCE-BASED COMPLEMENTARY & ALTERNATIVE MED. 1, 2–3 (2013).

112. Dawn Connelly, *A History of Aspirin*, PHARMACEUTICAL J. (Sep. 26, 2014), <http://www.pharmaceutical-journal.com/news-and-analysis/infographics/a-history-of-aspirin>.

113. *Id.*

generally. In the traditional medical cannabis sector, and among some researchers, this holistic approach to cannabis as an herbal remedy has been called the “entourage effect.”¹¹⁴

This dichotomy between the small molecule pharmaceutical and whole plant herbal approaches underlies the fundamental tension in medical cannabis today. Drug companies generally seek to identify a single active ingredient that can be developed into a drug product, which in turn can be studied for safety and effectiveness in rigorously controlled clinical trials for purposes of the FDA’s NDA process.¹¹⁵ This drug development model reflects the analytic framework in which most of Western science and technology has proceeded for the past few hundred years. Only by carefully isolating and testing a particular phenomenon can we learn anything useful about it. This approach has been focused to finer and finer levels of matter. Traditional medical cannabis providers instead operate in a world in which not only do they insist that preparations from whole portions of the plant—such as the flower—are essential for therapeutic benefit, but they also believe that different strains of cannabis produce demonstrably different effects.¹¹⁶

This Article does not seek to resolve any of these debates, but rather is intended to help all sides in the medical cannabis debates understand how the FDA will likely approach the matter. This Article also seeks to sketch three pathways in which we think medical cannabis

114. The term and concept “entourage effect” (sometimes “ensemble effect”) refers to the synergy and interaction between multiple molecules and compounds within cannabis and the interplay these chemicals have with one another when producing effects on the body, as opposed to simply considering the effects of a single active compound, like THC, in isolation. The term and concept were introduced to the scientific literature by Ben-Shabat, Mechoulam, and others. See Shimon Ben-Shabat et al., *An Entourage Effect: Inactive Endogenous Fatty Acid Glycerol Esters Enhance 2-Arachidonoyl-glycerol Cannabinoid Activity*, 353 EUROPEAN J. PHARMACOLOGY 23, 136 (1998); Raphael Mechoulam & Shimon Ben-Shabat, *From Gan-zi-gun-nu to Anandamide and 2-Arachidonoyl-glycerol: The Ongoing Story of Cannabis*, 16 NAT. PRODUCT REP. 131, 136 (1999); see also Russo, *supra* note 97, at 1344.

115. See *infra* Part III.

116. A similar set of perspectives that has been in the popular media recently centers on the debate over “whole foods,” calories, and sugars in our diet. See generally, e.g., MICHAEL POLLAN, *THE OMNIVORE’S DILEMMA: A NATURAL HISTORY OF FOUR MEALS* (2007) (analyzing the ethos and processes behind three modes of food-chains: “processed,” “organic,” and “neo-Paleolithic”). One side has taken the view that “calories are calories” and “sugars are sugars.” The other side opines that the form of our food, and its calories, and sugars, matters tremendously for metabolism, health, and fitness. Both sides can cite some current scientific research.

can proceed, compliant with FDA law, in the event descheduling occurs. We set out these pathways in Parts III and IV, which arguably fall on differing sides of this debate—or at least, they may appeal in different ways depending on one’s place within that debate.

The remainder of this Part reviews the current state of scientific understanding of cannabis, its constituents, and their effects on the human body. Cannabis plants sit within the genus *Cannabis* and family *Cannabaceae*.¹¹⁷ The latter includes the genera *Cannabis* and *Humulus* (hops), which has led to interesting notes in the cannabis and beer industries about similarities.¹¹⁸ Most of the taxonomic debate concerns whether there are two or more species within the genus—usually *cannabis sativa* and *cannabis indica*—or simply one (*cannabis sativa*) with different strains, varietals, or subspecies.¹¹⁹ An alternate account finds at least one other type as a possible species: *Cannabis ruderalis* Jan.¹²⁰ In this schema: *Cannabis sativa* L. are “tall, branched plants for fiber, seed, or psychoactive use”; *Cannabis indica* Lam. are “short, broad-leaved plants” from the Indian subcontinent; and *Cannabis ruderalis* Jan. are “short, unbranched ‘roadside’ plants usually weak in cannabinoids.”¹²¹

Much of the uncertainty in classification appears to be from the hardy proliferation of the plant, which has resulted in many varieties, both cultivated and as found in the wild.¹²² Again, this Article does not seek to resolve scientific or practitioner debates, but three points suffice in summary. First, the wide and distinctive varieties of cannabis—whether at a species level or lower—give ample grounds for traditional medical cannabis practitioners to promote the importance

117. THE HEALTH EFFECTS OF CANNABIS, *supra* note 11, at 44 (citing Mohammed Kuddus et al., *Cannabis sativa: An Ancient Wild Edible Plant of India*, 25 EMIRATES J. FOOD & AGRIC. 736, 737 (2013)).

118. *Id.*

119. *Id.* (citing Lucas Larsen, *Botany: The Cultivation of Weed*, 525 NATURE S4 (Sept. 24, 2015); ROBERT CLARKE & MARK MERLIN, *CANNABIS: EVOLUTION AND ETHNOBOTANY* (1st ed. 2016); Karl W. Hillig, *Genetic Evidence for Speciation of Cannabis (Cannabaceae)*, 52 GENETIC RESOURCES & CROP EVOLUTION 161 (2005); Ernest Small, *Evolution and Classification of Cannabis sativa (Marijuana, Hemp) in Relation to Human Utilization*, 81 BOTANICAL REV. 189 (2015)).

120. Russo, *supra* note 54, at 1616 (citing Richard Evans Schultes et al., *Cannabis: An Example of Taxonomic Neglect*, 23 BOTANICAL MUSEUM LEAFLETS HARV. U. 337 (1974); Loran C. Anderson, *Leaf Variation Among Cannabis Species from a Controlled Garden*, 28 BOTANICAL MUSEUM LEAFLETS HARV. U. 61 (1980)).

121. *Id.*

122. *See, e.g., id.*

of strains and their entourage effects.¹²³ In other words, the argument is not just that certain key chemicals like THC vary among strains, but also that many chemicals vary (i.e., that a compound may have the same molecular structure but work differently in the body depending on the varying other chemicals in the cannabis strain in which it appears).¹²⁴ Accordingly, from this view, using whole-plant derived product is critical, rather than an isolated strain-specific constituent like THC.¹²⁵ Second, as companies like Phylos Bioscience sequence the DNA of popular strains—and indeed seek to populate a “galaxy” of certified types—it has become clear that much of what is being passed as a particular strain in the traditional medical cannabis industry is far from uniform or exact.¹²⁶ And third, data generated by these genomic sequencers should enable more definitive answers to the classification debate in the near future.¹²⁷

Across all cannabis plants, sophisticated traditional medical cannabis practitioners and researchers identify three broad classes of substances that may generate medical or health benefits: cannabinoids; terpenoids; and flavonoids.¹²⁸ The first class is the most well-known as it contains THC and CBD. But significant confusion exists, especially as to the “psychoactive” attributes of molecules within this class.¹²⁹ The problem likely stems from the fact that all cannabinoids interact with the mammalian endocannabinoid system and other parts of the central nervous system.¹³⁰ Thus, all cannabinoids are neurologically active. However, THC stands out as a cannabinoid whose partial agonist binding to CB₁ receptors causes the noted psychological responses of euphoria, sensory perception shifts, and other characteristics referred to as getting high or stoned.¹³¹ Trying to distinguish synonymous terms like “psychoactive” and “psychotropic”

123. See *infra* notes 177–79 and accompanying text.

124. *Id.*

125. See *infra* note 179 and accompanying text.

126. See *Why Phylos Certified?*, PHYLOS, <https://phylos.bio/phylos-certified> (last visited Feb. 5, 2019) (“Cannabis plants are currently sold under unreliable names (not every “Blue Dream” is the same plant variety), meaning inconsistent experiences for everyone—from farmers to consumers.”).

127. See *supra* notes 122–25 and accompanying text.

128. See THE HEALTH EFFECTS OF CANNABIS, *supra* note 11, at 44 (citing AMERICAN HERBAL PHARMACOPOEIA (2013)); Russo, *supra* note 97, at 1344.

129. See THE HEALTH EFFECTS OF CANNABIS, *supra* note 11, at 47.

130. See *id.* at 46–48.

131. *Id.* at 51.

does not help.¹³² Instead, this Article refers to all cannabinoids as “neuro-active” and to THC as “psychoactive.” One further segmentation of cannabinoids is important: “phytocannabinoids” are those produced by plants through natural photosynthesis; “synthetic cannabinoids” are those produced artificially; “cannabimimetic agents” are also produced artificially but are designed to produce the results of a certain cannabinoid (usually THC) and not necessarily replicate its exact structure; and, as mentioned above, “endocannabinoids” are those produced by the mammalian body through its own natural processes.¹³³

The endocannabinoid system is now seen as “one of the key regulatory mechanisms in the brain controlling multiple events such as mood, pain, perception, learning and memory among others.”¹³⁴ The system may also play protective and reparative roles in traumatic brain injury and neurodegeneration.¹³⁵ Mammalian bodies produce endocannabinoids on-demand.¹³⁶

At the same time, estimates of phytocannabinoids occurring in cannabis range from sixty to more than 100.¹³⁷ The two most important at the moment, THC and CBD, are generated from the common parent precursor CBG.¹³⁸ To be accurate, the acid version of each of these cannabinoids is expressed in cannabis itself (e.g., Δ^9 -tetrahydrocannabinolic acid).¹³⁹ In such form, they are inert for most of the effects we associate them with. Ingesting in this form would not

132. These terms are nearly identical and trying to differentiate between them would not help determine how chemicals like THC and CBD work differently on a molecular level. *Compare Psychoactive*, MERRIAM WEBSTER (defining “psychoactive” as “affecting the mind or behavior”), <https://www.merriam-webster.com/dictionary/psychoactive> (last visited Feb. 5, 2019), *with Psychotropic*, MERRIAM WEBSTER (defining “psychotropic” as “acting on the mind”), <https://www.merriam-webster.com/dictionary/psychotropic> (last visited Feb. 5, 2019).

133. *See generally* Vincenzo di Marzo, Opinion, *New Approaches and Challenges to Targeting the Endocannabinoid System*, 17 NATURE REVIEWS: DRUG DISCOVERY 623 (2018); Debra A. Kendall & Guillermo A. Yudowski, *Cannabinoid Receptors in the Central Nervous System: Their Signaling and Roles in Disease*, 10 FRONTIERS IN CELLULAR NEUROSCIENCE 1 (Jan. 2017); *see also* THE HEALTH EFFECTS OF CANNABIS, *supra* note 11, at 44; Russo, *supra* note 97, at 1344.

134. Kendall & Yudowski, *supra* note 133, at 3.

135. *Id.*

136. *Id.*

137. Russo, *supra* note 97, at 1346; THE HEALTH EFFECTS OF CANNABIS, *supra* note 11, at 44.

138. Mei Wang et al., *Decarboxylation Study of Acidic Cannabinoids: A Novel Approach Using Ultra-High-Performance Supercritical Fluid Chromatography/Photodiode Array-Mass Spectrometry*, 1 CANNABIS & CANNABINOID RES. 262, 262 (2016).

139. *Id.* at 263.

induce the desired effects. They must be decarboxylated first, which in the case of traditional recreational and medical cannabis is generally accomplished through heating, resulting in the forms of THC and CBD that produce the sought-after effects.¹⁴⁰

The two different sets of cannabinoid receptors on various cells throughout the human body also play a key role in the effects of cannabinoids. Cannabinoid binding to CB₁ receptors can result in the psychoactive mood and perceptions shifts associated with getting high, as well as with therapeutic benefits.¹⁴¹ By contrast, CB₂ receptors are found predominantly within cells and tissues of the immune system and the gut.¹⁴² Cannabinoids binding to them may regulate inflammation, pain, and even neurodegeneration.¹⁴³ Many of the cannabinoids interact directly or indirectly with both CB₁ and CB₂ receptors.¹⁴⁴ Even more complexly, cannabinoids like THC and CBD can effectively interact with each other through the CB receptors.¹⁴⁵ For example, CBD appears to modulate the stronger and more negative effects of THC, such as anxiety.¹⁴⁶ Notably, Sativex, approved in the United Kingdom and elsewhere, but not in the United States, contains both Δ⁹-THC and CBD.¹⁴⁷

140. See Russo, *supra* note 97, at 1345.

141. See Kendall & Yudowski, *supra* note 133, at 1–2.

142. See, e.g., K.L. Wright et al., *Cannabinoid CB₂ Receptors in the Gastrointestinal Tract: A Regulatory System in States of Inflammation*, 153 BRIT. J. PHARMACOLOGY 263, 263 (2008).

143. *Id.*

144. See Kendall & Yudowski, *supra* note 133, at 4.

145. *Id.*

146. See Russo, *supra* note 97, at 1348. The mechanism and extent of this interaction remains the subject of considerable ongoing research with results that have not yet been reconciled. See, e.g., C. Klein et al., *Cannabidiol Potentiates Δ⁹-Tetrahydrocannabinol (THC) Behavioral Effects and Alters THC Pharmacokinetics During Acute and Chronic Treatment in Adolescent Rats*, 218 LIBERTAS ACADEMICA 443, 443 (2011) (finding that pretreatment with CBD intensified all behavioral effects of THC including anxiety); Daniel Thomas Malone et al., *Cannabidiol Reverses the Reduction in Social Interaction Produced by Low Dose Δ⁹-Tetrahydrocannabinol in Rats*, 93 PHARMACOLOGY BIOCHEMISTRY BEHAV. 91, 91 (2009) (finding that pretreatment with CBD reversed THC-induced decreases in interactions).

147. Sativex is an oromucosal spray that, as noted, contains both Δ⁹-THC and cannabidiol. The United Kingdom's medicine regulator approved Sativex in June 2010 to improve symptoms related to muscle stiffness or spasm caused by multiple sclerosis. See U.K. MEDS. & HEALTHCARE PRODS. REGULATORY AGENCY, PUBLIC ASSESSMENT REPORT DECENTRALISED PROCEDURE: SATIVEX OROMUCOSAL SPRAY 2 (2014). The drug is now approved in 25 countries but has not yet been approved in the United States. *Sativex®*, GW PHARMACEUTICALS, <https://www.gwpharm.com/healthcare->

Terpenoids, the key components of essential oils, are synthesized in cannabis as well.¹⁴⁸ Cannabis contains over 200 terpenoids.¹⁴⁹ It is terpenoids and not cannabinoids that give cannabis its distinctive aroma.¹⁵⁰ While there is debate about the efficacy of terpenoids for therapeutic uses, increased interest has correlated with studies showing measurable benefits in this century.¹⁵¹ The primary terpenoids in cannabis that may produce beneficial effects, alone or in conjunction with a cannabinoid, are: Limonene, α -Pinene, β -Myrcene, Linalool, β -Carophyllene, Carophyllene Oxide, Nerolidol, and Phytol.¹⁵²

Flavonoids are metabolites that play a role in pigmentation, UV filtration, nitrogen fixation, and other functions in plants.¹⁵³ They are sometimes referred to as bioflavonoids.¹⁵⁴ There appear to be twenty or more flavonoids in cannabis.¹⁵⁵ Those occurring only in cannabis have been called “cannaflavins.”¹⁵⁶ Flavonoids are pharmacologically active and some in the medical cannabis community believe they work in concert with terpenoids and other substances in cannabis plants.¹⁵⁷ They are less well-studied overall, in cannabis in particular, but have become a topic of interest, especially among those who promote the entourage effect.¹⁵⁸

professionals/sativex (last visited Feb. 5, 2019). This Article discuss other new drug products derived from cannabis in Part IV.

148. Russo, *supra* note 97, at 1345, 1349 (noting that terpenoids were “previously conceived as the quintessential fifth element, ‘life force’ or spirit . . . , and form the largest group of plant chemicals”). For more detail on the role of terpenes in essential oils, see Sangita Kumari et al., *EssOilDB: A Database of Essential Oils Reflecting Terpene Composition and Variability in the Plant Kingdom*, 2014 DATABASE 1, 2 (Jan. 2014).

149. Russo, *supra* note 97, at 1349.

150. *Id.*

151. *Id.* at 1350–52 (citing studies that indicate terpenoids can act as sleep aids, memory aids, anticonvulsants, antimalarials, and increase serotonin).

152. *Id.* at 1351.

153. Ulrike Mathesius, *Flavonoid Functions in Plants and Their Interactions with Other Organisms*, 7 PLANTS 30, 30–31 (June 2018), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6027123/pdf/plants-07-00030.pdf>.

154. See, e.g., Drugs for Human Use Containing Rutin, Quercetin, Hesperidin, or Bioflavonoids, 33 Fed. Reg. 818 (Jan. 23, 1968).

155. Patrick Bennett, *What Are Cannabis Flavonoids and What Do They Do?*, LEAFLY (Feb. 8, 2018), <https://www.leafly.com/news/cannabis-101/what-are-marijuana-flavonoids>.

156. *Id.*

157. See Angus Chen, *Some of the Parts: Is Marijuana’s “Entourage Effect” Scientifically Valid?*, SCI. AM. (April 20, 2017), <https://www.scientificamerican.com/article/some-of-the-parts-is-marijuana-s-ldquo-s-ldquo-entourage-effect-rdquo-scientifically-valid>.

158. *Id.*; see also *supra* note 114.

At the same time, scientific researchers are not opposed to studying other cannabis substances or even potential entourage effects,¹⁵⁹ but current supply issues severely limit such efforts.¹⁶⁰ The Schedule I status of much of the cannabis plant led the DEA and NIDA to restrict licensed research to a strain of cannabis produced by the University of Mississippi under contract with the federal government.¹⁶¹ This strain is not particularly potent nor high quality from traditional medical cannabis provider and user perspectives—even as it is deemed “research grade” by the government—and is not one used by dispensaries.¹⁶² Exacerbating this problem, NIDA research cannabis is often harvested and stored in a freezer for years before being distributed to researchers, further diminishing its potency (as well as likely degrading other substances such as essential oils).¹⁶³ But even if this were a relevant strain and delivered fresh to researchers, the limit to a single strain precludes exactly the kind of cross-strain comparisons that traditional medical cannabis providers believe provides the core basis for their practice.¹⁶⁴ NIDA research cannabis also traditionally was supplied only in plant form, precluding other important research avenues that would consider the forms and modes of delivery, such as conventional edible forms waxes for smoking or vaporizing, other concentrates, oils that are sometimes ingested, and topicals).¹⁶⁵

Changes initiated in 2016 are underway, however. NIDA began working with the University of Mississippi to at least provide strains with different concentrations of Δ^9 -THC and CBD.¹⁶⁶ Yet, this facilitates

159. See, e.g., Russo, *supra* note 97, at 1349–52 (citing several studies involving cannabis terpenoids).

160. See Chen, *supra* note 157.

161. See THE HEALTH EFFECTS OF CANNABIS, *supra* note 11, at 382 (explaining that the NIDA Drug Supply Program provides the only cannabis available for research); Alexander W. Campbell, *The Medical Marijuana Catch-22: How the Federal Monopoly on Marijuana Research Unfairly Handicaps the Rescheduling Movement*, 41 AM. J. L. & MED. 190, 200 (2015) (describing the oversight surrounding the marijuana manufacturer at the University of Mississippi and the requirements researchers must meet to use marijuana from there). In 2013, the First Circuit Court of Appeals upheld the DEA’s denial of a license for a Massachusetts university professor to cultivate his own marijuana for medical research on the grounds that he failed to demonstrate that current cannabis supply was inadequate. See *Craker v. DEA*, 714 F.3d 17, 18–19, 29 (1st Cir. 2013).

162. THE HEALTH EFFECTS OF CANNABIS, *supra* note 11, at 382.

163. *Id.* at 382–83.

164. See Chen, *supra* note 157 (describing how individual cannabis growers “have long been crossing plants to develop distinctive strains that purportedly do different things”).

165. THE HEALTH EFFECTS OF CANNABIS, *supra* note 11, at 383.

166. *Id.*

primarily research focusing on characterizing the biological activity of these two constituents, although it could also support research on the current interest in the interaction of THC and CBD. More helpfully, DEA also changed its policy to begin accepting applications for other research-grade cannabis providers, which could result in a supply that more closely matches that of private dispensaries.¹⁶⁷ However, no licenses have been granted as of publication. In the meantime, this state of affairs appears to have driven some important medical cannabis research overseas.¹⁶⁸

Both pharmaceutical and whole flower medical cannabis researchers have targeted a number of therapeutic fields. Some of these fields have roots in ancient practice or in the nascent pharmacological cannabis practices of the nineteenth and early twentieth century (before cannabis “prohibition”).¹⁶⁹ Pharmaceutical approaches tend to orient around cannabinoids (especially THC and CBD) and CB receptors because cannabinoids are seen as the primary “active ingredients” available from cannabis.¹⁷⁰ To be clear, the pharmaceutical industry is not only developing drugs derived from cannabis plant material, but also from synthetic cannabinoid products.¹⁷¹

Traditional medical cannabis practitioners and other researchers tend to pursue illnesses that might benefit from the amount of substances occurring in naturally-hybridized strains as delivered through whole flower, oils, extracts, or concentrates, the latter of which could reach pharmaceutical type levels of “active ingredients” such as CBD.¹⁷² Further, not all traditional medical cannabis practitioners insist on whole flower-based product. Some are fine advising pure THC concentrates (albeit, of course, in some form that does not deliver 100% THC to the patient). At the same time, formally-trained researchers including Mowgli Holmes, at Phylos Bioscience, and Ethan Russo, formerly at GW Pharmaceuticals, are among some of the strongest

167. *Id.* at 383–84 (citing Applications to Become Registered Under the Controlled Substances Act to Manufacture Marijuana to Supply Researchers in the United States, 81 Fed. Reg. 53,846 (Aug. 12, 2016)).

168. *See, e.g.,* Yardena Schwartz, *The Holy Land of Medical Marijuana*, U.S. NEWS & WORLD REP. (Apr. 11, 2017), <https://www.usnews.com/news/best-countries/articles/2017-04-11/israel-is-a-global-leader-in-marijuana-research> (illustrating how Israel has become a prime location for cannabis research).

169. *See supra* Part I.

170. *See* Russo, *supra* note 97, at 1345, 1348.

171. *See infra* Section IV.B.1 (tracing the history of synthetic cannabis drug development in the United States).

172. *See supra* notes 57–77 and accompanying text.

proponents of entourage effect therapies.¹⁷³ However, this does not always mean whole flower-based product. It can also mean pharmaceutical products like Sativex, where the manufacturer combines multiple substances for an overall desired effect and not just a single active ingredient.¹⁷⁴ Thus, there will likely be a continued focus on multiple cannabinoid products first, especially from the pharmaceutical side.¹⁷⁵ Richer preparations including at least certain terpenoids may follow. And of course, dietary supplement or whole flower-derived product will contain the full complement of the cannabinoids, terpenoids, and flavonoids in the cannabis strain's profile.

II. CANNABIS AND “MARIHUANA” UNDER THE CONTROLLED SUBSTANCES ACT

The CSA was enacted in 1970 as the cornerstone of a major push to combat what was perceived by some as an epidemic of “recreational” drug abuse, especially within the counterculture movement.¹⁷⁶ It consolidated various federal drug laws into a cohesive system of regulations.¹⁷⁷ The system created “Schedules,” or classifications, of controlled substances with different levels of regulation.¹⁷⁸ All scheduled controlled substances are restricted in production and distribution under registration and licensing requirements promulgated by the Attorney General, ultimately delegated in large part to the

173. See Chen, *supra* note 157.

174. *Id.*

175. A recent report by the National Academies of Science, *The Health Effects of Cannabis and Cannabinoids*, provides a useful list of the major health and disease areas being pursued by researchers (although the reader should note the varying levels of evidence for or against each: Chronic Pain; Cancer; Chemotherapy-Induced Nausea and Vomiting; Anorexia and Weight Loss; Irritable Bowel Syndrome; Epilepsy; Spasticity Associated with Multiple Sclerosis or Spinal Cord Injury; Tourette Syndrome; Amyotrophic Lateral Sclerosis; Huntington's Disease; Parkinson's Disease; Dystonia; Dementia; Glaucoma; Traumatic Brain Injury/Intracranial Hemorrhage; Addiction; Anxiety; Depression; Sleep Disorders; Posttraumatic Stress Disorder; Schizophrenia and Other Psychoses. See THE HEALTH EFFECTS OF CANNABIS, *supra* note 11, at xii.

176. See Title II of the Comprehensive Drug Abuse Prevention and Control Act of 1970, Pub. L. No. 91-513, 84 Stat. 1236, 1242 (codified at 21 U.S.C. §§ 801–904 (2012)); see also John Hudak, *How Racism and Bias Criminalized Marijuana*, WASH. POST (Apr. 28, 2014), <https://www.washingtonpost.com/news/in-theory/wp/2016/04/28/how-racism-and-bias-criminalized-marijuana/> (arguing marijuana's scheduling comes from President Nixon's contempt toward the counterculture movement and racial minorities).

177. See 84 Stat. at 1236–37.

178. 84 Stat. at 1247–52 (codified at 21 U.S.C. § 812 (2012)).

DEA.¹⁷⁹ The Attorney General—through the DOJ, DEA, and NIDA—licenses producers, distributors, and retailers, as well as health care providers who are able to write prescriptions for controlled substances.¹⁸⁰ The primary purpose of the CSA was to control stimulants, depressants, and hallucinogens.¹⁸¹ The stated concern was safety and the potential for addiction and abuse.¹⁸² Five Schedules were included in the statute, in descending order of restrictiveness.¹⁸³

Schedule I criteria are that the substance has “a high potential for abuse,” “no currently accepted medical use in treatment in the United States,” and “a lack of accepted safety for use of the drug or other substance under medical supervision.”¹⁸⁴ When initially enacted, Schedule I included certain enumerated opiates, opium derivatives (including heroin and morphine), and hallucinogens (including LSD, “marihuana,” tetrahydrocannabinols, mescaline, peyote, and psilocybin).¹⁸⁵ “Cannabimimetic agents” were later added to Schedule I and include “any substance that is a cannabinoid receptor type 1 (CB1 receptor) agonist as demonstrated by binding studies and functional assays within any of [certain enumerated molecular structural classes].”¹⁸⁶

Schedule II criteria also include “a high potential for abuse,” but the substances have “a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.”¹⁸⁷ The substances also have a risk of “severe psychological or physical dependence” when abused.¹⁸⁸ As initially set out, Schedule II included both general classes of substances (including opium and opiate generally, opium poppy and poppy straw, coca leaves and preparations from them, and injectable liquid forms of methamphetamines) and certain enumerated opiates (including fentanyl and methadone).¹⁸⁹

Schedule III loosened all three criteria.¹⁹⁰ These substances have a potential for abuse lower than those in Schedules I and II and a risk of

179. See 21 U.S.C. §§ 821–831.

180. See § 822; see also THE HEALTH EFFECTS OF CANNABIS, *supra* note 11, at 378–81.

181. H.R. REP. NO. 91-1444, pt. 1, at 6–7 (1970).

182. *Id.* at 1.

183. 21 U.S.C. § 812.

184. §§ 812(b)(1)(A)–(C).

185. See Pub. L. No. 91-513, 84 Stat. 1236, 1248–49 (1970).

186. 21 U.S.C. § 812(c), Schedule I(d)(2)(A).

187. §§ 812(b)(2)(A)–(B).

188. § 812(b)(2)(C).

189. See 84 Stat. at 1250.

190. See 21 U.S.C. § 812(b)(3).

only “moderate or low physical dependence or high psychological dependence.”¹⁹¹ Initial classes of substances included stimulants (amphetamine, phenmetrazine, non-injectable methamphetamine, and methylphenidate), certain enumerated depressants, nalorphine, and certain enumerated substances with quantified narcotic levels.¹⁹²

Schedule IV lowered the abuse and risk factors further. These substances have a low potential of abuse and limited physical or psychological dependence relative to substances in Schedule III.¹⁹³ A list of specific substances, including phenobarbital, was included in the initial Schedule.¹⁹⁴

Schedule V contains the lowest set of criteria. Abuse potential and risk factors are set to a level below all Schedule IV substances.¹⁹⁵ A single class of substances that include no more than certain quantified concentrations of narcotics along with other active medical ingredients was included in the original act.¹⁹⁶ An example would be cough medicine with not more than 200 milligrams of codeine per 100 milliliters or per 100 grams of the overall substance.¹⁹⁷

The definition of “marihuana” in the CSA was simply that which had already been codified in federal statutes since the Marihuana Tax Act:

[A]ll 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.¹⁹⁸

But with the advances in chemical and genetic research on cannabis taking place during the 1960s, the time was ripe for challenges as to whether “*Cannabis sativa* L.” in fact included all kinds of cannabis in the market. Fittingly, in a 1969 decision involving LSD and hallucinogenic drug pioneer, Dr. Timothy Leary, the Supreme Court cautiously opined in dicta that “it seems that there is only one species of marihuana,”

191. §§ 812(b)(3)(A), (C).

192. See 84 Stat. at 1251–52.

193. 21 U.S.C. §§ 812(b)(4)(A), (C).

194. See 84 Stat. at 1252.

195. 21 U.S.C. §§ 812(b)(5)(A), (C).

196. See 84 Stat. at 1252.

197. See *id.*

198. 84 Stat. at 1244 (codified at 21 U.S.C. § 802(16)); see also Marijuana Tax Act of 1937, Pub. L. No. 75-238, 50 Stat. 551 (codified at 26 U.S.C. § 4761(2)).

although the case was decided under the earlier Marihuana Tax Act statute and did not involve a direct challenge to the definition.¹⁹⁹

A decision the next year in a Pennsylvania federal court also decided under the earlier statute, expressly rejected the defendant's argument that "marihuana"—tied to *Cannabis sativa* L.—did not include Cannabis "indicia."²⁰⁰ In its examination of the legislative history of marijuana law, the court quoted Henry J. Anslinger, the Commissioner of Narcotics, when he spoke during congressional hearings on the taxation of marijuana:

[M]arihuana is the same as Indian hemp, and is sometimes found as a residual weed, and sometimes as the result of a dissemination of birdseed. It is known as cannabin, cannabis Americana or cannabis Sativa. Marihuana is the Mexican term for cannabis Indicia. We seem to have adopted the Mexican terminology, and we call it marihuana, which means good feeling.²⁰¹

For Schedule I drugs and substances, the CSA prohibits their manufacture, distribution, or dispensation, as well as their possession with intent to manufacture, distribute, or dispense.²⁰² Penalties include not only fines and imprisonment,²⁰³ but also criminal and civil forfeiture of property to the United States.²⁰⁴

199. *Leary v. United States*, 395 U.S. 6, 50 (1969) (citing lower court testimony of Dr. Richard Schultes, Director, Harvard Botanic Museum).

200. *United States v. Moore*, 330 F. Supp. 684, 686–87 (E.D. Pa. 1970) (citing Congressional legislative history, state court decisions, and scientific authorities for support).

201. *Id.* at 686 (quoting *Taxation of Marihuana: Hearings Before the Comm. on Ways and Means on H.R. 6385*, 75th Cong. 18 (1937) (statement of H.J. Anslinger, Commissioner of Narcotics)). It is unclear where Anslinger got the idea that "marihuana" meant "good feeling." The decision was affirmed by the U.S. Court of Appeals for the Third Circuit, *United States v. Moore*, 446 F.2d 448 (3d Cir. 1971), and certiorari was denied by the U.S. Supreme Court, *Moore v. United States*, 406 U.S. 909 (1972) (mem.). Subsequent federal court decisions were consistent. *See, e.g.*, *United States v. Gaines*, 489 F.2d 690, 690–91 (5th Cir. 1974) (affirming trial court's refusal to instruct jury that the statutory definition of marihuana only included *Cannabis sativa* L.); *United States v. King*, 485 F.2d 353, 360–61 (10th Cir. 1973) (holding a government chemist's testimony amply sufficient for prima facie case that the substance in defendant's possession was marijuana as defined in the statute, even though the chemist did not describe the marijuana as *Cannabis sativa* L.); *United States v. Rothberg*, 351 F. Supp. 1115, 1118 (E.D.N.Y. 1972), *aff'd*, 480 F.2d 534 (2d Cir. 1973) (rejecting defendants' argument that government had to prove the marijuana in question was *Cannabis sativa* L., rather than a different strain).

202. 21 U.S.C. § 841(a)(1) (2012).

203. § 841(b).

204. §§ 853(a), 881(a). Criminal forfeiture can occur where individuals have violated CSA provisions punishable by more than one year in prison. § 853(a).

The CSA specifically authorizes the Attorney General to add or remove items from the Schedules, including moving items from one Schedule to another.²⁰⁵ Any changes must be guided by the CSA's process, which includes requesting a scientific and medical evaluation and recommendation from the Secretary of Health and Human Services.²⁰⁶ Responsibility for the evaluation and recommendation has been delegated, in turn, to the FDA.²⁰⁷ The FDA must consider certain listed factors: the drug's actual or relative potential for abuse, scientific evidence of its pharmacological effect (if known), the state of current scientific knowledge regarding the drug, the drug's history and current pattern of abuse, the scope (and duration and significance) of abuse, its psychic or physiological dependence liability, the risk (if any) it presents to public health, and whether it is an "immediate precursor" of another controlled substance.²⁰⁸ The Secretary must recommend a specific Schedule (or removal, if appropriate), and this recommendation is binding as to scientific and medical matters.²⁰⁹

After the Secretary provides a recommendation, the Attorney General must use formal rulemaking to issue a final decision.²¹⁰ If the Secretary recommends that a drug not be controlled, the Attorney General may not control the drug.²¹¹ Where the United States is a signatory to a treaty, convention, or protocol establishing controls over a particular drug or substance, the Attorney General must add that drug or substance to what is deemed the most appropriate Schedule.²¹² This is particularly relevant where cannabis remains controlled under the Single Convention on Narcotic Drugs.²¹³ The FDA must alert the Attorney General when a NDA involves a drug that has a "stimulant, depressant, or hallucinogenic effect on the central nervous system," and

205. § 811(a).

206. § 811(b).

207. See generally 21 C.F.R. § 1308; see also *Controlled Substance Staff Functional Roles*, FDA, <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER> (last visited Feb. 5, 2019).

208. 21 U.S.C. §§ 811(b)–(c). A drug or substance that is an immediate precursor of another listed drug or substance may be placed in the same or higher Schedule. § 811(e).

209. § 811(b).

210. § 811(a).

211. § 811(b).

212. § 811(d).

213. United Nations Single Convention on Narcotic Drugs, 1961, art. 28, Mar. 20, 1961, 18 U.S.T. 1407, 520 U.N.T.S. 240 (establishing an international treaty to regulate drugs, including cannabis).

the drug appears to have abuse potential.²¹⁴ Any non-narcotic substance approved by the FDA to be sold over the counter shall be excluded from scheduling by regulation promulgated by the Attorney General.²¹⁵

In 2009, in light of the increasing number of states enacting medical marijuana laws, the DOJ issued a memo (the “Ogden Memo”) that deprioritized prosecution of individuals engaged in medical cannabis production, distribution, or use, provided they were compliant with state laws and did not otherwise pose any enhanced risks.²¹⁶ In the wake of Colorado’s and Washington’s respective initiatives to state-legalize recreational cannabis, the DOJ took a cautious response. Rather than taking any direct action against the states or officials within them tasked with implementing the recreational systems, the DOJ instead issued an internal guidance memo (the “Cole Memo”) to U.S. attorneys.²¹⁷ It recommended that U.S. attorneys use a set of drug enforcement priorities in deciding where and how to allocate limited government resources to cannabis prosecutions.²¹⁸ The guidance was particularly directed to attorneys in states with “robust” state cannabis regulatory regimes.²¹⁹ The eight priorities are:

- (1) preventing the distribution of marijuana to minors;
- (2) preventing revenue from the sale of marijuana from going to criminal enterprises, gangs, and cartels;
- (3) preventing the diversion of marijuana from states where it is legal under state law in some form to other states;
- (4) preventing state-authorized marijuana activity from being used as a cover or pretext for the trafficking of other illegal drugs or other illegal activity;
- (5) preventing violence and the use of firearms in the cultivation and distribution of marijuana;

214. § 811(f).

215. § 811(g)(1).

216. Memorandum from Deputy Attorney Gen. David W. Ogden on Investigations & Prosecutions in States Authorizing the Medical Use of Marijuana to Selected United States Attorneys (Oct. 19, 2009), <https://www.justice.gov/sites/default/files/opa/legacy/2009/10/19/medical-marijuana.pdf>.

217. Memorandum from Deputy Attorney Gen. James M. Cole on Guidance Regarding Marijuana Enforcement to All United States Attorneys (Aug. 29, 2013) [hereinafter Cole Memo], <https://www.justice.gov/iso/opa/resources/3052013829132756857467.pdf>.

218. *Id.*

219. *Id.* (noting that a “robust” regulatory system would address the same priorities the DOJ addresses in enforcement, including prohibiting access to minors and preventing illicit trade that funds criminal enterprises).

- (6) preventing drugged driving and the exacerbation of other adverse public health consequences associated with marijuana use;
- (7) preventing the growing of marijuana on public lands and the attendant public safety and environmental dangers posed by marijuana production on public lands; and
- (8) preventing marijuana possession or use on federal property.²²⁰

State regulatory regimes, such as that of Washington State, were set up expressly to avoid tripping any of these eight prosecution priorities, which also appeared in an earlier memo issued by Cole.²²¹ However, in 2018, Attorney General Sessions rescinded the Cole Memo and other related guidance documents, and thus all participants in state-legal cannabis systems are now subject to the regular discretion of their local U.S. Attorney to prosecute federal crimes.²²² At the same time, the so-called Rohrabacher-Blumenauer Amendment, an appropriations bill rider that has been reapproved for the past few years,²²³ prohibits the DOJ from using any congressionally-appropriated funds for cannabis prosecutions for businesses or individuals operating under robust state medical cannabis regulatory systems.²²⁴ Notwithstanding this prohibition, the DOJ continued its prosecution of a California dispensary until a federal judge recently rebuked the DOJ's theory of why its actions were not technically a use of appropriated funds.²²⁵ While this ruling might seem to be a major victory for regulated cannabis businesses, the DOJ's willingness to go to court to protect its ability to prosecute cannabis CSA violations, regardless of both the guidance of

220. *Id.*

221. *See generally* WASH. REV. CODE ANN. § 69.51A (West 2015).

222. *See* Memorandum from Attorney Gen. Jefferson B. Sessions, III on Marijuana Enforcement to United States Attorneys (Jan. 4, 2018), <https://www.justice.gov/opa/press-release/file/1022196/download>.

223. *See* Pub. L. No. 115-141, § 538, 132 Stat. 348 (2018); Pub. L. No. 115-31, § 537, 131 Stat. 135, 228 (2017); Pub. L. No. 114-112, § 542, 129 Stat. 2242, 2332 (2016); Pub. L. No. 114-113, § 542, 129 Stat. 2242, 2332 (2015); Pub. L. No. 113-235, § 538, 128 Stat. 2130, 2217 (2014).

224. *See* Consolidated Appropriations Act, Pub. L. No. 115-141, § 538 (2018) (providing that no funds from the Act may be used to prevent the states listed in the Amendment from implementing their own laws legalizing, to whatever extent, the medical use of cannabis).

225. *United States v. Marin All. for Med. Marijuana*, 139 F. Supp. 3d 1039, 1040, 1044 (N.D. Cal. 2015) (attacking the “contradiction inherent in the [DOJ’s] assertion that enjoining any one medical marijuana dispensary . . . does not impede California’s implementation of its medical marijuana laws”). The United States entered a notice of appeal in December 2015 but moved to dismiss its appeal the following spring.

the Cole Memo and the congressional appropriations bills, suggests that the DOJ is not quite ready to give up cannabis enforcement.

In a much-publicized development, Congress “legalized” hemp in 2018 by changing the definitions of marihuana and THC in the CSA.²²⁶ First, this reveals the dubious position of those who assert hemp as some kind of separate cousin species to cannabis. The Agriculture Improvement Act²²⁷ effectively defines hemp as *Cannabis sativa* with THC concentration of not more than 0.3 percent on a dry weight basis.²²⁸ Second, the descheduling of “hemp” and Commissioner Gottlieb’s response underscore this Article’s thesis that descheduling cannabis will not result in the free production, marketing, and distribution that proponents have claimed. Instead, the FDA will continue to regulate any product containing ingredients such as THC and CBD that are themselves currently regulated as drugs, as well as any medical claims made by a producer of any products, regardless of whether those products or their ingredients are scheduled under the CSA.

III. FDA REGULATION RELEVANT TO MEDICAL CANNABIS

The FDA regulates a wide variety of medical and consumer products sold in the United States—not just foods and drugs, but also dietary supplements, medical devices, cosmetics, and tobacco products.²²⁹ The agency’s authority to regulate an item is triggered when that item satisfies a definition in the primary statute implemented by the agency, the FDCA.²³⁰ For instance, if an item meets the definition of “drug” in § 201(g) the FDCA, the FDA has jurisdiction over the item and applies its rules and policies relating to drugs.²³¹

Two threshold points about the FDA’s jurisdiction are important to understand. First, the statutory definitions for the various regulated categories—such as “drug” and “dietary supplement”—do not always align with common usage of the terms in question. Their meanings have been fleshed out by the agency and courts, leading to rules that

226. See Agriculture Improvement Act of 2018, Pub. L. No. 115-334.

227. Pub. L. No. 115-334 (2018).

228. *Id.*

229. *What Does FDA Regulate?*, FDA, <https://www.fda.gov/aboutfda/transparency/basics/ucm194879.htm> (last visited Feb. 5, 2019).

230. 21 U.S.C. §§ 301–399h (2012).

231. § 321(g)(1). Throughout this Article, statutory references in the text use the provisions as numbered in the FDCA, rather than as numbered the U.S. Code. Section 201(g) of the FDCA is codified at 21 U.S.C. § 321(g).

might not be evident from looking at the statute alone.²³² And the definitions do not take the same approach to classifying items. For instance, one definition might consider the form of the item, another the actual use of the item, and another the claims made about the item.²³³ Complicating matters further, some definitions overlap. It is possible for a single item to be both a cosmetic and a drug, for instance, and regulated under both sets of authorities.²³⁴

Second, the FDA has authority only with respect to products shipped in interstate commerce. Congress enacted the FDCA pursuant to its power to regulate commerce among the states,²³⁵ and the statutory provisions governing agency jurisdiction therefore focus on products that will be shipped in interstate commerce as well as those that have already been shipped in interstate commerce.²³⁶ The agency also takes the position that it may regulate products containing components (such as ingredients) previously shipped in interstate commerce, and the courts have generally deferred to the agency on this point.²³⁷ Most medical

232. See, e.g., *Meserey v. United States*, 447 F. Supp. 548, 553 (D. Nev. 1977) (explaining that “[r]egardless of the actual physical effect of the product, once it is established that its intended use brings it within the drug definition, it will be deemed a drug for purposes of the Act”); *United States v. Frank*, 189 F. 195, 199 (S.D. Ohio 1911) (“[I]f any substance or mixture is intended to be used for the cure, mitigation, or prevention of disease of either man or other animals, it is nevertheless a drug whether it is recognized in the Pharmacopoeia . . . or not.”).

233. See *United States v. Hazel Bishop, Inc.*, 409 F.2d 734, 739 (2d Cir. 1969) (“Regardless of the actual physical effect of a product, it will be deemed a drug for purposes of the Act where the labeling and promotional claims intended to show uses that bring it within the drug definition.”); *Meserey*, 447 F. Supp. at 553 (explaining that “[r]egardless of the actual physical effect of the product,” once the product’s intended use is established as one that falls within the statute, it will be deemed a drug covered by the FDCA).

234. *Is It a Cosmetic, a Drug, or Both? (Or Is It Soap?)*, FDA, <https://www.fda.gov/cosmetics/guidanceregulation/lawsregulations/ucm074201>. (last visited Feb. 5, 2019) (“[A] shampoo is a cosmetic because its intended use is to cleanse the hair. An antidandruff treatment is a drug because its intended use is to treat dandruff. Consequently, an antidandruff shampoo is both a cosmetic and a drug.”).

235. *United States v. Walsh*, 331 U.S. 432, 434 (1947) (“The Federal Food, Drug, and Cosmetic Act rests upon the constitutional power resident in Congress to regulate interstate commerce.”).

236. See, e.g., 21 U.S.C. § 331 (2012) (prohibiting certain acts, including the introduction of misbranded or adulterated foods, drugs, devices, cosmetics, or tobacco products into interstate commerce).

237. E.g., *United States v. Regenerative Scis., LLC*, 741 F.3d 1314, 1320–21, 1326 (D.C. Cir. 2014) (affirming the FDA’s regulatory authority over the stem cell mixture at issue on the grounds that the mixture contained certain elements, specifically the antibiotic doxycycline, that were transported through interstate commerce prior to their incorporation into the mixture).

treatments and consumer products travel in interstate commerce, so the interstate commerce requirement generally does not meaningfully constrain the FDA's authority. After descheduling, however, some cannabis-based products could be made, sold, and used only within the borders of one state, without any component that traveled in interstate commerce. In these cases, the FDA would have no jurisdiction.²³⁸

A product containing or derived from cannabis, or containing components derived from cannabis, is most likely to be regulated by the FDA as a drug, food or food additive, or dietary supplement. The category will depend on the product. Because the product will contain plant-derived ingredients, the FDA may also consider it a "botanical product"—but this is a descriptive term, not a regulatory classification.²³⁹

Section II.A, discusses regulation of cannabis-based products as drugs. Next, Section II.B and Section II.C explain how FDA would regulate a food or a dietary supplement that contained cannabis or a cannabis constituent. Section II.D considers the possibility that a product comprising cannabis or derived from cannabis might fall into a different FDA-regulated category or, indeed, outside the FDA's purview altogether due to the statutory requirement for interstate

238. Cf. Patricia J. Zettler, *Pharmaceutical Federalism*, 92 IND. L.J. 845, 879 (2017) ("Because the FDA's jurisdiction is limited to drugs that move in interstate commerce (including drugs with components that move in interstate commerce), medical marijuana laws could be written to avoid the FDA altogether by permitting only wholly *intrastate* production and sale of marijuana."). In this situation, however, state laws might authorize (or prohibit) sale. As both Professor Zettler and Professor Noah have pointed out, various state laws authorized the local production and sale of laetrile for the treatment of cancer in the 1970s and 1980s, even though the FDA had not approved the treatment. *Id.*; see also Lars Noah, *State Affronts to Federal Primacy in the Licensure of Pharmaceutical Products*, 2016 MICH. ST. L. REV. 1, 22–23 (noting that after the FDA "acted against [Laetrile] in the 1970s, numerous states legalized the use of this purported treatment for cancer"). The interstate commerce limitation in the FDCA has similarly prompted the FDA to stay its hand with respect to purely intrastate sale of raw milk products. See *Pub. Citizen v. Heckler*, 653 F. Supp. 1229, 1235 (D.D.C. 1986) (explaining that the FDA declined to ban sales of raw milk because most raw milk products were marketed exclusively in intrastate commerce and the agency did not have adequate legal authority on the facts available at the time to prohibit intrastate marketing of raw milk); *Requirements Affecting Raw Milk for Human Consumption in Interstate Commerce*, 52 Fed. Reg. 29,509 (Aug. 10, 1987) (to be codified at 21 C.F.R. pt. 131).

239. CDER Small Bus. & Indus. Assistance, *Botanical Drug Review*, FDA/CDER SBIA CHRONICLES (Nov. 17, 2015), <https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm472934.pdf> ("Botanical products may be classified as foods, dietary supplements, drugs, medical devices, or cosmetics, depending on their 'intended use.'").

commerce. Part IV continues the discussion of the current statutory framework (as interpreted by the FDA) and the current regulatory framework (as applied by the FDA) and, in places, note positions that the FDA might take—without exploring whether this approach would in the end withstand legal challenge.

A. *Medical Cannabis as “Drug”*

Explicit or implicit claims that a product containing cannabis (or a cannabis constituent) could treat disease, or even simply affect the functioning of the body, would turn that product into a “new drug” that requires premarket approval from the FDA.²⁴⁰ The research required to support premarket approval of a new drug is expensive and time consuming,²⁴¹ and some cannabis-based products could present novel scientific and regulatory questions for the agency, potentially slowing the process and adding risk. The agency has signaled its support for cannabis-based drugs and may be flexible with regulatory requirements in some situations, but there is no escaping the fact that the cost of taking a cannabis-based product through the FDA’s new drug approval paradigm could place this pathway out of reach for most entities providing medical cannabis today.

1. *Regulation of medical cannabis under the FDA’s new drug authorities*

Any product containing or made from cannabis would be deemed a “drug” by the FDA if it were associated with medical claims.²⁴² Section 201 of the FDCA defines a “drug” as any article (item) “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man.”²⁴³ The term “drug” also includes any article “intended to affect the structure or function of the body of man” (unless it is a food).²⁴⁴ Finally, anything intended as a “component” of a drug is also a drug.²⁴⁵ Under this definition, the FDA’s authority is triggered by the “intended

240. See *United States v. Cruetz*, 144 F. Supp. 229, 230, 235 (D. Ill. 1956) (holding that because the “defendant orally represented” that an herb tonic “was a remedy for treatment of arthritis,” the tonic was considered a drug and subject to regulation under the FDCA).

241. News Release, Cost of Clinical Trials for New Drug FDA Approval are Fraction of Total Tab, Johns Hopkins Bloomberg School of Public Health (Sept. 24, 2018) (describing study findings that FDA clinical trials cost a median of \$19 million dollars, which makes up “one percent of the average total cost of developing a new drug”).

242. 21 U.S.C. § 321(g) (2012).

243. § 321(g)(1)(B).

244. § 321(g)(1)(C).

245. § 321(g)(1)(D).

use” of an item. “Intended use” does not refer to the subjective intent of the company selling the product, nor does it refer to the purchaser’s intentions.²⁴⁶ Instead, intended use is measured objectively—generally on the basis of the claims made by the persons legally responsible for the product in interstate commerce.²⁴⁷ Thus, it usually turns on claims made in labeling, advertising, and other promotion.²⁴⁸

Drug claims need not be explicit. If a company implies its product can be used to treat disease, the FDA may conclude that the product is a drug.²⁴⁹ And the term “disease” should be understood broadly. Any claim relating to treatment of a medical condition—for instance, easing the symptoms (such as muscle spasms) of multiple sclerosis, reducing nausea associated with chemotherapy, increasing appetite in patients with chronic illness such as HIV, or relieving pain and inflammation of arthritis—will be viewed as a drug claim by the FDA.²⁵⁰ These claims turn the product into a drug even if the product does not work as described.²⁵¹

Any item is a “drug” for purposes of the FDA’s authority if it has the requisite intended use.²⁵² The agency’s drug authority will apply

246. See *Nat’l Nutritional Foods Ass’n v. Mathews*, 557 F.2d 325, 334 (2d Cir. 1977) (“In determining whether an article is a ‘drug’ because of an intended therapeutic use, the FDA is not bound by the manufacturer’s subjective claims of intent but can find . . . intent on the basis of objective evidence.”).

247. 21 C.F.R. § 201.128 (2018) (stating that “intent is determined by such persons’ expressions or may be shown by the circumstances surrounding the distribution of the article”).
248. The claims need not be physically attached to the product (e.g., on the label). See *Kordel v. United States*, 335 U.S. 345, 350 (1948) (finding that “[o]ne article or thing is accompanied by another when it supplements or explains it”).

249. See, e.g., Patricia J. Zettler et al., *Closing the Regulatory Gap for Synthetic Nicotine*, 59 B.C. L. REV. 1933, 1944 (2018) (noting that the FDA regulates smoking cessation aids as drugs based on the implied claims that they lower the risk of disease).

250. See *United States v. Lane Labs–USA, Inc.*, 324 F. Supp. 2d 547, 569 (D.N.J. 2004) (finding that “through its promotional material . . . [the defendant] promoted [its products] for the diagnosis, cure, mitigation, treatment, or prevention of diseases, namely cancer and HIV/AIDS,” and making them drugs under the FDCA); *United States v. Cruz*, 144 F. Supp. 229, 230, 235 (E.D. Ill. 1956) (holding that because the “defendant orally represented” that its herb tonic “was a remedy for treatment of arthritis,” it was considered a drug under the FDCA).

251. The definition of “drug” focuses on the item’s intended use, not its actual effect in the body.

252. This is not to say, however, that anything intended to treat a disease is a drug. FDA also regulates “devices,” which are similarly intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease or intended to affect the structure or function of the body. 21 U.S.C. §§ 321(h) (2012). Such an item will be a device, rather than a drug, if (1) it is an “instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article,” (2) it does

whether the product is composed of dried cannabis flower, derived from a cannabinoid (or terpenoid or flavonoid), extracted from the plant, or composed of synthetic compounds identical to (or similar to) these botanically-derived alternatives. FDA authority will apply no matter what form the product takes—whether it is sold in a tin like chewing tobacco, sold dried for smoking, sold in an oil form for use with a diffuser, or baked into a cookie. For instance, the FDA sent a warning letter to General Mills in May 2009, concluding that because the company promoted Cheerios[®] Toasted Whole Grain Oat Cereal for lowering cholesterol and thus for treatment, mitigation, and prevention of coronary heart disease, the breakfast cereal was also a “drug” and would be regulated as a drug.²⁵³ Drug claims will establish a drug’s intended use and turn the item into a drug, for FDA purposes.

“Drug” status under the FDA framework would trigger a variety of regulatory requirements. For instance the manufacturer would be required to comply with “current good manufacturing practices” (cGMP).²⁵⁴ The FDA’s cGMP regulations impose requirements relating to the creation and training of a quality control unit, design and features of any buildings and facilities used, design and maintenance of equipment used, production and process controls, and recordkeeping, among other things.²⁵⁵ Failure to comply with current cGMP would render the product adulterated and could expose the company to enforcement action, including criminal prosecution.²⁵⁶

Also, the FDA would have jurisdiction over the product’s “labeling,” meaning any “written, printed, or graphic materials” associated with the product.²⁵⁷ If the agency concluded the product could be sold over the counter,²⁵⁸ the manufacturer would need to comply with the

not “achieve its primary intended purpose through chemical action within or on the body,” and (3) it is “not dependent upon being metabolized for the achievement of its primary intended purpose.” *Id.*

253. Warning Letter from FDA to General Mills (May 5, 2009), <http://wayback.archive-it.org/7993/20170112195733/http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2009/ucm162943.htm>.

254. 21 U.S.C. § 351(a) (2012) (deeming a drug “adulterated” if “the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated and administered in conformity with current good manufacturing practice”).

255. *See generally* 21 C.F.R. pt. 211 (2018).

256. *See* 21 U.S.C. § 331(a), § 332, § 333.

257. § 321(m) (defining labeling as “all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article”).

258. *See infra* Section III.C.

agency's nonprescription drug labeling regulations and, among other things, generally include a "Drug Facts" panel on the outside container.²⁵⁹ If the FDA instead concluded that prescriptions would be needed, the company would need to comply with the agency's prescription drug labeling rules.²⁶⁰ The agency could also take enforcement action if any labeling—written, printed, or graphic materials—were "false or misleading in any particular." This would include taking action if the labeling omitted material information, such as the consequences from customary or usual use of the product.²⁶¹ Again, these rules would apply simply because the product bore a medical claim and therefore became a "drug"—no matter what form the product took.

The FDA would almost certainly also deem a cannabis drug to be a "new drug," which is a separate statutory category requiring premarket approval. A drug is a "new drug" unless two things are true: (1) it is "generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in the labeling thereof," and (2) it has been marketed for a material time and to a material extent under those conditions.²⁶² Conventionally, this is referred to as being "generally recognized . . . as safe and effective" or "GRASE."²⁶³ The FDA determines whether each product is GRASE, conducting the inquiry product by product, rather than active ingredient by active ingredient.²⁶⁴ And the inquiry is specific to the conditions described in that product's labeling—its intended use, as well as its route of administration, dosage form, and strength.²⁶⁵ In other words, the specific drug product (not cannabis itself, or cannabis for a particular type of use, such as pain relief) must be GRASE. If it is not, the product is a new drug, which means it cannot be shipped in interstate commerce without either (1) an approved NDA,

259. See 21 C.F.R. § 201.66(c).

260. See *infra* Section III.A.3.

261. 21 U.S.C. §§ 321(n), 352(a).

262. § 321(p).

263. *Id.*

264. See *United States v. Generix Drug Corp.*, 460 U.S. 453, 459 (1983) (concluding that the term "drug" refers to "entire drug products, complete with active and inactive ingredients").

265. 21 U.S.C. § 321(p) (defining a drug as a new drug if it is not GRASE "under the conditions prescribed, recommended, or suggested in the labeling thereof").

which permits commercial marketing, or (2) effective investigational new drug application (IND), which permits testing in humans.²⁶⁶

The FDA has consistently treated cannabis-based drugs as “new drugs” under the FDCA. For instance, in the 1970s, the agency permitted INDs for the use of cannabis to treat a variety of ailments, including refractory glaucoma and anorexia associated with AIDS.²⁶⁷ Although the IND regulatory mechanism normally governs clinical trials, the INDs permitted here were for compassionate use programs. Unlike clinical trials, these programs were not intended to generate information for purposes of new drug approval. They were instead designed primarily to permit treatment of a patient’s disease or condition.²⁶⁸ While these early “treatment INDs” are no longer active, the FDA has since permitted dozens of INDs for true clinical trials of cannabis and cannabis-based products.²⁶⁹ In addition, the FDA has approved three NDAs for synthetic cannabinoids as well as one NDA for a naturally derived cannabinoid drug product.²⁷⁰

In view of these precedents, the FDA would likely conclude that any drug containing or derived from cannabis is a new drug.²⁷¹ Although

266. § 355(a).

267. MACK & JOY, *supra* note 81, at 159–61.

268. The government established the program initially to settle a civil lawsuit brought by Robert Randall, who sought cannabis for treatment of his glaucoma. The government eventually agreed to supply medical cannabis—in cigarette form—to several other people through the same mechanism. *Kuromiya v. United States*, 78 F. Supp. 2d 367, 368 (E.D. Pa. 1999); *see also* Moira Gibbons, *The Cannabis Conundrum: Medication v. Regulation*, 24 HEALTH LAW. 1, 5 (2011). The National Institute on Drug Abuse (NIDA), part of the National Institutes of Health (NIH), cultivated and distributed the cannabis. MACK & JOY, *supra* note 81, at 160.

269. The program shut down in 1991, but the government continued to supply the thirteen patients that it had approved by that time. *Kuromiya*, 78 F. Supp. 2d at 370; MACK & JOY, *supra* note 81, at 160. For a discussion of current clinical trials, *see infra* Section IV.B.

270. *See infra* Section IV.A.

271. In November 2017, the FDA received a citizen petition asking it to confirm that cannabis and THC are not only drugs but also new drugs—that is, not generally recognized as safe and effective. *See* Drug Watch Int’l, Inc. Citizen Petition, No. FDA-2017-P-6692 (Nov. 21, 2017), <https://www.regulations.gov/document?D=FDA-2017-P-6692-0001>. The petition relies on the fact that, at the time of its filing, the FDA had approved three synthetic cannabinoid drugs under the new drug provisions. *Id.* at 4. On July 2, 2018, the FDA denied the citizen petition, refusing to issue a “negative monograph specifically stating that unapproved new OTC marijuana and THC products are not GRAS/E and [] subject to” regulation, but nonetheless finding that “these products are ‘new drugs’” under the FDCA. Response from FDA to Drug Watch Int’l, Inc., No. FDA-2017-P-6692-0042 (July 2, 2018), <https://www.regulations.gov/document?D=FDA-2017-P-6692-0042>.

a drug may be exempt from the FDA's new drug authorities, it is unlikely that either exemption would cover a drug containing or derived from cannabis.²⁷² First, a particular product might be deemed GRASE and therefore not a new drug. Since the 1960s, however, the FDA has interpreted the GRASE exemption to require "the same quantity and quality of scientific evidence that is required to obtain approval of an application for the product."²⁷³ The Supreme Court has accepted the FDA's approach, reasoning that any other approach would deprive the agency of jurisdiction over a drug that, if it *were* subject to the agency's jurisdiction, could not be marketed.²⁷⁴ And again, the new drug inquiry is product by product and specific to the conditions of use described in the labeling. Extensive published research on medical cannabis uses, broadly speaking, will not satisfy the standard. The agency would expect "substantial evidence" that a particular product was safe and effective for a particular use.²⁷⁵ In this case, the manufacturer might as well seek approval of a marketing application.

Second, a product might be "grandfathered," and therefore not a new drug. Under the original grandfather clause, a drug product on the market before passage of the FDCA in 1938 was not a "new drug" if "its labeling contained the same representations concerning the conditions of its use."²⁷⁶ When Congress amended the statute in 1962 to require that new drug applications contain effectiveness data, it extended the grandfather clause, exempting any drug that was excluded prior to 1962, so long as its composition and labeling did not change.²⁷⁷ In effect, a drug that is not GRASE is nevertheless exempt from the new drug provisions if it was regulated under the Pure Food and Drugs Act of 1906 and if its labeling at the time contained the same representations as now concerning the conditions of its use. It would be exceptionally difficult for a company to satisfy the documentation

272. It would still be a "drug" subject to the agency's drug regulations, including (as noted) current good manufacturing practice and labeling requirements, and probably prescription status.

273. 21 C.F.R. § 314.200(e)(1) (2018). This Article describes this evidentiary burden in the next Subpart.

274. See *Weinberger v. Hynson, Westcott & Dunning, Inc.*, 412 U.S. 609, 631 (1973) ("[W]e cannot construe § 201(p) to deprive FDA of jurisdiction over a drug which, if subject to FDA regulation, could not be marketed because it had not passed the [FDA's] 'substantial evidence' test.").

275. *Id.* at 617–19.

276. 21 U.S.C. § 321(p) (2012).

277. Drug Amendments Act of 1962, Pub. L. No. 87-781, § 107(c), 76 Stat. 780, 789.

requirements that the FDA has put in place for grandfather status.²⁷⁸ The agency requires evidence of “past and present quantitative formulas, labeling, and evidence of marketing.”²⁷⁹ And, like GRASE status, grandfather status is product-specific.²⁸⁰ The FDA has rejected arguments about cannabis products to date based on the sufficiency of the evidence presented.²⁸¹

278. See 21 C.F.R. § 314.200(e)(2) (providing that “[a] contention that a drug product is exempt” under § 201(p) of the act or the § 107(c) amendments must be supported by sufficient evidence).

279. *Id.*

280. The FDA will not make decisions about grandfathering on a class-wide basis. See, e.g., Response from FDA to Alston & Bird LLP, No. FDA-2012-P-0189 (Nov. 12, 2015), <https://www.regulations.gov/document?D=FDA-2012-P-0189-0006> (denying petition to confirm grandfather status of cocaine hydrochloride, noting disagreement with petitioner’s premise “that a determination as to whether drug products are exempt from the new drug safety and effectiveness requirements . . . by virtue of the 1938 grandfather clause can or should be made on a class-wide (i.e., non-product-specific) basis,” and adding that “determinations with respect to ‘grandfather’ status are made on a product-specific basis”).

281. In 2000, the FDA rejected a petition arguing that various products prepared from “home-grown cannabis” were exempt from the “new drug” authorities under the grandfather clause. See *Klopper & Mikuriya Citizen Petition*, No. FDA-1999-P-2922 (formerly Docket No. 99-1865/CP1) (May 21, 1999). The petitioners had described specific formulations, uses, and labeling on the market prior to the 1938 statute, including formulations marketed by Parke, Davis, & Company (which included “pressed flowering tops” sold by the ounce) for analgesic purposes, spasmodic disorders, and neuralgia; extracts sold by Eli Lilly & Company as analgesics and for migraines; “flowering top of the female plant” sold by Merck to increase the appetite; and the “dried flowering tops of the female plant” sold by Squibb for epilepsy. *Id.* The agency denied the petition because the petitioners had not presented evidence that the drug products for which they sought grandfather status were “the same drug products that were marketed” prior to 1938. Response from FDA to *Klopper & Mikuriya*, No. FDA-1999-P-2922 (Dec. 29, 2000). A grandfather argument must be supported by (among other things) an “exact quantitative formulation of the drug (both active and inactive ingredients).” *Id.* It must also be supported by documents to show that the labeling has not changed. The FDA also took the position that because cannabis is a controlled substance and must bear a “C” designation in the labeling, the labeling has changed sufficiently to revoke grandfather status. If cannabis were descheduled, the FDA could not deny grandfather status on this ground.

A still-pending petition submitted in 2011 attempts to overcome the documentation hurdles with respect to two additional products: bulk cannabis (in pressed, loose leaf, sifted, grounded, or powdered forms) and cannabis in tincture or liquid form as manufactured and labeled by the Lloyd Brothers Corporation. See *Mikuriya & McPike Citizen Petition*, No. FDA-2011-P-0671 (Sept. 9, 2011), <https://www.regulations.gov/document?D=FDA-2011-P-0671-0001>. The petitioners provide details about the Lloyd Brothers distilling process, details about the company’s marketing time line, and copies of the labels showing the percentage of alcohol present. *Id.*

A company need not petition the agency asking for confirmation that its product is GRASE or grandfathered. Instead, it may reach this conclusion on the basis of evidence in its possession and proceed to market. If the company is correct, the product is a drug subject to the FDA's drug authorities. But the FDA is likely to disagree with this assessment for a drug containing or derived from cannabis, and a company that erred would face enforcement action—up to and including criminal prosecution.²⁸² The Authors therefore assume that any commercial product containing or derived from cannabis that is intended for a medical use will require an approved NDA.²⁸³

2. *Pathway to market under the new drug authorities*

An NDA must describe the product, including its composition and how it is made, and demonstrate that the product is safe and effective when used as described in its labeling.²⁸⁴ An applicant describes the product and manufacturing process in the “[c]hemistry, manufacturing, and controls” (“CMC”) section of the NDA, and it substantiates the product's safety and effectiveness with preclinical (animal and laboratory) and clinical (human) data.²⁸⁵

282. 21 U.S.C. § 333(a) (2012).

283. There is another possibility: new drug status and enforcement discretion because the cannabis is undetectable. The National Drug Code Directory on the FDA's website lists numerous marketed homeopathic drugs that list *cannabis sativa* as an ingredient. See *National Drug Code Directory*, FDA, <https://www.accessdata.fda.gov/scripts/cder/ndc> (last visited Feb. 5, 2019). Home Sweet Homeopathics, for instance, appears to market a homeopathic medicine for migraine containing “cannabis sativa 30c.” *Id.* (select “labeler” from the drop down menu; then search for “Home Sweet Homeopathics”). BioEnergetics, Inc. appears to market a homeopathic medicine for allergies containing *cannabis sativa* pollen. *Id.* (select “labeler” from the drop down menu; then search for “BioEnergetics, Inc.”). The practice of homeopathy assumes that disease symptoms can be cured by small doses of substances that would cause similar symptoms in healthy people. The cannabis in a homeopathic product labeled as containing diluted cannabis is likely to be undetectable. Homeopathic medicines are nevertheless “drugs” and, indeed, likely all “new drugs” that require preapproval. The FDA has historically exercised enforcement discretion, unless safety issues arose. See generally FDA, DRUG PRODUCTS LABELED AS HOMEOPATHIC: GUIDANCE FOR FDA STAFF AND INDUSTRY (2017), <https://www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm589373.pdf>; CPG Sec. 400.400 *Conditions Under Which Homeopathic Drugs May be Marketed*, FDA, <https://www.fda.gov/iceci/compliancemanuals/compliancepolicyguidancemanual/ucm074360.htm> (last updated Mar. 20, 2015). It is unlikely to exercise this discretion if the cannabis-derived active ingredient can be detectable.

284. 21 C.F.R. § 314.50(d)(1).

285. § 314.50(d)(1), 314.50(d)(5)(iv).

Some new drugs containing, or derived from, cannabis would qualify as botanical drugs, in which case they might benefit from the agency's emerging and more flexible approach to botanical NDAs.²⁸⁶ The FDA has published guidance to encourage the development of botanical drugs,²⁸⁷ and in 2003 it created a Botanical Review Team (BRT) to assist in review of botanical NDAs.²⁸⁸ The guidance describes greater flexibility with respect to some application requirements, and the BRT appears to be pivotal in ensuring the agency exercises this flexibility.²⁸⁹ Using this more flexible approach, the FDA has now approved two botanical drugs: Veregen (sinecatechins) for the treatment of genital and perianal warts, and Mytesi (crofelemer) for the symptomatic relief of non-infectious diarrhea in adult patients with HIV/AIDS on anti-retroviral therapy.²⁹⁰

286. A botanical NDA proposes a drug containing plant-derived ingredients. According to agency officials, interest in botanical drugs has been increasing. Between 1982 and 2007, the agency received more than 350 requests to conduct clinical trials and requests for meetings about clinical trials. Shaw T. Chen et al., *New Therapies from Old Medicines*, 26 NATURE BIOTECH. 1077, 1077 (Oct. 2008).

287. See generally FDA, BOTANICAL DRUG DEVELOPMENT: GUIDANCE FOR INDUSTRY (2016) [hereinafter BOTANICAL GUIDANCE].

288. A reviewer from the BRT provides a "pharmacognosy review" which, among other things, evaluates the identity of the plant used in the botanical drug product, evaluates the applicant's raw material characterization and control, and evaluates previous human experience with the botanical product. The botanical NDA is otherwise reviewed by the same FDA scientific staff within the Office of New Drug Products (OND) as any other NDA. Chen, *supra* note 286, at 1077–78. See generally FDA, CTR. DRUG EVALUATION & RES., OFFICE OF PHARM. QUALITY, MAPP 5210.9 REV 1, MANUAL OF POLICIES AND PROCEDURES: REVIEW OF BOTANICAL DRUG PRODUCTS (2016) [hereinafter REVIEW OF BOTANICAL DRUG PRODUCTS].

289. See REVIEW OF BOTANICAL DRUG PRODUCTS, *supra* note 288, at 9 (discussing the BRT's role).

290. FDA, CTR. FOR DRUG EVALUATION & RES., APPROVAL PACKAGE FOR: APPLICATION NO. 202292ORIG1s000 (2012) [hereinafter FULYZAQ APPROVAL PACKAGE], https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202292Orig1s000Approval.pdf (approving Fulyzaq); FDA, CTR. FOR DRUG EVALUATION & RES., APPROVAL PACKAGE FOR: APPLICATION NO. 21-902 (2006) [hereinafter VEREGEN APPROVAL PACKAGE], https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021902s000_approval.pdf (approving Veregen). The names of these products have changed since their initial approval. In June 2007, FDA approved a supplemental NDA to reflect a change in the nonproprietary name for Veregens from kunecatechins to sinecatechins. See FDA, CTR. FOR DRUG EVALUATION & RES., APPROVAL OF NDA 21-902/S-001, (June 1, 2007), https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2007/021902s001ltr.pdf. In March 2018, FDA approved a supplemental NDA to reflect a change in the proprietary name of Fulyzaq to Mytesi. See FDA, CTR. FOR DRUG EVALUATION & RES., APPROVAL OF NDA 202292/S-006 (Mar. 6, 2018), https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2018/202292Orig1s006ltr.pdf. The text of this Article uses the current names rather than the names at the time of initial approval.

FDA officials cite the agency's work on botanical drug development as evidence that the agency "actively" supports the development of drugs from cannabis.²⁹¹ But there are two reasons to be cautious. First, the botanical NDA framework does not apply to drugs containing highly-purified substances simply derived from naturally occurring sources.²⁹² Many commonly-used drugs contain active ingredients derived from plant sources and subsequently are highly processed and purified.²⁹³ The FDA gives the example of paclitaxel, originally derived from an extract of the yew tree.²⁹⁴ The agency does not consider these botanical drugs, and they do not benefit from the flexibility enjoyed by the companies that developed Veregen and Mytesi.²⁹⁵ Likewise, a highly processed and purified drug derived from an extract of the cannabis plant does not enjoy the same flexibility that attaches to drugs the FDA deems botanical. As a result, the traditional new drug development and approval paradigm described below will apply to some drug products derived from cannabis.²⁹⁶ The more flexible

291. Douglas C. Throckmorton, Meeting Presentation, *FDA Regulation of Marijuana: Past Actions, Future Plans* (April 12, 2016), <https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM498077.pdf>.

292. BOTANICAL GUIDANCE, *supra* note 287, at 1.

293. See Kate Wong, *Mother Nature's Medicine Cabinet*, SCIENTIFIC AMERICAN (Apr. 9, 2001), <https://www.scientificamerican.com/article/mother-natures-medicine-c> (providing common examples such as aspirin).

294. BOTANICAL GUIDANCE, *supra* note 287, at 2. Paclitaxel was originally made from the bark of *Taxus brevifolia*, the Pacific yew tree. *Success Story: Taxol*, NATIONAL CANCER INST., https://dtp.cancer.gov/timeline/flash/success_stories/S2_taxol.htm. Eventually a starting material could be extracted from other *Taxus* trees, including the common *Taxus baccata* (European yew). *Id.* This starting material was collected from plants cultivated in public and private parks and gardens as well as plantations in Europe. *E.g.*, FDA, CTR. FOR DRUG EVALUATION & RES., NDA 20-262/S-026, ENVIRONMENTAL ASSESSMENT AND FINDING OF NO SIGNIFICANT IMPACT FOR TAXOL (PACLITAXEL) INJECTION (Nov. 6, 1997), https://www.accessdata.fda.gov/drugsatfda_docs/nda/98/020262s026s027s028_taxol_chemr_EA_phrmr.pdf.

295. Veregen is made from the dried leaves of *Camellia sinensis*, a green tea plant, grown on specific farms. FDA, CTR FOR DRUG EVALUATION & RES., APPLICATION NO. 21-902, BOTANICAL REVIEW (Sept. 15, 2006) [hereinafter VEREGEN BOTANICAL REVIEW], https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021902s000_botanicalr.pdf. The drug substance in Mytesi—crofelemer—is extracted from *Croton lechleri*, also known as dragon's blood or tree's blood, harvested from the wild in South America. FDA, CTR FOR DRUG EVALUATION & RES., APPLICATION NO. 202292ORIG1S000, SUMMARY REVIEW (Dec. 14, 2012) [hereinafter FULYZAQ SUMMARY REVIEW], https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202292Orig1s000SumR.pdf.

296. As this Article discusses in Part IV, the FDA recently approved a drug containing a highly purified extract of cannabis, and although the agency did not deem the drug a botanical, it invited the BRT to participate in review of the

approach to development and approval of botanical drugs—also described below—may apply to others.

Second, agency documents relating to approval of Veregen and Mytesi illustrate that although the FDA may be willing to take a more flexible approach with respect to certain portions of the NDA, there is a potential for significant disputes between the BRT and the usual reviewers in the Office of New Drug.²⁹⁷ This disagreement may require resolution by agency leadership. The need for leadership involvement could make it risky to count on the exercise of flexibility for a cannabis-based botanical NDA and important to engage with the agency early regarding plans to file a botanical NDA.

a. Chemistry, manufacturing, and controls

The CMC section must describe and provide data on the composition, manufacture, and specifications of both the drug substance (active ingredient) and the finished drug product (that is, in its final form for the patient).²⁹⁸ Describing the active ingredient means describing its physical and chemical characteristics and its stability; explaining how it is made (or isolated and purified, for instance); describing the controls used during manufacturing; and laying out the specifics that are needed to ensure its identity, strength, quality, and purity.²⁹⁹ Describing the product also includes listing the components used in its manufacture (and identifying their manufacturer and specifications), describing the manufacturing procedures and in-process controls used, and laying out the specifications needed to ensure the product's strength, quality, purity, potency, and bioavailability.³⁰⁰

The primary challenges for a botanical NDA are uncertainty about the botanical drug's active constituents, heterogeneity of the drug substance, and inconsistency from batch-to-batch.³⁰¹ These issues will complicate preparation and review of the CMC section of the NDA.³⁰²

application. See EPIDIOLEX PRODUCT QUALITY REVIEW(S), *infra* note 571. But it does not appear from the review documents that the applicant needed, or that the FDA exercised, the same sort of flexibility with respect to application requirements as it applied when approving Veregen and Mytesi.

297. FULYZAQ SUMMARY REVIEW, *supra* note 295; VEREGEN APPROVAL PACKAGE, *supra* note 290.

298. 21 C.F.R. § 314.50(d)(1)(i) (2018).

299. § 314.50(d)(1).

300. § 314.50(d)(1)(ii)(a).

301. BOTANICAL GUIDANCE, *supra* note 287, at 4.

302. 21 C.F.R. § 314.50(d)(1)(i).

The FDA's guidance document indicates that "therapeutic consistency" can be supported using a totality of the evidence approach," if the applicant submits information relating to the botanical raw material, quality control through chemical testing and manufacturing control, and biological assays or even clinical data.³⁰³ Quality control of the drug substance may consider factors such as strength by dry weight, chemical identification of active constituents (if known) or chemical constituents, quantification of active constituents (if known) or chemical constituents, and tests for residual pesticides.³⁰⁴ A biological assay would need to reflect the drug's known or intended mechanism of action.³⁰⁵ If the active constituents are not known or quantifiable, it may be important to develop an assay to assess batch potency and activity relative to a reference standard.³⁰⁶ The chemistry section should also include a thorough review of past human experience with the raw materials and known constituents.³⁰⁷

The application of a "totality of the evidence" for botanical drugs means that some drugs that would not pass a traditional CMC review may survive review with the support of the Botanical Review Team.³⁰⁸ The primary chemistry reviewer in the Office of New Drugs considering Mytesi, for instance, concluded that issues relating to the identity, strength, purity, and quality of the drug substance and drug product precluded approval.³⁰⁹ The botanical reviewer, by way of contrast, argued that these concerns stemmed from a "strict reading" of the regulations and definitions of "identity," "active ingredient," and "purity" from a "pure small molecule drug perspective."³¹⁰ He argued that the regulations should be interpreted in a way that would

303. *Id.*; see also *Botanical Drug Review*, *supra* note 239, at 2 (noting that the FDA will use a "totality of the evidence" approach, in order to overcome limitations in the ability to characterize the active ingredient (or mixture) and in order to respond to concerns about heterogeneity and batch-to-batch variability). Describing the raw material includes explaining the agricultural and collection practices used. BOTANICAL GUIDANCE, *supra* note 287, at 4.

304. BOTANICAL GUIDANCE, *supra* note 287, at 10–11.

305. *Id.* at 4.

306. *Id.* at 10.

307. *Id.* at 7–8.

308. *Botanical Drug Review*, *supra* note 239 (indicating that the CMC documentation for a botanical drug may be different from that for a synthetic or highly purified drug).

309. FULYZAQ SUMMARY REVIEW, *supra* note 295, at 4; see also FDA, CTR. FOR DRUG EVALUATION AND RES., MEMORANDUM: BOTANICAL SECONDARY REVIEW OF NDA 202292 8–11 (2012), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202292Orig1s000BotanicalR.pdf.

310. FULYZAQ SUMMARY REVIEW, *supra* note 295, at 2.

“accommodate the complex nature of botanical drug substance.”³¹¹ For example, he wrote, “the ‘identity’ of botanicals must include, in addition to the standard chemical analyses, the source of raw materials and other non-CMC data—e.g., identification of species, geographic location of harvesting, processing, and bioassay, if available.”³¹² The Division Deputy Director agreed with the botanical reviewer’s view that “botanical new drugs can rarely have CMC specifications as precise as those of pure chemical drugs,” and “it is especially difficult to determine for botanical drugs with unknown number and identities of active ingredients (such as crofelemer) whether the future marketing batches will have the same therapeutic effects as that observed in clinical trials.”³¹³ Ultimately, the Director of the Center for Drug Evaluation and Research made the call, concluding—possibly in light of the “urgent need” for the product, which was intended for treatment of diarrhea in patients with HIV/AIDS—that “all of the CMC characterization” was not needed.³¹⁴ This history suggests that the agency’s willingness to be flexible in any particular case may depend a great deal on the views of a single botanical reviewer. It could also depend on the support of agency leadership, who may focus on broader questions of public health.

b. Preclinical and clinical data

An NDA also contains several sections establishing the product’s safety and effectiveness.³¹⁵ Generating the data in these sections requires a stepwise process beginning with laboratory and animal studies, (“preclinical” or “nonclinical” research), followed by several phases of human (“clinical”) trials that culminate in pivotal trials establishing effectiveness.³¹⁶

311. *Id.*

312. *Id.* The botanical reviewer played a key role in pushing the agency’s thinking further. For instance, he proposed a variety of ways to address uncertainty about batch-to-batch variability that did not appear in the 2004 version of the guidance document then in effect. These included “pre-CMC” steps (such as controlling collection of raw materials to eco-geographic regions with good agricultural and collection practices) and “post-CMC” evidence (such as clinical evidence that therapeutic effect is not affected by batch-to-batch variation). *Id.* at 4–5.

313. *Id.* at 4.

314. *Id.* at 12.

315. 21 C.F.R. § 314.50(d)(2)–(5) (2018).

316. FULZYAQ SUMMARY REVIEW, *supra* note 295, at 5–6.

The general goal of preclinical research is to collect the data necessary to support the safety of early clinical trials.³¹⁷ In practice, the FDA expects both pharmacology tests, which consider how the drug works on various physiological systems and how the body processes the drug, and toxicology tests, which assess the drug's short-term and long-term adverse effects.³¹⁸ The applicant submits its preclinical data in an IND. The amount of newly generated preclinical data needed for a botanical IND will depend on the human experience with the botanical drug to date.³¹⁹ But the FDA expects rigorous data on the nonclinical pharmacology and toxicology of the precise drug substance being developed, which means that anecdotal reports about the safety and effectiveness of cannabis—even if based on decades of illicit use or even reports of lawful medical use prior to enactment of the CSA—will not suffice. These data could reduce the amount of nonclinical testing required by the FDA, but they will not replace it.³²⁰

After the FDA permits an IND to go into effect, the company may conduct human testing.³²¹ The agency expects the pre-approval clinical testing process to advance through stages, from small groups of healthy volunteers, at the outset, to large multi-site trials in patients, designed and executed to provide statistically robust proof of safety and efficacy.³²² The agency's regulations describe three phases of trials, but marching through three sequential, non-overlapping phases of testing is not required and may not always be the most effective or efficient way to proceed.³²³ The final pivotal trials are designed to

317. *Id.* at 9.

318. 21 C.F.R. § 312.23.

319. *Id.*

320. The recently-enacted 21st Century Cures Act does not change this. *See generally* Pub. L. No. 114-255, 130 Stat. 1033 (2016). Congress directed the FDA to evaluate the potential use of “real world evidence” in approval decisions, but only in decisions to approve new indications for already approved drugs. *See* 130 Stat. at 1096–98. Moreover, this new provision of the statute does not alter the standard of approval, including the “substantial evidence” standard. *Id.*

321. *The Drug Development Process, Step 3: Clinical Research*, FDA, <https://www.fda.gov/forpatients/approvals/drugs/ucm405622> (last visited Feb. 5, 2019).

322. *Id.*

323. § 312.21. Phase 1 trials generally involve administering the investigational drug to a very small number of healthy individuals primarily to gather safety data, such as safe dosage for future tests. A company might use patients rather than healthy volunteers, however, if the drug is very potent or toxic and use in healthy volunteers would raise ethical issues. Phase 2 trials are designed to gather additional short-term safety data and dose range findings, but also effectiveness data. They usually involve a small number of patients, perhaps as many as several hundred. Phase 3 studies are designed to determine

establish that the drug satisfies the statutory approval standard: “substantial evidence” of effectiveness.³²⁴ Substantial evidence means evidence consisting of “adequate and well-controlled” clinical trials, on the basis of which qualified experts could “fairly and responsibly” conclude that the drug has the effect claimed.³²⁵

The FDA’s regulations flesh out the characteristics of an “adequate and well-controlled” trial.³²⁶ Such a trial has a protocol with a clear statement of objectives and a summary of the proposed method of analysis.³²⁷ It should use a design that permits a valid comparison with a control to provide a quantitative assessment of the drug’s effect, and the effect should be measured in a way that is well-defined and reliable.³²⁸ Subjects should be selected in a way that ensures they have the disease or condition being studied, and they should be assigned to treatment and control groups in a way that minimizes bias and ensures the arms are comparable.³²⁹ Additional measures should be taken to minimize bias on the part of the subjects as well as other participants in the trial, such as the investigators conducting the trial.³³⁰ Finally, the study report should include an appropriate statistical analysis of the results, sufficient to assess the drug’s effects.³³¹

whether the drug is safe and effective for the target indication and to more precisely identify any drug-related adverse effects. They typically involve several hundred to several thousand patients and multiple sites, often in multiple countries. *Id.*

324. 21 U.S.C. § 355(f) (2012).

325. § 355(d). The FDA generally expects two adequate and well-controlled trials, however, Congress amended the FDCA in 1997 to confirm that the agency may approve a drug on the basis of one, combined with “confirmatory evidence.” *See* Food and Drug Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296, 2313.

326. *See* 21 C.F.R. § 314.126; *see also* Lietzan, *supra* note 46, at 51–54 (2018).

327. § 314.126(b)(1).

328. § 314.126(b)(2).

329. § 314.126(b)(3).

330. § 314.126(b)(4).

331. § 314.126(b)(7). The gold standard approach is a randomized, double-blind, placebo-controlled hypothesis-testing trial pursuant to a written protocol with a prespecified data analysis plan. *E.g.*, John Concato et al., *Randomized, Controlled Trials, Observational Studies, and the Hierarchy of Research Designs*, 342 *NEW ENGLAND J. MED.* 1887 (2000); Laura E. Bothwell et al., *Assessing the Gold Standard—Lessons from the History of RCTs*, 374 *NEW ENGLAND J. MED.* 2175 (2016). That said, the substantial evidence standard can be surprisingly flexible when circumstances necessitate flexibility. The FDA has approved new drugs on the basis of a single trial, on the basis of a single study in fewer than 10 patients, on the basis of studies without blinding or controls, and—indeed—without any efficacy testing in humans. *See, e.g.*, Frank J. Sasinowski & Alexander J. Varond, *FDA’s Flexibility in Subpart H Approvals: Assessing Quantum of Effectiveness Evidence*, 71 *FOOD & DRUG L.J.* 135, 139–41 (2016) (studying nineteen

The clinical data requirements for approval of a botanical drug do not differ from the clinical data requirements for a non-botanical drug.³³² Phase 3 trials of a botanical drug, including a drug containing cannabis, would have the same purpose and design requirements as any other phase 3 trials. Clinical development of botanical drugs does, however, face some special issues, and clinical development of a cannabis-based botanical drug would face these issues.

First, a botanical drug substance can differ in its characteristics over the course of a drug development program.³³³ For instance, changes in the agricultural and collection practices for the raw material, or changes in the manufacturing process as result of process optimization, may lead to changes in drug substance composition.³³⁴ Preclinical and clinical testing results that use earlier versions of the drug substance generally cannot be used in a marketing application without “bridging” studies that compare the versions.³³⁵

Second, a botanical drug substance may vary in chemical composition from batch-to-batch. The FDA will expect an applicant to explore the impact of batch-to-batch variability on the therapeutic effect of the botanical drug product and, in particular, to support an argument that expected variations will not cause a meaningful difference in therapeutic effect.³³⁶ The agency has suggested using multiple batches in phase 3 trials, which may help an applicant understand (1) which variations are clinically relevant and (2) if they are clinically relevant, the range of variability that can be tolerated to maintain the product’s identity, safety, and efficacy.³³⁷

Third, depending on the route of administration and therapeutic goal, it may be difficult to design an adequately blinded clinical trial with objective endpoints.³³⁸ In some cases, it may be necessary to use a botanical in the control drug in order to mask the presence (or

approvals granted by the FDA through its accelerated approval process for diseases and illnesses other than cancer and AIDS).

332. See, e.g., VEREGEN BOTANICAL REVIEW, *supra* note 295, at 2 (2006) (“For clinical data to support marketing approval, there should be no difference between botanical and non-botanical drugs.”).

333. Other drugs evolve during development, but the FDA has flagged this as an issue for botanical drugs in particular.

334. BOTANICAL GUIDANCE, *supra* note 287, at 6.

335. *Id.*

336. *Id.* at 15–16.

337. *Id.*

338. *Id.* at 12.

absence) of the active drug.³³⁹ Senior leadership at the agency has also questioned whether blinding is possible if an investigational cannabis-based drug is administered through combustion (smoking) and have expressed concern about the subjectivity of the endpoints needed for many therapeutic goals of cannabis-based products.³⁴⁰ Subjective endpoints can reduce the reliability of positive results from a trial and can lead the FDA to reject marketing applications.³⁴¹

Finally, there is an open question of whether and how the FDA's combination drug regulation will apply.³⁴² Under this regulation, the sponsor of a drug product containing two active components must demonstrate that each component makes a contribution to the total effect that the combination is represented to have.³⁴³ Traditionally, if both ingredients are directed to the same sign or symptom, the FDA expects a "factorial" study, which demonstrates that the combination has a larger treatment effect than either active ingredient alone.³⁴⁴ The agency has proposed to consider fresh or physically processed material derived from a single part of a single species of a plant as a single botanical raw material.³⁴⁵ Thus a botanical drug product derived from a single part of a plant would not be subject to the fixed combination drug regulation.³⁴⁶ In contrast, a botanical product composed of multiple and easily separable parts of a single species of plant (e.g., flowers and bark of a woody plant) would continue to be subject to the combination drug requirements.³⁴⁷ The agency has proposed waiving this regulation for a traditional botanical drug composed of multiple raw materials in a fixed ratio, at least if there are so many active ingredients that factorial studies to assess the contribution of each would be infeasible.³⁴⁸ Other botanical drug products would be

339. *Id.*

340. *See Marijuana Trials Should Aim for Higher Standard: Superiority to Marinol, FDA's Temple Suggests*, PINK SHEET (Feb. 24, 1997).

341. FDA, GUIDANCE FOR INDUSTRY, INVESTIGATORS, AND REVIEWERS: EXPLORATORY IND STUDIES 11 (2006).

342. *See generally* 21 C.F.R. § 300.50 (2018).

343. § 300.50(a).

344. Fixed-Combination and Co-Packaged Drugs: Applications for Approval and Combinations of Active Ingredients Under Consideration for Inclusion in the Over-the-Counter Monograph, 80 Fed. Reg. 79,776, 79,785 (Dec. 23, 2015) (to be codified at 21 C.F.R. pts. 300, 330, and 610).

345. *Id.* at 79,780.

346. *Botanical Drug Review*, *supra* note 239, at 2.

347. *Id.*

348. 80 Fed. Reg. at 79,787.

deemed fixed combination drugs even though derived from a single botanical raw substance.³⁴⁹

c. Route of administration

State-regulated medical cannabis today is mostly inhaled (vaporized or combusted), although increasing amounts are administered orally (for instance, in gel caps and oils) or even topically.³⁵⁰ A company developing a medical cannabis product for FDA approval could in theory consider any route of administration. A drug's route of administration can affect its dosing as well as its safety and effectiveness;³⁵¹ however, the route of administration will dictate some data requirements.³⁵² As discussed in Section IV.A, the four approved cannabinoid drugs are administered orally.³⁵³ Other routes of administration may face additional hurdles at the agency.

The prospects for inhaled products, in particular, are unclear. Generally, inhaled drug products fall into three categories: metered dose inhalers, dry powder inhalers, and nebulizers.³⁵⁴ Some ongoing medical cannabis clinical research involves inhaled products; many involve combustion (smoking), but at least one involves a metered dose inhaler.³⁵⁵ But the agency has expressed skepticism. When discussing medical cannabis, FDA leadership recently indicated the

349. *Id.* at 79,781.

350. Mary Barna Bridgeman & Daniel T. Abazia, *Medicinal Cannabis: History, Pharmacology, and Implications for the Acute Care Setting*, 42 PHARMACY & THERAPEUTICS 180, 183 (2017).

351. This is known to be true of cannabis in particular. *Id.* (“The method of administration can impact the onset, intensity, and duration of psychoactive effects; effects on organ systems; and the addictive potential and negative consequences associated with use.”).

352. If a drug is meant to be inhaled, for instance, the FDA requires inhalation toxicity studies and may require carcinogenicity studies. FDA, NONCLINICAL SAFETY EVALUATION OF REFORMULATED DRUG PRODUCTS AND PRODUCTS INTENDED FOR ADMINISTRATION BY AN ALTERNATE ROUTE: GUIDANCE FOR INDUSTRY AND REVIEW STAFF 6 (2015).

353. *See infra* Section IV.A.

354. Shuguang Hou et al., *Practical, Regulatory and Clinical Considerations for Development of Inhalation Drug Products*, 10 ASIAN J. PHARM. SCI. 490, 491, 495–96 (2015) (defining metered dose inhalers as a suspension- or solution-based formulation of drugs propelled by hydrofluoroalkane propellants; dry powder inhalers as “a blend of micronized drug powder with larger carrier particles”; and nebulizers as a drug “formulated in aqueous solution or suspension, which is atomized into fine droplets via an external nebulization source”).

355. NCT02729623, *The Pharmacokinetics, Safety, and Ease of Use of a Portable Metered-Dose Cannabis Inhaler*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/show/NCT02729623> (last updated July 25, 2016).

agency prefers that inhaled drugs be intended to treat the lungs.³⁵⁶ Most drugs approved for delivery through the lungs are intended to treat the lungs in some fashion.³⁵⁷ The agency's resistance to inhalation could be overcome, however, with solid data on the effectiveness of this route of administration—such as evidence that inhalation leads to more consistent dosing than oral delivery.³⁵⁸

Inhalation by combustion would face a higher hurdle. Agency officials have consistently expressed skepticism that combustion of cannabis would allow delivery of a consistent dose.³⁵⁹ The FDA would expect an applicant to address the risk of pulmonary cancer and other respiratory tract diseases, such as chronic obstructive pulmonary disease, particularly if the combustible product were intended for chronic use. This could entail long-term safety studies before approval, and—depending on the intended use—some findings might preclude

356. Brenda Sandburg, *Gottlieb on Medical Marijuana: Smoking is Not Effective Way to Deliver API*, PINK SHEET (Apr. 19, 2018), <https://pink.pharmaintelligence.informa.com/PS122944/Gottlieb-On-Medical-Marijuana-Smoking-Is-Not-Effective-Way-To-Deliver-API> (quoting Scott Gottlieb, the Commissioner of Food and Drugs, as saying, “We generally would prefer not to deliver drugs through the lung unless we were treating the lung in some fashion”).

357. *Id.* For instance, Proventil-HFA (albuterol sulfate) and Flovent (fluticasone propionate) are marketed in pressurized metered dose inhalers for treatment of bronchospasm and asthma, respectively. Shuguang, *supra* note 354, at 493. Tobi Podhaler (tobramycin) is marketed as a powder for inhalation, which a patient self-administers for management of cystic fibrosis with *Pseudomonas aeruginosa*, using a proprietary device. *Id.* at 493, 497. AstraZeneca markets Pulmicort Respules (budesonide) for asthma in a suspension (liquid) for use with a nebulizer, which turns the liquid into a mist for inhalation into the lungs. *Id.* at 493.

358. Some research suggests that inhaled THC reaches its peak level in the body “nearly instantaneously” due to direct absorption by the capillaries in the lungs, leading to more consistent levels of the drug than an oral formulation. MACK & JOY, *supra* note 81, at 143, 203.

359. *Researching the Potential Medical Benefits and Risks of Marijuana*, FDA (2016) [hereinafter *Researching Marijuana*], <https://www.fda.gov/newsevents/testimony/ucm511057> (“When the Institute of Medicine (IOM) reviewed the clinical use of marijuana, it identified the problems associated with obtaining consistent dosing using smoked products and recommended that clinical trials involving marijuana should be conducted with the goal of developing safe, alternative delivery systems”); Sandburg, *supra* note 356 (quoting Commissioner Gottlieb that “the best way to deliver an active pharmaceutical ingredient is in a measured dose in a form where you can purify the ingredient and you know what you are getting and you can demonstrate dose effect and you can provide a reliable treatment to a patient,” which “generally is probably not going to come from something that is smoked”).

approval.³⁶⁰ Although the FDA permits numerous clinical trials of smoked cannabis for medical conditions, the agency's view seems to be that "the purpose of clinical trials of smoked cannabis would not be to develop cannabis as a licensed drug but rather to serve as a first step toward the development of non-smoked rapid-onset cannabinoid delivery systems."³⁶¹

Cannabis-based drugs presented in dosage forms that are not intended for inhalation (especially combustion) are less likely to raise complex regulatory issues and less likely to meet resistance from the agency. But each route of administration and dosage form will present issues for consideration. Topically administered drugs in solution or gel form, for instance, may present safety issues if physical contact with others can transfer the active ingredient.³⁶² Concerns about transfer could lead to additional premarket testing requirements and, if appropriate, special safety controls after approval.³⁶³ The agency's

360. See Ethan Russo et al., *Current Status and Future of Cannabis Research*, CLINICAL RESEARCHER 58, 59 (Apr. 2015) ("Meanwhile, although cannabis smoking may not be epidemiologically linked to lung cancer, it is responsible for chronic cough, sputum, and cytological changes, which render smoked cannabis an impossible candidate for approval as a prescription product in most jurisdictions."). Because the approval decision requires benefits and risks to be considered together, it is likely that even these risks would be acceptable to the agency for some uses.

361. *Researching Marijuana*, *supra* note 359. If the agency permitted an inhalable cannabis-based product, the product might be considered a "combination product" (combining a drug and device). The phrase "combination product" includes a drug and device that are physically combined and produced as a single entity (such as a patch that delivers an active ingredient), as well as a drug and device that are packaged together (such as a nebulizer and suspension). 21 C.F.R. § 3.2(e) (2018). In this case, the company would need to consider both drug and medical device regulatory issues. As a practical matter, the analysis is unlikely to change. A combination product's "primary mode of action"—the single mode of action that provides its most important therapeutic action—dictates which part of the FDA will review the premarket submission. 21 U.S.C. § 353(g)(1)(C) (2012). The Center for Drug Evaluation and Research (CDER) would almost certainly take the lead on premarket review of a cannabis-derived drug product. Combination products are typically regulated under the marketing authorization associated with the component that provides the primary mode of action, meaning that this product would probably still require only an NDA. See 21 U.S.C. § 353(g)(1)(D). In some cases, though, the agency will require a second premarket submission tied to the second constituent part. An alternative in this case would be to use a device that the FDA has already approved or cleared for the market.

362. See, e.g., MEDICATION GUIDE: ANDROGEL (2016), https://www.rxabbvie.com/pdf/androgel1_62_medguide.pdf (advising users to wash their hands "right away" after application).

363. For instance, testosterone in gel form is approved for treatment of men with a testosterone deficiency but it can rub off on women and children, causing early puberty in a child. Companies developing topical testosterone products are generally

guidance documents and precedents are key to understanding what might be required in any particular case, but it is safe to say that orally administered products in traditional dosage forms (tablet, capsule, and solution) are the least likely to face unexpected regulatory hurdles.

3. *Approval and risk management*

Approval of a new drug represents the FDA's conclusion that the benefits of the drug outweigh its risks when the drug is used in accordance with its approved labeling.³⁶⁴ The agency would make several additional risk management decisions when approving a cannabis-based drug.

First, the FDA would likely designate a cannabis-derived drug product as a prescription product. Prescription status is required for any drug that is "not safe for use except under the supervision of" licensed prescribers because of its "toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use."³⁶⁵ Although the FDA considers these and related factors when deciding whether to switch a drug from prescription to nonprescription status,³⁶⁶ as a practical matter, almost every new drug

required to conduct transfer studies, and the drugs are approved with special risk management measures. For instance, Androgel® (testosterone) is distributed with a "Medication Guide" that instructs patients to apply the drug to areas of their shoulders, upper arms, and abdomen that will be covered by a t-shirt and to wash their hands immediately. *See id.*

364. *See* 21 C.F.R. § 314.50(d)(5)(viii) (requiring NDAs to discuss "why the benefits exceed the risks under the conditions stated in the labeling"); *see also* United States v. Rutherford, 442 U.S. 544, 555 (1979) ("[T]he [FDA] generally considers a drug safe when the expected therapeutic gain justifies the risk entailed by its use."); FDA, CRITICAL PATH OPPORTUNITIES REPORT R-8 (March 2006), <http://wayback.archive-it.org/7993/20180125142845/https://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/UCM077254.pdf> (suggesting approval once "uncertainty" about benefit-risk balance has been "reduced to an acceptable level").

365. 21 U.S.C. § 353(b). If cannabis and THC were rescheduled rather than descheduled, the CSA would require that the product be sold only on prescription. *See* 21 C.F.R. § 1306.11 (requiring a written prescription for the distribution of any Schedule II substance); § 1306.21 (requiring a prescription for the distribution of any Schedule III, IV, or V substance).

366. The FDA considers a variety of factors, such as the ability of patients to self-diagnose and follow treatment instructions, public health considerations, such as whether a prescription requirement would be an impediment to timely treatment in emergency situations, and possibly even social policy. *See generally* Peter Barton Hutt, *A Legal Framework for Future Decisions on Transferring Drugs from Prescription to Nonprescription Status*, 37 FOOD DRUG COSM. L.J. 427 (1982).

is first approved today as a prescription drug.³⁶⁷ The agency might also be reluctant to permit a cannabis-based drug to be available over the counter if others are limited to prescription status—particularly if the prescription products are intended for treatment of serious conditions and generally require a physician’s involvement. Some active ingredients are available in both prescription and nonprescription form,³⁶⁸ but the possibility that patients needing medical attention might self-treat with the nonprescription cannabis-based product would give the agency pause.

Second, as a prescription drug, a cannabis-based drug—whether edible, inhaled, ingested, or applied topically—would require FDA-approved labeling for prescribers. Agency regulations specify the format and content of this labeling, which is meant to summarize and distill the safety and effectiveness information in the marketing application so that prescribers can make informed judgments about treatment.³⁶⁹ In addition to information about the preclinical and clinical studies supporting approval, the labeling must describe the overall adverse reaction profile of the drug based on the entire safety database, as well as clinically significant adverse reactions and other safety hazards.³⁷⁰ The labeling must present information about “drug abuse” and “dependence,” even if the drug is not controlled, describe clinically significant interactions with other prescription medicines (as well as nonprescription drugs, foods, and dietary supplements), discuss use in special populations such as pregnant and breastfeeding women, and advise about the signs and symptoms of overdose and recommended treatment of overdose.³⁷¹

Third, in some cases, the FDA might decide that the risks associated with the product require the adoption of special risk management measures. The agency could, for example, require the company to distribute patient labeling, a “Medication Guide,” explaining the key risks associated with the drug and any special measures that should be taken (such as avoiding driving and consumption of alcohol) when using the drug.³⁷² If the FDA concludes that the drug’s benefits

367. *Id.* at 428.

368. Examples include ibuprofen and fluticasone propionate.

369. *See* 21 C.F.R. § 201.57; Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3,922 (Jan. 24, 2006) (to be codified at 21 C.F.R. pts. 201, 314, and 601).

370. 71 Fed. Reg. at 3,922.

371. *Id.* at 3,994.

372. 21 C.F.R. §§ 208.1, 208.20.

outweigh its risks only with special risk management measures in place, it will require the company to implement a “risk evaluation and mitigation strategy.”³⁷³ In particular, if necessary to mitigate a specific serious risk listed in the drug’s labeling, the agency can impose use and distribution restrictions.³⁷⁴ These might include limiting the drug to prescribers with special training or requiring that all patients be entered in a registry.³⁷⁵ Particularly if the agency had concerns about dependence or misuse of a cannabis-based drug product, it might impose access restrictions. Descheduling of cannabis, THC, and cannabimimetics would not preclude this.

Nevertheless, the risks and benefits of a new drug are never fully understood at the time of approval. This would be true of any cannabis-based new drug product, despite the long history of medical and non-medical use of cannabis.³⁷⁶ The FDA’s concern is the safety and effectiveness of the particular dosage form, strength, patient population, and use at issue. Risk management, which includes monitoring and responding to risk, is therefore the dominant feature of postmarket regulation of new drugs.³⁷⁷ The FDA may require a company to conduct postmarket testing, as a condition of approval, to assess known risks or even to assess signals that emerged during premarket testing.³⁷⁸ Both approved botanical drugs were subject to postmarket testing obligations.³⁷⁹ And regardless of whether the agency imposed postmarket testing as a condition of approval, any company that held an approved NDA for a cannabis-based drug product would be required to evaluate and report any adverse events of which it became aware.³⁸⁰ These reports, in turn, could lead to

373. *Risk Evaluation and Mitigation Strategies (REMS)*, FDA, <https://www.fda.gov/Drugs/DrugSafety/REMS/default.htm> (last updated Feb. 2, 2018).

374. 21 U.S.C. § 355-1(f)(3) (2012).

375. §§ 355-1(f)(3)(A), (F).

376. Russo, *supra* note 54, at 1614.

377. 21 U.S.C. § 355-1.

378. *See* § 355(o)(3).

379. For instance, the FDA required Salix Pharmaceuticals, which holds the NDA for Mytesi, to conduct two rodent carcinogenicity studies. *See* FDA, CTR. DRUG EVALUATION & RES., NDA APPROVAL: NDA 202292, https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/202292Orig1s000ltr.pdf (last visited Feb. 5, 2019). The company also committed to an *in vitro* and an *in vivo* study in humans to further explore the pharmacodynamics of crofelemer, as well as additional analytical work and additional work on its bioassays. *Id.*

380. *See* 21 C.F.R. § 314.80 (2018).

labeling changes or more significant requirements, such as new studies or access restrictions.³⁸¹

The Poison Prevention Packaging Act of 1970 (PPPA)³⁸² would also apply to cannabis-derived drug products and might require the manufacturer to adopt special packaging.³⁸³ The PPPA applies to any food or drug customarily produced or distributed for sale for consumption or use by individuals in or about the household.³⁸⁴ The Consumer Product Safety Commission's implementing regulations require that any prescription drug intended for oral administration be packaged in accordance with its "special packaging" standards.³⁸⁵ The general idea is that the packaging must be reasonably convenient for adults to open and yet designed so that young children cannot easily obtain the contents.³⁸⁶ Thus, the company would have to use packaging that provided a specified degree of child resistance, confirmed using testing procedures also specified in the regulations.³⁸⁷ At the same time, the packaging would need to satisfy "ease of adult opening" standards, which must be similarly tested in both senior adults and younger adults according to the agency's testing standards.³⁸⁸

4. Consequences of using the new drug pathway

The new drug research and development process is notoriously expensive and risky. For a new chemical entity, it can take ten to twelve years and cost more than \$1 billion.³⁸⁹ Prior and longstanding use of cannabis for medical and non-medical purposes may reduce some of the risk, for instance, by identifying promising uses and suggesting the appropriate dosing. Also, the agency's flexibility with botanical NDAs may reduce some of the cost, where it applies. Pursuing new drug approval for medical cannabis after descheduling could, however, still cost hundreds of millions of dollars. This will put the process out of

381. 21 U.S.C. §§ 355(o)(3)–(4); 21 C.F.R. § 201.57(c)(6)(i).

382. Pub. L. No. 91-601, 84 Stat. 1670 (codified at 15 U.S.C. §§ 1471–77).

383. § 1472.

384. § 1471(2).

385. 16 C.F.R. § 1700.14(a)(10).

386. § 1700.14.

387. §§ 1700.15, 1700.20.

388. § 1700.15.

389. Joseph A. DiMasi et al., *Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs*, 47 J. HEALTH ECON. 20, 25–27 (2016) (estimating average out-of-pocket cost per approved compound of \$1.4 billion and total preapproval cost of \$2.56 billion); Erika Lietzan, *The Myths of Data Exclusivity*, 20 LEWIS & CLARK L. REV. 91, 107–08 (2016) (discussing range of estimates for the length of time and cost of developing a new drug).

reach for most entities currently providing medical cannabis.³⁹⁰ Yet avoiding the new drug approval process is not an option; medical claims on any product in interstate commerce will trigger the FDA's new drug authorities and require an approved NDA.³⁹¹

Even well-established biopharmaceutical companies might eschew development of cannabis-based products. It is not clear a cannabis-based product would enjoy enough exclusivity in the market for a company to recoup its investment and earn a profit. U.S. law provides exclusivity (as an incentive for new drug research) through two mechanisms—patent protection and regulatory exclusivity—but the value of these for cannabis-based drugs is unclear.³⁹² Patent protection would preclude any other company from making, using, or selling the patented invention for a fixed period of time.³⁹³ But a company could not patent the cannabis plant itself, and it may not be possible to patent the medical uses of cannabis that have been known for years.³⁹⁴ It may be possible to patent genetically engineered cannabis plants, methods of cultivating the plants, and methods of manufacturing cannabis-based products. Newer methods of treatment and delivery devices, among other things, may also be patentable.³⁹⁵ And regulatory exclusivity will prevent submission, or in some cases approval, of other applications at the FDA for a fixed period of time.³⁹⁶ Patent protection and regulatory exclusivity could motivate the larger companies to invest

390. See Alex Halperin, *What Will Rescheduling Marijuana Mean for the Pot Industry?*, ROLLING STONE (Apr. 20, 2016), <https://www.rollingstone.com/culture/culture-news/what-will-rescheduling-marijuana-mean-for-the-pot-industry-203124> (“If the federal government determines that medical marijuana must be subjected to FDA approval, companies would have to enter a process that can take years to complete and cost more than \$1 billion per product. Few, if any, cannabis companies in the U.S. have the resources for that, which might open the door for Big Pharma to muscle in and take over the business.”).

391. See *supra* Section III.A.1.

392. Lietzan, *supra* note 46, at 56 (2018).

393. See 21 U.S.C. §§ 355(c)(3)(E), 355(j)(5)(F).

394. See 35 U.S.C. § 102(a)(1) (preventing a person from obtaining a patent if the product was “described in printed publication, or in public use, or otherwise available to the public” before the patent was filed).

395. See generally Gretchen L. Temeles et al., *IP Protection and the Cannabis Industry: Strategies and Trends*, LEGAL INTELLIGENCER (April 2, 2018, 2:10 PM), <https://www.law.com/thelegalintelligencer/2018/04/02/ip-protection-and-the-cannabis-industry-strategies-and-trends> (describing cannabis-related patents to date).

396. *E.g.*, 21 U.S.C. § 355(j)(5)(F)(ii) (prohibiting submission of a generic drug application for five years after approval of a new chemical entity, meaning an active moiety not previously approved in an NDA); 21 U.S.C. § 360cc (providing seven years of “orphan drug” exclusivity for drugs approved for treatment of rare diseases).

in the research and development needed for approval of a cannabis-based product. These companies could, however, be concerned about competition from cannabis-based products that are labeled for other conditions or, indeed, that are marketed without medical claims at all. Without a reasonable assurance of actual exclusivity in the marketplace, these companies might pursue other projects instead.

B. Medical Cannabis as (or in) Food

Cannabis as it is currently sold and used is unlikely to qualify as food in itself, and an extract from cannabis presented as a single-ingredient product would similarly not qualify. Rather than focusing on intended use as it does for drugs, the FDCA defines food by its actual use. Food, thus, is any “article[] used for food or drink for man.”³⁹⁷ The FDA interprets this to mean any item consumed primarily “for taste, aroma, or nutritional value.”³⁹⁸

Arguably, neither cannabis nor a single-ingredient cannabis extract product would satisfy this test. There is, however, some evidence that cannabis seeds, leaves, and other parts of the plant were historically eaten as food, whether by themselves or in combination with other foodstuffs.³⁹⁹ Seed cakes were popular in the ancient world, and oil seems to have been consumed just like other plant oils.⁴⁰⁰ Further, these uses would not have decarboxylated the THC or CBD contained in the raw plant materials (unless the foods were cooked or baked), which means the strongest and most notable effects of cannabis were probably not obtained.⁴⁰¹ This suggests that ancient populations may have valued cannabis components for their nutritive value. If true seed cakes and other cannabis-based foods were re-introduced to the market and consumed primarily for their nutritive value, as was apparently the case in the ancient world, the FDA might apply its food authorities.⁴⁰² Among other things, the food would be adulterated if it

397. 21 U.S.C. § 321(f)(1).

398. *Nutrilab, Inc. v. Schweiker*, 547 F. Supp. 880, 883 (N.D. Ill. 1982), *aff'd*, 713 F.2d 335 (7th Cir. 1983).

399. *See supra* Section I.B.

400. *See e.g.*, Zuardi, *supra* note 64, at 154.

401. *Id.* at 154, 156.

402. For instance, as discussed in note 430, the agency permits the use of hulled hemp seed, hemp seed protein powder, and hemp seed oil in certain foods, provided these ingredients meet certain specifications. In some cases, however, there is a risk the FDA would resist the characterization as food (or a food ingredient) and deem the product an unlawfully marketed dietary supplement, for reasons discussed in Section IV.B.

was “ordinarily . . . injurious” to health or if it contained a pesticide residue that exceeded an established tolerance, or for which no tolerance had been established.⁴⁰³

As discussed in this part, however, there are also substantial impediments to simply adding cannabis, or an extract from cannabis, to a conventional food such as a cookie, candy, or beverage. These impediments include the rule that foods cannot contain new drugs (the drug exclusion rule) and the fact that, as a single ingredient among many, cannabis (and a cannabis constituent) would probably be deemed a “food additive” requiring premarket approval.

1. *The drug exclusion rule: the 301(ll) problem*

It is unlawful to include either dronabinol (Δ^9 -THC) or CBD in a conventional food because these substances now appear in products regulated as new drugs.⁴⁰⁴ As discussed later in this Article, the FDA has approved two NDAs for dronabinol and an NDA for CBD.⁴⁰⁵ Under the drug exclusion rule of § 301(ll) of the FDCA, a food containing a substance that is an active ingredient of an approved drug product—or an active ingredient of a product in clinical trials that have been made public—cannot be shipped in interstate commerce.⁴⁰⁶ Although there are ways to avoid the drug exclusion rule, these are not promising for cannabis-based foods.

403. 21 U.S.C. §§ 342(a)(1)–(2), 348(a) (2012). Pesticide issues could be significant. There are no pesticides approved for use on cannabis plants. Jenna H. Bishop, Note, *Weeding the Garden of Pesticide Regulation: When the Marijuana Industry Goes Unchecked*, 65 *DRAKE L. REV.* 224, 226 (2017). At the same time, studies “overwhelmingly reveal that growers are choosing to use unapproved and unregulated pesticides.” *Id.* But these problems are not insurmountable. Indeed, the responsible segments of the industry are well aware that pesticide issues need to be addressed for all cannabis products, not just those that might be positioned as conventional food.

404. Even if there were no drug exclusion, the FDA might take the position that intentionally adding dronabinol or CBD to a food product in amounts known to affect the body constitutes evidence that the product is intended to address disease or affect the structure or function of the body. *Cf.* Zettler, *supra* note 249, at 1965 (discussing a warning letter to distributor of “Magic Power Coffee,” which contained an analogue of sildenafil, the active ingredient of Viagra).

405. *See infra* Section IV.B.1.

406. 21 U.S.C. § 331(ll). The FDA focuses on the whether the food is or contains a substance that is the same active moiety as the new drug in question. The source of the substance does not matter. Thus, for instance, the rule applies even if the substance derives from a plant classified as “hemp” and exempt from the Controlled Substances Act pursuant section 12619 of the Agriculture Improvement Act of 2018, Pub. L. 115-334 (amending 21 U.S.C. §§ 802(16), 812(c)). *See* Statement on Signing of the Agriculture Improvement Act, *supra* note 49.

First, § 301(II) contains an exception for a substance marketed in food *before* the drug in question was approved or the trials started.⁴⁰⁷ But the agency requires that the substance be overtly marketed in the food, for instance with references in the label.⁴⁰⁸ The FDA would probably refuse to consider marketing in violation of federal law, including the CSA.⁴⁰⁹ Moreover, the FDA has already concluded that “THC” and CBD must be excluded from foods in interstate commerce.⁴¹⁰ That said, it has invited evidence and arguments to the contrary.⁴¹¹ In addition, its claim about “THC” may be overbroad. The agency has approved products containing dronabinol, which is a synthetic Δ^9 -THC, but cannabis also contains several variants of Δ^8 -THC.⁴¹² These are also referred to as “THC” but may not be barred by the drug exclusion rule.

Second, the drug exclusion rule “precludes only the specific active ingredients already present in new drugs.”⁴¹³ “A company can avoid the drug exclusion by adding a different cannabinoid (or terpenoid or flavonoid) from cannabis—rather than dronabinol or CBD—to its food.”⁴¹⁴ But it will be important to do so overtly—“calling out the precise cannabinoid in the food label”—as soon as possible after descheduling.⁴¹⁵ “As soon as one of these other cannabinoids is the subject of a publicly known clinical trial, it will be too late to add it to a food.”⁴¹⁶

407. § 331(II)(1).

408. *E.g.*, FDA, DIETARY SUPPLEMENTS: NEW DIETARY INGREDIENT NOTIFICATIONS AND RELATED ISSUES: GUIDANCE FOR INDUSTRY 44 (2016) [hereafter NDI GUIDANCE]; FDA Response to Biostratum, Inc., No. FDA-2005-P-0259 (formerly Docket No. 2005P-0305/CP1) (Jan. 12, 2009), <https://www.regulations.gov/document?D=FDA-2005-P-0259-0004> (explaining that the “relevant inquiry” for determining whether a substance prohibited by the drug exclusion rule is whether a company was also marketing the substance alone as a food or dietary “by . . . making claims about the [substance] or otherwise highlighting its presence in the product”).

409. Alice Mead, *The Legal Status of Cannabis (Marijuana) and Cannabidiol (CBD) Under U.S. Law*, 70 EPILEPSY & BEHAVIOR 288, 290 (2017).

410. *FDA and Marijuana: Questions and Answers*, FDA (June 25, 2018), <https://www.fda.gov/newsevents/publichealthfocus/ucm421168> [hereafter *Marijuana Q&A*].

411. *Id.*

412. See MARIJUANA AND MEDICINE, *supra* note 92, at 24–25.

413. Erika Lietzan, *Cannabis and the Often Overlooked Drug Exclusion Rule*, OBJECTIVE INTENT BLOG (Sep. 18, 2018), <https://objectiveintent.blog/2018/09/19/cannabis-and-the-often-overlooked-drug-exclusion-rule>.

414. *Id.*

415. *Id.*

416. *Id.*

Third, a company might be able to “avoid the drug exclusion rule by manufacturing and selling conventional food products with dronabinol or CBD purely within the confines of a single state.”⁴¹⁷ To be sure, the FDA has asserted jurisdiction over medical treatments involving substances prepared purely on premises or within a state when it can identify a component (raw material) that had been shipped in interstate commerce.⁴¹⁸ But doing so rests on the phrasing of an enforcement provision that would not apply here. The FDA generally proceeds under § 301(k) of the statute, which prohibits misbranding or adulteration after an item has been shipped in interstate commerce.⁴¹⁹ But § 301(l) is drafted differently, prohibiting interstate shipment of a food after addition of a new drug.⁴²⁰ It is not clear that the FDA could act under § 301(l) with respect to a food made with dronabinol or CBD and sold within the same state, even if it contained a component (which is also a “food”)—such as flour—that had been shipped in interstate commerce.

2. *Regulation as a food additive: the 402(a) problem*

Even if a company avoided the drug exclusion rule (for instance, by adding a new cannabinoid, terpenoid, or flavonoid to its food), it would still need to grapple with the FDA’s food additive rules. Generally speaking, every ingredient in a food sold in interstate commerce is a food additive, subject to preapproval requirements, unless an exception applies.⁴²¹ The FDCA defines “food additive” as “any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component

417. *Id.*

418. *See* *United States v. Regenerative Scis. LLC*, 741 F.3d 1314, 1320–21 (D.C. Cir. 2014); *see also* *Complaint for Permanent Injunction, United States v. California Stem Cell Treatment Ctr.*, No. 5:18-CV-1005 (C.D. Cal. 2018), 2018 WL 2144859; Warning Letter from FDA to Dr. Drew Varano (Apr. 5, 2010), <https://wayback.archive-it.org/7993/20170112062943/http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2010/ucm207651.htm>.

419. *See* 21 U.S.C. § 331(k) (2012) (prohibiting any act with respect to a food or drug that (1) is done while the article is held for sale after shipment in interstate commerce and (2) renders the article adulterated or misbranded).

420. *See* § 331(l) (preventing the introduction into interstate commerce of a food to which a drug has already been added).

421. *See* § 321(s) (providing exceptions for substances that are generally recognized as safe, as well as certain pesticide chemicals, color additives, new animal drugs, and dietary supplements).

or otherwise affecting the characteristics of any food.”⁴²² Even food itself becomes a food additive if it is used as a component in another food.

A company wishing to add a non-excluded cannabis constituent (other than dronabinol or CBD) to a conventional food would need to obtain approval of a food additive petition unless it determined that an exception applied.⁴²³ A petition, in turn, must contain information about the additive itself (its “chemical identity and composition”), information about the manufacturing process and facility, and the controls used to ensure that the additive’s composition is consistent.⁴²⁴ It must also contain data on the technical effects of the food additive, as well as data from safety studies.⁴²⁵ Generating these data and securing the FDA’s approval of a food additive petition can take six years or longer.⁴²⁶

The key exception carves out a substance “generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown . . . to be safe under the conditions of its intended use.”⁴²⁷ Put another way, if the cannabis constituent were generally recognized as safe (GRAS) under the specific conditions of use intended, meaning safe at a particular level in a particular type of food, it would not be considered a food additive. A company could determine on its own that a particular cannabis constituent was GRAS for use in the particular food the company marketed.⁴²⁸ Federal law does not require a company to seek the FDA’s approval, or even the agency’s agreement, that the product is

422. *Id.*

423. See § 348(b); see also *Determining the Regulatory Status of a Food Ingredient*, FDA, <https://www.fda.gov/food/ingredientpackaginglabeling/foodadditivesingredients/ucm228269> (last updated Sept. 20, 2018).

424. See 21 C.F.R. § 171.1(b) (2018).

425. *Id.*

426. Inst. of Med.: Food Forum, *Enhancing the Regulatory Decision-Making Approval Process for Direct Food Ingredient Technologies* 2, 29 n.230 (1999).

427. 21 U.S.C. § 321(s).

428. A substance is GRAS if shown safe using “scientific procedures” or, if it was used in food before January 1, 1958, shown safe “through experience based on common use in food.” 21 C.F.R. § 170.30(a). The FDA interprets this to require “common knowledge throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food that there is reasonable certainty that the substance is not harmful under the conditions of its intended use.” *Id.*

GRAS.⁴²⁹ But if the agency disagreed with the company's judgment call,⁴³⁰ the ingredient would be an unapproved food additive, which would mean the conventional food containing this ingredient was adulterated under § 402(a) of the FDCA.⁴³¹ A company that shipped or received the food in interstate commerce could face enforcement action, up to and including criminal prosecution.⁴³² Even if the food itself was not shipped in interstate commerce, the FDA could take enforcement action if another ingredient was shipped in interstate commerce.⁴³³

3. *No claims could be made*

If a company avoided the drug exclusion issue and § 402(a), it might be able to add a cannabis constituent to a conventional food. But

429. The FDA has created a formal process for voluntary GRAS notifications. *See generally* 21 C.F.R. §§ 170.203–170.285. This does not result in regulatory certainty; the agency will typically respond only that it has “no questions at this time.”

430. The agency has published various lists of substances it recognizes as GRAS. Although the lists are not meant to be exhaustive, they do not include cannabis. *See* 21 C.F.R. pts. 182, 184, 186. In December 2018, however, the FDA issued three “no questions” letters in connection with voluntary GRAS notifications relating to the use of hulled hemp seed, hemp seed protein powder, and hemp seed oil in various foods. Hemp seeds are the seeds of the *Cannabis sativa* plant, and the specific ingredients that were the subject of the GRAS notifications contained only trace amounts of THC and CBD. *See FDA Responds to Three GRAS Notices for Hemp Seed-Derived Ingredients for Use in Human Food*, FDA (Dec. 20, 2018), <https://www.fda.gov/Food/NewsEvents/ConstituentUpdates/ucm628910> (describing the FDA's response to GRAS Notice Nos. GRN 000765, 000771, 000778). As a result, these constituents can be marketed in the specified foods without food additive approval.

431. Section 402(a) of the FDCA deems a food adulterated if it contains a food additive that is unsafe within the meaning of 21 U.S.C. § 348. *See* 21 U.S.C. § 342(a)(2)(C)(i); *see also* § 348 (declaring a food additive unsafe unless it complies with a food additive regulation).

432. *See* §§ 331(a), (c). To be sure, the FDA has not acted against foods containing cannabis that are sold in recreational cannabis law states. As mentioned above, this is probably because the sales are illegal under the CSA in the first instance. Robert J. MacCoun & Michelle M. Mello, *Half-Baked—The Retail Promotion of Marijuana Edibles*, 372 *NEW ENG. J. MED.* 989, 990 (2015); *see also* Paul R. Larkin, *Marijuana Edibles and “Gummy Bears,”* 66 *BUFF. L. REV.* 313, 349–56, 359 (2018) (discussing three reasons the FDA may have refrained from acting, including that the agency chose to avoid getting embroiled in disputes over the proper role of the federal government with respect to state cannabis laws and an overly broad reading of the Rohrabacher-Blumenauer Amendment).

433. The agency would reason that the food—for instance, a cookie—was adulterated by the addition of an unapproved food additive subsequent to the interstate shipment of one of its components—the flour. *See* 21 U.S.C. § 331(k); *see also* Complaint for Permanent Injunction ¶ 13, 15, 47–49, 55, *United States v. Cal. Stem Cell Treatment Ctr.*, No. 5:18-CV-1005, (C.D. Cal. 2018), 2018 WL 2144859.

federal law would not permit the company to make any claims about the food relating to the presence of the cannabinoid.

First, the FDA would not permit a “structure/function” claim (such as “helps maintain a calm disposition”) relating to the cannabis constituent. While the agency freely permits structure/function claims on dietary supplements,⁴³⁴ it permits these claims on conventional foods only if the claimed effect is achieved through the “nutritive value” of the food or nutrient.⁴³⁵ In a related context, the agency defines “nutritive value” to mean the item’s “value in sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients, or providing energy.”⁴³⁶ Thus although the FDA will permit structure/function claims referring to the role of well-known nutrients such as calcium and vitamin C, it would probably not permit a structure/function claim relating to non-nutritive effects of cannabis constituents.⁴³⁷ It might be possible to make a structure/function claim for a food containing cannabis constituents with nutritive value (such as seeds and leaves in a hemp cake), but the FDA would permit only claims about effects related to the nutritive benefit.

Second, the FDA would not permit any claim relating to the treatment, prevention, or cure of a disease, such as cancer. A disease claim will always turn a substance into a drug and usually also trigger the requirement to hold an approved NDA.⁴³⁸ It would not matter that the commercial product was presented to consumers as a conventional food. A product can fall into more than one regulatory category and be regulated under both sets of rules at the same time.⁴³⁹ A conventional food containing cannabis, with a disease claim relating to the cannabis, would be regulated as both a food and a drug.

Third, even though there is a special exception for “health claims” on foods and dietary supplements, the FDA would probably not permit a health claim on a conventional food based on the presence of a

434. See *supra* Section IV.B.

435. Food Labeling; Requirements for Nutrient Content Claims, Health Claims, and Statements of Nutritional Support for Dietary Supplements, 62 Fed. Reg. 49,859, 48960 (Sept. 23, 1997) (to be codified at 21 C.F.R. pt. 101).

436. 21 C.F.R. § 101.14(a)(3) (2018).

437. It might be possible to challenge the FDA’s approach to structure/function claims on conventional foods as inconsistent with the statute, but exploring this argument is beyond the scope of this Article.

438. See *supra* notes 250, 288 and accompanying text.

439. See, e.g., *supra* note 240 and accompanying text.

cannabis constituent in this food.⁴⁴⁰ A health claim characterizes the relationship of a substance to a disease or health-related condition.⁴⁴¹ The agency's regulations provide that a health claim must satisfy certain basic eligibility requirements before it can even be considered.⁴⁴² A typical health claim for a conventional food relates to decreased dietary level of a substance (such as lower saturated fat).⁴⁴³ For example, the agency has authorized "diets low in sodium may reduce the risk of high blood pressure, a disease associated with many factors" on a food that satisfies the agency's nutrient content requirements for "low sodium" food.⁴⁴⁴ If a health claim is based on the presence of a substance other than decreased dietary levels, the substance must be used in the conventional food for a traditional food purpose.⁴⁴⁵

440. Moreover, the agency's permission is necessary. There are three ways this can happen. First, the agency may expressly authorize a claim, in a regulation, if it finds that the claim is supported by the "totality of publicly available scientific evidence" and that there is "significant scientific agreement" among qualified experts that the claim is supported by this evidence. 21 U.S.C. § 343(r)(3)(B); 21 C.F.R. § 101.14(c). Second, a series of First Amendment rulings require the agency to exercise enforcement discretion with respect to claims that do not rise to this statutory standard, if appropriate disclaimers have been added. *E.g.*, *Pearson v. Shalala*, 164 F.3d 650, 653–54, 657 (D.C. Cir. 1999). The FDA expects a company to submit a petition for a qualified health claim, however, with the scientific data supporting the proposed claim. *See Guidance for Industry: Interim Procedures for Qualified Health Claims in the Labeling of Conventional Human Food and Human Dietary Supplements*, FDA (July 2003), <https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm053832.htm#intro>. Third, another federal agency with responsibility for human nutrition research or for protecting public health might publish an authoritative statement concerning the relationship between the substance and a disease or health-related condition. The FDA has the opportunity to modify or even prohibit a claim published by another agency. *See Guidance for Industry: Notification of a Health Claim or Nutrient Content Claim Based on an Authoritative Statement of a Scientific Body*, FDA (June 11, 1998) [hereinafter *Health Claim Guidance*], <https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/LabelingNutrition/ucm056975>.

441. 21 U.S.C. § 343(r)(1)(B). The FDA defines a "disease or health-related condition" in this context as "damage to an organ, part, structure, or system of the body such that it does not function properly (e.g., cardiovascular disease), or a state of health leading to such dysfunctioning (e.g., hypertension)." 21 C.F.R. § 101.14(a)(5).

442. *See Health Claim Guidance, supra* note 440.

443. 21 C.F.R. § 101.14(b)(2).

444. § 101.74.

445. § 101.14(b)(3) ("The substance must . . . contribute taste, aroma, or nutritive value, or any other technical effect listed in § 170.3(o) of this chapter, to the food and must retain that attribute when consumed at levels that are necessary to justify a claim"); *see also* Food Labeling; General Requirements for Health Claims for Food, 58 Fed. Reg. 2,478, 2,499 (Jan. 6, 1993) (to be codified at 21 C.F.R. pts. 20 and 101). Permitted

In effect, the substance must contribute taste, aroma, or nutritive value.⁴⁴⁶ The FDA probably would not permit a health claim on conventional food based on the presence of a cannabinoid because the cannabinoid would not be serving one of these traditional food purposes. It is conceivable the agency would permit a health claim about another cannabis constituent grounded in the nutritive value of that constituent.

4. *Risk of the FDA invoking new drug authorities*

The path forward for a food containing a cannabis constituent requires solving the drug exclusion issue (for instance, by ensuring the food contains only constituents that have not been studied or approved in new drugs, which excludes at least dronabinol and CBD), avoiding § 402(a) (through approval of a food additive petition or a GRAS determination), and making no claims relating to the *medical* benefits of cannabis in the food (though perhaps making health claims tied to *nutritive* benefits, with the agency's permission). But there would still be a non-trivial risk that the FDA would classify the product as a drug.

The FDA's regulations state that a product's intended use is determined by the expressions of the person legally responsible for its labeling, but it may also be shown "by the circumstances surrounding the distribution of the article."⁴⁴⁷ These include the circumstance that the item is, with this person's knowledge, "offered and used for a purpose for which it is neither labeled nor advertised."⁴⁴⁸ In 1980, the United States Court of Appeals for the D.C. Circuit added that the intended use of a product is determined "from its label, accompanying labeling, promotional claims, advertising, and *any other relevant source*."⁴⁴⁹ The full impact of the language in the regulation and court decision is unsettled. But the FDA concluded that balloons filled with nitrous oxide (laughing gas) and distributed in the parking lot of a rock concert at RFK Stadium were "drugs" even though the sellers made no claims about the intended use of the balloons.⁴⁵⁰ A federal

"technical effects" in food include use as an anti-caking agent, curing or pickling agent, emulsifier, or leavening agent, among other things. 21 C.F.R. § 170.3(o).

446. 21 C.F.R. § 101.14(b)(3). Nutritive value, in this context, means "value in sustaining human existence by such processes as promoting growth, replacing loss of essential nutrients, or providing energy." § 101.14(a)(3).

447. § 201.128.

448. *Id.*

449. *Action on Smoking & Health v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980) (emphasis added) (quoting *Hanson v. United States*, 417 F. Supp. 30, 35 (D. Minn. 1976)).

450. *United States v. Travia*, 180 F. Supp. 2d 115, 116, 118–19 (D.C. Cir. 2001).

district court agreed with the FDA that the balloons were intended to affect the structure or function of the body, reasoning that “the sellers did not need to label or advertise their product, as the environment provided the necessary information between buyer and seller.”⁴⁵¹ If the agency were concerned about the safety of conventional foods containing cannabis constituents, it might invoke this theory and argue that the products were drugs. This would, in turn, trigger the agency’s new drug authorities and render the products illegal. But it would be a controversial position for the agency to take.

If a company managed to move forward with a conventional food containing a cannabis constituent, the agency’s regulations and policies relating to food would apply.⁴⁵² In addition to the pesticide residue issue already flagged, these would include a variety of affirmative labeling requirements.⁴⁵³ For example, unless an exemption applied, the company would need to provide nutrition information in the form of a “Nutrition Facts” box.⁴⁵⁴ In addition, the agency’s many regulations implementing the FDA Food Safety Modernization Act⁴⁵⁵ would also apply. Thus, among other things, unless an exemption applied, the company would need to establish and

451. *Id.* at 119.

452. These rules therefore apply to any foods containing the hemp seed derived food ingredients for which FDA issued GRAS response letters in December 2018. *See supra* note 430.

453. *See* 21 U.S.C. §§ 343(i)(1)–(2), 343(q). Products marketed as imitations of well-known products that do not themselves contain cannabis or one of its constituents would likely draw warning letters, on the theory that the labeling was misleading, particularly if children were the primary consumers of the imitated products. § 343(a). Examples might include “Rasta Reeses” (packaged to resemble Reese’s Peanut Butter Cups), “Keef Kat” (KitKat), and “Buddafinger” (Butterfinger), all currently on the market. *See* MacCoun, *supra* note 432, at 990. The FDA recently took action against vendors of e-cigarette liquids that were labeled to look like children’s juices and candies, on the theory that the products were misbranded, because their labeling and/or advertising was false or misleading—in that they imitated other products. *E.g.*, Warning Letter from FDA to NEwhere Inc. d/b/a Mad Hatter Juice (May 1, 2018), <https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm618146>.

454. 21 U.S.C. § 343(q)(1); Food Labeling; Serving Sizes of Foods that Can Reasonably be Consumed at One Eating Occasion; Dual-Column Labeling; Updating, Modifying, and Establishing Certain Reference Amounts Customarily Consumed; Serving Size for Breath Mints; and Technical Amendments, 81 Fed. Reg. 34,000, 34,000 (May 27, 2016) (to be codified at 21 C.F.R. pt. 101). Numerous exemptions apply, including for foods produced by very small businesses, food sold in small packages, and foods served in restaurants (including bakeries) for immediate consumption on the premises. 21 C.F.R. § 101.9(j).

455. Pub. L. No. 111-353, 124 Stat. 3885 (2011).

implement a food safety system that includes hazard analysis and risk-based preventive controls (HARPC).⁴⁵⁶ Further, any facility that manufactures, processes, packs, or holds food for consumption—including one that is HARPC-exempt—must comply with cGMP for food.⁴⁵⁷

C. *Medical Cannabis in Dietary Supplements*

Dietary supplements are considered a type of food, but they are defined separately in the FDCA and subject to slightly different rules. As a result, there is a narrow path forward for marketing dietary supplements containing cannabis constituents.⁴⁵⁸ There are at least four significant constraints to keep in mind.

First, a dietary supplement cannot lawfully contain either dronabinol or CBD. The FDCA imposes a “drug exclusion” for dietary supplements, just as it does for conventional foods.⁴⁵⁹ A substance cannot be classified as a “dietary supplement” if it has been approved as a new drug or if it has been authorized for investigation as a new drug, the clinical trials have started, and the trials are public knowledge.⁴⁶⁰ The FDA already takes the position that this exclusion means THC and CBD cannot be added to dietary supplements.⁴⁶¹ There are options for avoiding the exclusion rule similar to those

456. 21 C.F.R. § 117.126; Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Human Food, 80 Fed. Reg. 55,908, 55,911 (Sept. 17, 2015) (to be codified in 21 C.F.R.). This entails analyzing the hazards, designing and implementing the controls, monitoring the effectiveness of the controls, maintaining records of the monitoring, and establishing corrective actions for problems, which must be documented. A small company that marketed its cannabis-containing conventional food directly to consumers could qualify for an exemption and modified HARPC requirements. 21 C.F.R. § 117.5(a).

457. 80 Fed. Reg. at 55,911; 21 C.F.R. §§ 117.10–117.110. To give another example, if the FDA has issued a standard of identity for the food in question, the cannabis-derived constituent could not be added to the food unless doing so was permitted by the applicable standard of identity. 21 U.S.C. § 343(g).

458. Dietary supplements may contain herbs or botanicals, as well as concentrates, metabolites, constituents, or extracts of herbs or botanicals, among other things. 21 U.S.C. § 321(ff). Cannabinoids would presumably qualify as extracts of an herb or other botanical.

459. § 321(ff)(3)(B).

460. *Id.*

461. *Marijuana Q&A*, *supra* note 410. It has sent numerous warning letters to companies marketing cannabidiol in supposed dietary supplements, citing this provision. See *Warning Letters and Test Results for Cannabidiol-Related Products*, FDA, <https://www.fda.gov/newsevents/publichealthfocus/ucm484109> (last updated Nov. 2, 2017) (providing examples of FDA warning letters sent out in 2017 regarding the marketing of products containing CBD).

discussed in the last part of this Article.⁴⁶² For example, if the substance was marketed in dietary supplement or food form before the drug was approved or the trials started, the drug exclusion rule does not apply.⁴⁶³ The agency does not think this exception applies, but it has invited evidence and arguments to the contrary.⁴⁶⁴ Other cannabis constituents, however, could presumably be presented in dietary supplements. There may also be room to argue that the agency's claim about "THC" is overbroad because it has approved only dronabinol (Δ^9 -THC).

Today, numerous companies sell hemp extracts that contain CBD, in interstate commerce.⁴⁶⁵ These products are positioned as dietary supplements and marketed illegally, as the FDA has explained in various Warning Letters.⁴⁶⁶ For instance, the agency issued a Warning Letter in October 2017 to Stanley Brothers Social Enterprises, which operates as "CW Hemp" and markets "Charlotte's Web" through the internet.⁴⁶⁷ The FDA's letter took the position that certain claims on the website (e.g., claiming the product's "anti-tumoral" and "anti-cancer" benefits) rendered Charlotte's Web a "new drug" which may not be shipped in interstate commerce without an approved application.⁴⁶⁸ The company appears to have removed the drug claims from its website and promotional materials, focusing instead, for instance, on "a sense of calm and focus."⁴⁶⁹ As of August 2018, however, it is still distributing Charlotte's Web in interstate commerce.⁴⁷⁰ The company may be missing the second violation cited

462. See *infra* Part IV.

463. § 321(ff)(3)(B).

464. *Marijuana Q&A*, *supra* note 410.

465. See, e.g., *Shop CBD*, CHARLOTTE'S WEB™ HEMP EXTRACT, <https://www.cwhemp.com/all-charlottes-web-cannabinoid-hemp-cbd-supplements> (last visited Feb. 5, 2019).

466. The FDA issues a Warning Letter when it finds significant violations of the statute, which it defines as "violations that may lead to enforcement action if not promptly and adequately corrected." FDA, REGULATORY PROCEDURES MANUAL § 4-1-1 (2018), <https://www.fda.gov/downloads/iceci/compliancemanuals/regulatoryproceduresmanual/ucm074330.pdf>.

467. Warning Letter from FDA to Stanley Brothers Social Enterprises, LLC (Oct. 31, 2017) [hereinafter Stanley Warning Letter], <https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm583192>. Charlotte's Web is a type of CBD manufactured by the Stanley Brothers. See *Our Company*, CHARLOTTE'S WEB™ HEMP EXTRACT, <https://investors.cwhemp.com/our-company/default.aspx> (last visited Feb. 5, 2019).

468. Stanley Warning Letter, *supra* note 467, at 3.

469. *Charlotte's Web Benefits: What Charlotte's Web Can Do For You*, CHARLOTTE'S WEB™ HEMP EXTRACT, <https://www.cwhemp.com> (last visited Feb. 5, 2019).

470. *Id.*

in the Warning Letter because CBD has been the subject of new drug clinical trials (and in fact is now the subject of an approved new drug), and no company may distribute dietary supplements containing CBD.⁴⁷¹ In other words, either the disease claim *or* the presence of CBD is sufficient to trigger enforcement action. A Warning Letter does not commit the FDA to enforcement action, but the recent approval of a new drug containing CBD (discussed in Part IV) could prompt the agency to act without further notice.⁴⁷²

Second, any dietary supplement containing a non-excluded cannabis constituent must be sold to consumers in a form intended for ingestion.⁴⁷³ This means a tablet, capsule, powder, softgel, liquid, or another ingestible form that is not represented as conventional food or as a meal replacement.⁴⁷⁴ Further, no dietary supplement can be represented for use as a conventional food or meal replacement.⁴⁷⁵ This precludes putting a cannabis constituent in a conventional food (such as a brownie) that is then recharacterized as a dietary supplement. It should be possible to market “edible” dietary supplements containing cannabis constituents, but it is important to avoid the appearance of a conventional food as well as the use of any terms (such as “beverage”) in the labeling that would cause the FDA to categorize the product represented as a conventional food.⁴⁷⁶ And because a dietary supplement must be intended for ingestion, it is not possible to present a cannabis-based product in a form that cannot be ingested—such as an inhaler, gel, or patch—and characterize that product as a dietary supplement.⁴⁷⁷

471. Stanley Warning Letter, *supra* note 467, at 2.

472. REGULATORY PROCEDURES MANUAL, *supra* note 466, § 4-1-1 (2018) (“violations . . . may lead to enforcement”) (emphasis added); *see also infra* Part IV. Indeed, after Congress removed hemp from the Controlled Substances Act in December 2018, the FDA issued a statement noting the “proliferation” of products containing cannabis-derived substances, reminding the public that it is unlawful to market CBD in dietary supplements, and promising to take any enforcement action needed. *See* Statement on Signing of the Agriculture Improvement Act, *supra* note 49.

473. *See* 21 U.S.C. § 321(ff)(2)(A)(i) (2012).

474. *Id.*; *see also* § 350(c)(1)(B); *United States v. Ten Cartons, Ener-B Nasal Gel*, 888 F. Supp. 381, 396 (E.D.N.Y. 1995).

475. § 321(ff)(2)(B).

476. *See generally* FDA, GUIDANCE FOR INDUSTRY: DISTINGUISHING LIQUID DIETARY SUPPLEMENTS FROM BEVERAGES (2014), <https://www.fda.gov/downloads/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/DietarySupplements/UCM381220.pdf>.

477. *See* 21 U.S.C. §§ 321(ff)(2)(A)(i), 350(c)(1)(B).

Third, a company pursuing this strategy would probably need to submit a premarket notification to the FDA with results from premarket safety testing. This is because a cannabis constituent (including a non-excluded cannabinoid) would probably be considered a “new dietary ingredient.” If the substance had been marketed in dietary supplements before October 15, 1994, it would not be considered a new dietary ingredient.⁴⁷⁸ But the agency requires rigorous documentation of prior marketing—such as business records, mail-order catalogs, magazine advertisements, and sales contracts.⁴⁷⁹ It is unlikely that sufficient evidence would exist for any substance derived from cannabis, especially a cannabinoid other than dronabinol and cannabidiol.⁴⁸⁰ Any other dietary ingredient—one used in supplements for the first time after October 15, 1994—would be considered a “new dietary ingredient.”⁴⁸¹

Because a cannabis constituent would be a new dietary ingredient, there would be two bases for marketing it in a dietary supplement. To begin with, a company could market a dietary supplement containing this new dietary ingredient if the dietary ingredient was previously present in the food supply “as an article used for food in a form in which the food has not been chemically altered.”⁴⁸² The FDA interprets this to mean the ingredient was marketed in the same chemical form as a distinct conventional food or conventional food ingredient.⁴⁸³ A new cannabis constituent (other than dronabinol or CBD) would probably not satisfy this standard.

In the alternative, a company could market a dietary supplement containing this new dietary ingredient if there was a “history of use or other evidence of safety” establishing that, when used according to the directions in its labeling, the ingredient will “reasonably be expected

478. 21 U.S.C. §§ 350b(a), 350b(d). Any dietary ingredient marketed prior to that date is considered an “old” dietary ingredient and does not require a premarket notification. But it must have been marketed as a dietary ingredient, meaning in or as a dietary supplement. NDI GUIDANCE, *supra* note 408, at 14.

479. NDI GUIDANCE, *supra* note 408, at 17–18. The FDA also might not accept evidence relating to illegal marketing.

480. The FDA would not consider an ingredient’s previous marketing as a conventional food or marketing for non-food use as evidence that the substance was an old dietary ingredient. *Id.* at 19. Changes in the manufacturing process since 1994 would turn the dietary ingredient into a new dietary ingredient, if they altered the identity of the ingredient or changed its properties or even its purity or impurities. *Id.* at 21.

481. 21 U.S.C. § 350b(d).

482. § 350b(a)(1).

483. NDI GUIDANCE, *supra* note 408, at 23, 25–26.

to be safe.”⁴⁸⁴ This would allow the company to test its cannabinoid to support its use as a dietary ingredient in a dietary supplement. In this case, the company would submit a “new dietary ingredient notification” (“NDI notification”) at least seventy-five days before it planned to introduce the supplement to the market, providing the basis for its conclusion that the supplement satisfies the statutory safety standard.⁴⁸⁵ Although preparing an NDI notification is not as expensive and time consuming as preparing a food additive petition (let alone a new drug application), the burden is still significant.⁴⁸⁶ The company would need to provide detailed chemistry information and a description of its manufacturing process, including analytical testing and specifications used.⁴⁸⁷ For a botanical drug, the agency would expect to see information about the conditions of propagation and cultivation, as well as production methods. For an extract of a botanical, the agency would require additional manufacturing information (including, for instance, measures taken to control adulterants such as pesticides and heavy metals). The amount of safety data required from testing in animals and humans would depend on a variety of considerations, such as whether the supplement was intended for daily chronic or intermittent use, whether there was documented historical use and the nature of that use, and the information from that historical use.⁴⁸⁸ In the absence of any history, the agency would generally require a battery of studies, some of which could last up to two years.⁴⁸⁹

Fourth, a dietary supplement containing a cannabis constituent could not be the subject of a disease claim or health claim. Any claim that the supplement could mitigate, treat, prevent, or cure a disease would render the supplement an unapproved new drug subject to enforcement action.⁴⁹⁰ Also, as noted, the FDA may permit “health claims” on dietary supplements if the standards for their inclusion are satisfied.⁴⁹¹ But the agency is unlikely even to consider a health claim

484. § 350b(a)(2).

485. *Id.* It is not necessary to wait for formal approval. Many companies wait for a “no objection” letter, but it is legally permissible to wait for seventy-five days and then, in the absence of a response from the agency, begin marketing. NDI GUIDANCE, *supra* note 408, at 50.

486. *See generally* NDI GUIDANCE, *supra* note 408, at 55–95 (describing what must be included in the notification).

487. *Id.* at 55–56.

488. *Id.* at 67, 72.

489. *Id.* at 77.

490. *See* 21 U.S.C. §§ 321(g)(1), (p) (2012).

491. *See supra* note 440.

for a cannabis constituent. It defines a health claim as one that characterizes the relationship of a “substance” to a disease or health-related condition and defines a food “substance” as a specific food or component of food.⁴⁹² Whether the substance occurs naturally in food or has been added, however, it must serve a traditional food purpose—taste, aroma, or nutritive value (or a technical role such as preservation)—at the levels necessary to justify the health claim.⁴⁹³ Cannabinoids are unlikely to satisfy this standard, although terpenoids, flavonoids, and other cannabis constituents might have nutritive value and qualify.

Taking these four limitations into account, there is a limited path forward for dietary supplements. It should be possible to market a new (non-dronabinol and non-CBD) cannabis constituent in an ingestible form as a dietary supplement, provided that: (1) the product is not represented as a conventional food, and (2) premarket safety testing and premarket notification requirements have been satisfied.⁴⁹⁴ A company could not make disease claims or health claims with respect to a cannabinoid constituent, but it could possibly make “structure/function” claims (and maybe, although this would require the agency’s permission, which we view as unlikely, a health claim grounded in nutritive value) for other cannabis constituents.⁴⁹⁵ Unlike structure/function claims for conventional foods, structure/function claims for dietary supplements need not be based on the nutritive value of the supplement.⁴⁹⁶ The FDA does, however, carefully police the line between permissible structure/function claims and impermissible disease claims. For example, it would not be permissible to refer to the symptom of a disease (such as pain associated with arthritis), nor would it be permissible to suggest that the supplement is a substitute for an approved drug. The agency would likely permit a claim such as “helps to maintain a healthy appetite,” but it might not permit a claim such as “helps to maintain a healthy appetite during

492. 21 C.F.R. §§ 101.14(a)(1)–(2) (2018).

493. Food Labeling; General Requirements for Health Claims for Food, 58 Fed. Reg. 2,478, 2,480 (Jan. 6, 1993) (to be codified at 21 C.F.R. pts. 20 and 101).

494. See *supra* notes 463–93 and accompanying text.

495. Regulations on Statements Made for Dietary Supplements Concerning the Effect of the Product on the Structure or Function of the Body, 65 Fed. Reg. 1,000, 1,000 (Jan. 6, 2000) (to be codified at 21 C.F.R. pt. 101) (adopting regulations governing permissible structure/function claims for dietary supplements).

496. Food Labeling; Requirements for Nutrient Content Claims, Health Claims, and Statements of Nutritional Support for Dietary Supplements, 62 Fed. Reg. 49,859, 49,860–61 (Sept. 23, 1997) (to be codified at 21 C.F.R. pt. 101).

treatment for cancer.”⁴⁹⁷ Any structure/function claim would require substantiation. The FDA applies the same standard as the Federal Trade Commission, meaning it expects “competent and reliable scientific evidence,” which it explains means “tests, analyses, research, studies, or other evidence based on the expertise of professionals in the relevant area, that has been conducted and evaluated in an objective manner by persons qualified to do so, using procedures generally accepted in the profession to yield accurate and reliable results.”⁴⁹⁸

D. *The Possibility of Non-Regulation, with Caveats*

The preceding parts of this Article did not exhaust the possible ways cannabis could be commercialized after descheduling. We note a few additional possibilities below and explain how they would be handled (if at all) by the FDA.⁴⁹⁹

First, the cannabis flower might simply be sold for recreational smoking. Purely intrastate transactions (in which the cannabis is grown, sold, and smoked within one state) would not trigger the FDA’s jurisdiction.⁵⁰⁰ This is true even if the seller made claims about using the cannabis to treat a disease or other health conditions.⁵⁰¹ There is a solid argument that *interstate* transactions of cannabis only for

497. The FDA’s regulations prohibit claims suggesting that a product “treats, prevents, or mitigates adverse events associated with a therapy for a disease, if the adverse events constitute disease.” 21 C.F.R. § 101.93(g)(2)(ix) (2018). The agency gives the example of “helps individuals using antibiotics to maintain normal intestinal flora” (impermissible disease claim) and “helps maintain healthy intestinal flora” (permissible structure/function claim). 65 Fed. Reg. at 1,029. If the FDA concluded loss of appetite (anorexia) were a medical condition, it would not permit the claim described in the text.

498. *Guidance for Industry: Substantiation for Dietary Supplement Claims Made Under Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act*, FDA (Dec. 2008), <https://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/dietarysupplements/ucm073200>.

499. Additional possibilities might be inclusion of cannabis or ingredients derived from cannabis in animal drugs or animal food or feed. Some of the rules governing animal food and drugs are similar to those applicable to human food and drugs, but there are additional considerations. For instance, a food additive in animal feed can, if there is a residue remaining in the edible tissue of the animal, become an indirect food additive in human food, triggering the human food additive rules, which are different from the food additive rules for animal feed.

500. 21 U.S.C. § 355(a) (2012) (“No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval . . . is effective with respect to such drug.”).

501. §§ 331(a)–(d) (specifically limiting prohibited acts to those in interstate commerce).

recreational smoking also would not trigger the FDA's jurisdiction.⁵⁰² But if the seller (in interstate commerce) made claims about treating a disease or about affecting the structure or functioning of the body, the FDA would deem the cannabis a drug.⁵⁰³ Thus, claims that smoking the cannabis would promote relaxation, mitigate insomnia, reduce anxiety, or maintain the appetite would turn the cannabis into a regulated drug. In the absence of these claims, the agency might try to assert its drug authorities on the theory that the product's design or the circumstances surrounding its use demonstrated its intended use as a drug.⁵⁰⁴ But doing so would be controversial.

Second, the same analytical framework would apply if a cannabis oil were marketed as a consumer product—for instance an essential oil sold for aromatherapy or with a vaporizer that can generate a mist for inhaling. Such a product would not qualify as a dietary supplement because it is not intended for ingestion.⁵⁰⁵ For FDA purposes, it is either a drug or it is nothing. If the product is associated with a disease claim or a structure/function claim and moves in interstate commerce, then the FDA will treat it as a drug—whether it appears in a soap, lotion, massage oil, or bottle for vaporizing. The agency does not prioritize enforcement with respect to structure/function claims (such as “helps you sleep”) on essential oils like lavender because the risk to consumers is negligible. But its calculus would change for a cannabis

502. The FDA would have jurisdiction only if the intended use of the cannabis triggered the agency's drug authorities under § 201(p). And intended use usually turns on claims made in labeling, advertising, and other promotion. *See supra* Section III.A.

503. *See* § 321(g) (defining “drug”).

504. *See infra* Section IV.A (discussing the government's reasoning that nitrous oxide balloons distributed at a rock concert constituted “drugs” due to the circumstances surrounding their distribution). The FDA might also try to rely simply on the company's *knowledge* that consumers *use* its product for medical purposes. *See* 21 C.F.R. § 201.128 (2018) (“But if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than the ones for which he offers it, he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.”). The “knowledge prong” of the intended use regulation has been controversial for more than sixty years, however. It faces substantial opposition from regulated industries, and it is seldom used (at least, not without *other* evidence as well). *E.g.*, Medical Information Working Group Citizen Petition, No. FDA-2013-P-1079, at 17–19 (Sept. 3, 2013), <http://www.miwg.org/sites/default/files/7%20MIWG%20Citizen%20Petition%20%282013%29%2C%20Docket%20No%20FDA-2013-P-1079.pdf>.

505. *See* 21 U.S.C. § 321(ff)(2)(A)(i) (defining “dietary supplement” as “a product that is intended for ingestion”).

constituent product that actually affected the functioning of the body. The agency would likely take enforcement action if the manufacturer made drug claims. It is also possible the agency would find an intended drug use even without claims—based on the company’s knowledge of actual use in the market or perhaps its design.⁵⁰⁶

Third, a company might place a cannabis constituent in a cream or lotion (or another similar topically applied product) and position the product as a cosmetic. An item is a “cosmetic” for FDA purposes if it is intended for “cleansing, beautifying, promoting attractiveness, or altering the appearance” or if it is a component of such an item.⁵⁰⁷ Cosmetics are less heavily-regulated than food and drugs.⁵⁰⁸ As always, any disease or structure/function claim would turn this item into a drug, even if the item also satisfied the definition of cosmetic.⁵⁰⁹ Thus, a skin oil with a cannabis extract would be regulated as a cosmetic and as a drug if the labeling made a disease claim. But if the company made no claims about the presence of the cannabis constituent and genuinely marketed the product for cosmetic purposes, the agency might leave the company alone.⁵¹⁰ This could change if the cannabis constituent had an impact on the structure or function of the body; for instance, if it was systemically absorbed and biologically active.⁵¹¹ The FDA has occasionally asserted that it could infer a supposed cosmetic’s intended drug use from its active ingredients.⁵¹²

506. 21 C.F.R. § 201.128; *see also supra* note 406 and accompanying text.

507. 21 U.S.C. § 321(i).

508. The FDCA prohibits various acts relating to cosmetic misbranding and adulteration, which allow the agency to take enforcement action in a variety of situations, including when a cosmetic contains a “deleterious substance which may render it injurious” when used as directed. § 361(a).

509. *See supra* notes 435–37 and accompanying text.

510. If a company simply removed the drug claims from its product and attempted to position the resulting product as a cosmetic, without correcting consumer impressions and perhaps even *with* disclaimers, FDA might still find a drug intended use. *See United States v. Undetermined Quantities of an Article of Drug Labeled as “Exachol,”* 716 F. Supp. 787, 791 (S.D.N.Y. 1989) (“Courts have recognized that where years later customers purchase a product in reliance on the therapeutic claims of the previous literature marketed with that product, the court may use such literature to determine the intent in marketing the product despite a later disclaimer”); *see also* Zettler, *supra* note 249, at 1958 n.143.

511. For a discussion of FDA regulation of structure/function claims, *see supra* notes 435–37 and accompanying text.

512. *E.g.*, Warning Letter from FDA to Lifetech Resources LLC (Apr. 18, 2011), <https://wayback.archive-it.org/7993/20170111100914/http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2011/ucm251951.htm> (stating that the “presence of the prostaglandin analog . . . along with appearance claims such as

Finally, a company might add cannabis to a currently-marketed tobacco product or add a cannabis extract to that tobacco product—for instance, a cigarette. In this case, the cannabis (or extract) would be considered a tobacco additive.⁵¹³ The tobacco product itself, now modified with a new additive, would be considered a “new tobacco product” subject to a premarket approval requirement unless an exemption applied.⁵¹⁴ Separately, the FDCA provides that once an item satisfies the definition of “tobacco product,” it cannot be sold in combination with any other product regulated under the FDCA.⁵¹⁵ Put another way, dual classification (as a tobacco product and a new drug, for instance) is not permissible. This provision would be triggered if the company made any claims about the new ingredient that triggered a different FDA regulatory authority.⁵¹⁶ The FDA gives the example of adding a mouthwash (which might be a drug or a cosmetic) to the ingredients of a cigarette and identifying the cigarette as containing mouthwash.⁵¹⁷ Moreover, the definition of “tobacco product” excludes “an article that is a drug” under § 201 of the FDCA.⁵¹⁸ As a result, if a company added cannabis or an extract to a cigarette and made structure/function claims, the product in question would be deemed a “drug” rather than a “tobacco product,” and would be a new drug marketed illegally without an approved NDA. Indeed, the FDA might infer a drug intended use on the basis of the additive’s identity and actual use of the product—even in the absence of claims—with the same result.

‘enhance the appearance of your lashes and brows’ . . . indicate that your products are intended to affect the structure or function of the body”); *Cosmetic Products Containing Certain Hormone Ingredients*; Notice of Proposed Rulemaking, 58 Fed. Reg. 47,611, 47 611 (Sept. 9, 1993) (to be codified at 21 C.F.R. pts. 700 and 701) (proposing a rule that would declare any cosmetic product containing more than a specified amount of pregnenolone acetate or progesterone was an unapproved new drug regardless of claims made).

513. 21 U.S.C. § 387(1).

514. §§ 387j(a)(1)–(2).

515. § 321(rr).

516. § 321(rr)(4).

517. FDA, DRAFT GUIDANCE FOR INDUSTRY AND FDA STAFF: THE SCOPE OF THE PROHIBITION AGAINST MARKETING A TOBACCO PRODUCT IN COMBINATION WITH ANOTHER ARTICLE OR PRODUCT REGULATED UNDER THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 4 (Sept. 30, 2009), <https://www.fda.gov/downloads/TobaccoProducts/Labeling/RulesRegulationsGuidance/UCM259896.pdf>.

518. § 321(rr).

E. Summary

Any product containing a cannabis constituent will be regulated as a “new drug” by the FDA if the company responsible for the product makes claims about its medical uses and if the product (or any component of the product) crosses state lines. This will, in turn, require the company to conduct a rigorous research program proving the product’s safety and effectiveness before the product can be launched in the market. There is no reasonable pathway forward for conventional foods containing or comprising cannabis constituents if those foods (or any of their ingredients) cross state lines, with the likely sole exception of certain hemp seed ingredients that appear to be GRAS. Any other cannabis constituent would need to be chemically distinct from those already under clinical investigation or approved as new drugs—such as dronabinol (synthetic Δ^9 -THC) and CBD—and either GRAS or an approved food additive. It may be possible to market a cannabis product in traditional dietary supplement form (such as capsules) or another ingestible form (such as liquid drops) but, again, only if the cannabis constituents chemically distinct from those already under clinical investigation or approved as new drugs. Permitted dietary supplements could require several years of premarket safety testing and could not be marketed with medical claims, but it should be possible to claim that they support the healthy structure and functioning of the body. The FDA derives its jurisdiction from statutory provisions, however, that expressly require the movement of products in interstate commerce. This means the agency will not regulate cannabis grown, sold, and consumed entirely within the borders of a single state, even if that cannabis is sold with claims about treatment of disease. So, too, with conventional foods and dietary supplements. But if any ingredient (such as the gelatin used to make a capsule for a dietary supplement) travels in interstate commerce, the agency could—and likely would—assert its authority.

IV. THREE PATHWAYS FOR FEDERAL LEGAL MEDICAL CANNABIS FOLLOWING DESCHEDULING

Based on the analysis in Part III, the Authors believe that if cannabis and THC are descheduled, there are three pathways forward under FDA law for medical cannabis.

A. Medical Cannabis Providers Engaged in Purely Intrastate Operations

The first pathway forward represents, in a sense, continuation of the traditional medical cannabis industry—sale of whole plant-based products, by small operations, to locally-based consumers. Cannabis that is grown, sold, and used entirely within the borders of one state will not fall within the FDA’s jurisdiction.⁵¹⁹ This is true even if the seller makes medical claims about the product and if those claims are made in media, such as on the internet, that are accessible outside the state.⁵²⁰ Not only does the FDA derive its power from the Commerce Clause, but the FDCA is drafted even more narrowly.⁵²¹ It is not sufficient for the agency to find a connection with interstate commerce; it generally must also find that a product or component of the product traveled in interstate commerce.⁵²²

But there are reasons to be cautious about this pathway. To begin with, if the FDA is concerned about the claims made or about the safety of the product, it will strain to find a component that traveled in interstate commerce. Any inactive ingredient will qualify.⁵²³ In addition, the agency takes the position that sale of a product in one state for consumer use in another state constitutes introduction of that product into interstate commerce.⁵²⁴ This will include not only online sales to residents of other states but in-person sales if the purchasers cross state lines. Moreover, violation of the FDCA is a strict liability

519. See §§ 331(a)–(d) (specifically limiting prohibited acts to those in interstate commerce).

520. See generally § 331 (listing prohibited acts does not include making claims about a product in the media).

521. U.S. CONST. art. I, § 8, cl. 3.

522. 21 U.S.C. § 331.

523. § 321(f) (defining food to include any article “used for components” of another food); § 321(g) (defining a drug to include any “article intended for use as a component” of another drug).

524. Thus, for instance, the agency has taken enforcement action against dairy farms that sell raw milk (which cannot be sold in interstate commerce) to buyers residing in other states. *E.g.*, *United States v. Organic Pastures Dairy Co.*, 708 F. Supp. 2d 1005 (E.D. Ca. 2010) (enjoining dairy that sold raw milk to out-of-state customers).

offense;⁵²⁵ a seller's ignorance of the purchaser's out-of-state status would presumably be irrelevant. This effectively places the burden on the medical cannabis business to ensure that transactions are purely intrastate.⁵²⁶ There is no real prospect for creative circumvention of the intrastate requirement, for instance through a "buyer's club."⁵²⁷ The FDA is likely to view these as shams, much as it does interstate "cow-share" arrangements, which are an attempt to circumvent the prohibition on sale of raw milk in interstate commerce.⁵²⁸ Finally, the fact that the FDA has no jurisdiction over medical cannabis does not

525. See *United States v. Park*, 421 U.S. 658 (1975) (affirming the conviction of an individual unaware of the violation of law, following a jury instruction that stated "the individual is or could be liable under the statute, even if he did not consciously do wrong").

526. This does not mean that advertising and promotion cannot *reach* persons out of state, including through the internet. After all, the availability of medical cannabis in a state could prompt people to move into the state. The FDA does not derive its statutory authority from the reach of advertising and promotion, but rather from the movement of products (or their components) in commerce.

527. Members of a buyer's club pay membership dues to the organization, which provides items or services free of charge to its members. The theory is that without purchasing transactions, shipments of products (such as a cannabis-derived drug or raw milk) from a club to its members across state lines do not constitute shipment in interstate commerce. The FDA rejects this theory, reasoning that the FDCA does not "recognize an exception to . . . prohibited conduct based on the nature of the contractual arrangement between the distributor and consumer." *E.g.*, Memorandum in Support of Government's Motion for Summary Judgment, *United States v. Allgyer*, Civil Action No. 5:11CV02651 LS (Dec. 6, 2011), 2011 WL 7416103.

528. The sale of raw milk in one state for consumer use in another state constitutes introduction of raw milk into *interstate* commerce, in violation of FDA regulations. See 21 C.F.R. § 1240.61(a) (2018). But more than half of the states in this country permit the sale of raw milk directly to consumers. See *State Milk Laws*, NAT'L CONF. ST. LEGISLATURES (Aug. 29, 2016), <http://www.ncsl.org/research/agriculture-and-rural-development/raw-milk-2012>. Dairy farms in states that have legalized the sale of raw milk have attempted to avoid the prohibition on interstate shipments by establishing "cow-share" arrangements, pursuant to which consumers combine resources to purchase a cow. Some states permit (intrastate) cow sharing arrangements, but the FDA views interstate cow sharing as a sham. *Cf.* *United States v. Allgyer*, No. 11-02651, 2012 WL 355261, at *3-5 (E.D. Pa. 2012) (enjoining a Pennsylvania dairy farm operator from delivering raw milk to individuals in other states who joined a buyer's club that leased his cows). Some dairy farms instead establish "farm-share" arrangements. See *Share Agreements: Cowshares, Goatshare, Herdshares, Farmshares*, REALMILK.COM (Nov. 26, 2003), <http://www.realmilk.com/herdshares/share-agreements>. In this case, the consumer shares ownership in the farm and receives profits in the form of raw milk. The FDA would also view an interstate farm sharing arrangement as a sham.

mean that the product will be unregulated. States such as Washington already regulate medical cannabis.⁵²⁹

B. Development of Pharmaceutical Products Containing Cannabis Constituents and Synthetic Cannabinoids

The second pathway forward takes the classical Western approach of small molecule drug development for a product containing a cannabis constituent or a synthetic cannabinoid. Indeed, the FDA has already approved several new drugs containing synthetic cannabinoids as well as one new drug containing CBD. These approvals shed some light on what this second pathway might look like after descheduling.

1. Synthetic cannabinoids

The pharmaceutical industry turned to synthetic cannabinoid products in the early 1980s, perhaps in part because scheduling of cannabis under the CSA made it difficult to secure botanical raw materials for naturally-derived products. Unimed Pharmaceuticals, later acquired by Solvay (now AbbVie), brought the first synthetic cannabinoid to market.

Marinol capsules contain synthetic Δ^9 -THC, assigned the nonproprietary (generic) name “dronabinol.”⁵³⁰ Each capsule contains dronabinol dissolved in sesame oil with other inactive ingredients.⁵³¹ Oral delivery of dronabinol presented manufacturing

529. See, e.g., WASH. REV. CODE § 69.51.080 (2018).

530. The nomenclature conventions of the International Union of Pure and Applied Chemistry (IUPAC) guide the generation of the chemical name for a drug. Under the FDCA, every drug also has an “established” name, which is a shorter simpler nonproprietary name and by convention appears in parenthesis after any brand name (typically trademarked) the manufacturer may have adopted for its product. 21 U.S.C. § 352(e)(1) (2012); see also *Use of Drug Name Terms Policy*, FDA, <https://www.fda.gov/drugs/developmentapprovalprocess/formsubmissionrequirements/electronicmissions/datastandardsmanualmonographs/ucm071638> (last updated Oct. 3, 2014). As a practical matter the established name is usually the drug’s “United States adopted name” (USAN) assigned by the USAN Council, a small group of individuals that includes a representative from the American Medical Association (AMA) as well as the FDA. See *USAN Council*, AM. MED. ASS’N, <https://www.ama-assn.org/about/united-states-adopted-names/usan-council> (last visited Feb. 5, 2019); Designated Names; Revocation of List of Official Names of Drugs, 49 Fed. Reg. 37,574 (Sept. 25, 1984) (to be codified at 21 C.F.R. pt. 299). “THC” is an abbreviation for “tetrahydrocannabinol.” Dronabinol is the established name for Δ^9 -THC.

531. MACK & JOY, *supra* note 81, at 202; see also FDA, MARINOL PACKAGE INSERT § 11 (Aug. 28, 2017), https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018651s0291bl.pdf.

and development challenges. For instance, only a small fraction of the dronabinol present in a capsule reaches its target in the body, in part because it is not water soluble.⁵³² In addition, dronabinol takes effect slowly, reaching its full effect in two to four hours after dosing.⁵³³ These issues have led researchers to explore other routes of administration, including inhalation and sublingual products (administered under the tongue).⁵³⁴ To date, however, this research has not borne fruit.⁵³⁵ One complicating factor may have been that a faster onset of action, though desirable from a therapeutic potential, is associated with a higher potential for misuse.⁵³⁶

Approval and commercial launch of Marinol took an unusually long time, but the factors driving delay would not affect a new cannabis-derived drug after descheduling. The FDA initially approved Marinol in May 1985 for “treatment of the nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional anti-emetic treatment.”⁵³⁷ The company supported approval with pivotal effectiveness data from 454 cancer patients who received a total of 750 courses of treatment.⁵³⁸ But the FDA took nearly four years to approve the NDA.⁵³⁹ After Unimed filed its NDA in June 1981, the agency took three years to issue an approvable letter, which it subsequently rescinded.⁵⁴⁰ The agency did not issue a final approval letter until the summer of 1985.⁵⁴¹ Today, an

532. MACK & JOY, *supra* note 81, at 143.

533. *Id.* at 203.

534. *Id.* at 206.

535. *See generally id.* at 205–06.

536. *Id.*

537. *Unimed’s Marinol Is Headed out of Group C and into the Marketplace*, PINK SHEET (Jun. 10, 1985) [hereinafter *Marinol into the Marketplace*], <https://pink.pharmaintelligence.informa.com/PS008469/unimeds-marinol-is-headed-out-of-group-c-and-into-the-marketplace>.

538. FDA, MARINOL LABEL, NDA 18-651/S-025 AND S-026 6 (June 21, 2006), https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018651s025s026lbl.pdf. In these patients, the drug’s effectiveness varied, with the greatest benefit seen in patients receiving cytotoxic therapy with MOPP for Hodgkin’s lymphoma and non-Hodgkin’s lymphoma. *Id.*

539. *Marinol into the Marketplace*, *supra* note 537.

540. *Unimed’s Marinol NDA Will Be Resubmitted*, PINK SHEET (Nov. 12, 1984) [hereinafter *Marinol Resubmitted*], <https://pink.pharmaintelligence.informa.com/PS007485/unimeds-marinol-nda-will-be-resubmitted>.

541. *Marinol into the Marketplace*, *supra* note 537. While the NDA was pending, the National Cancer Institute—which had been deeply involved in the development of dronabinol by conducting or funding much of the preclinical and clinical work that

NDA for a new cannabinoid would be subject to user fees and would receive an “action date” for the FDA decision, typically eight or twelve months from submission.⁵⁴² The launch of Marinol was further delayed when the DEA took an unusually long time to reschedule the drug from Schedule I to Schedule II, but this would not be a consideration if cannabis and THC were descheduled.⁵⁴³

Marinol has also faced challenges in the marketplace. The drug can cause adverse psychiatric reactions, such as exacerbation of mania, depression, and schizophrenia, and cognitive impairment.⁵⁴⁴ These side effects are dose dependent and may be more common in elderly patients, who are more likely to be undergoing cancer treatment in the first instance.⁵⁴⁵ Other central nervous system adverse reactions commonly noted in clinical trials have included paranoid reactions, abnormal thinking, confusion, amnesia, depersonalization, and hallucinations.⁵⁴⁶ Combined with the access restrictions inherent in scheduling, these considerations may have limited the product’s sales for its initial indication—treatment of nausea and vomiting due to chemotherapy.⁵⁴⁷ Reglan (metoclopramide) was also approved for relief

supported approval—distributed the drug for free to more than 25,000 patients. MACK & JOY, *supra* note 81, at 143–44; *Marinol Resubmitted*, *supra* note 540.

542. See 21 U.S.C. § 379h (2012). The FDA’s current goals are to act within ten months of the sixty-day filing date for a standard application and within six months of the sixty-day filing date for a priority application. FDA, PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022 4 <https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf>.

543. *Roxane Will Begin Marketing Unimed’s Marinol in Early May*, PINK SHEET (Apr. 7, 1986), <https://pink.pharmaintelligence.informa.com/PS009947/roxane-will-begin-marketing-unimeds-marinol-in-early-may>. The delay at DEA stemmed in part from a related petition at the agency and the Administration’s initial plan, which was opposed by the American Medical Association, to deem off-label prescribing a violation of the Controlled Substances Act. *DEA Schedule II Prescribing Limitations for Dronabinol*, PINK SHEET (Feb. 3, 1986), <https://pink.pharmaintelligence.informa.com/PS009616/dea-schedule-ii-prescribing-limitations-for-dronabinol>; *Marinol DEA Scheduling*, PINK SHEET (Dec. 16, 1985), <https://pink.pharmaintelligence.informa.com/PS009414/Marinol-DEA-scheduling>.

544. MARINOL PACKAGE INSERT, *supra* note 531, § 5.1.

545. *Id.* §§ 5.1, 8.5; MACK & JOY, *supra* note 81, 143.

546. MARINOL PACKAGE INSERT, *supra* note 531, § 6.1.

547. MACK & JOY, *supra* note 81, at 144–45. Indeed, the company estimated that rescheduling Marinol would increase sales 15 to 20 percent, and DEA did so in July 1999. *Id.*; see also *Roxane/Unimed Marinol Now Refillable Following DEA Down-Scheduling*, PINK SHEET (July 12, 1999), <https://pink.pharmaintelligence.informa.com/PS034484/RoxaneUnimed-Marinol-Now-Refillable-Following-DEA-DownScheduling>.

of nausea and vomiting due to chemotherapy and remained the standard of care despite significant side effects.⁵⁴⁸ And sales of Marinol for nausea and vomiting declined after the FDA approved Zofran (ondansetron) in January 1991 for essentially the same indication.⁵⁴⁹ Sales improved after the FDA-approved Marinol in December 1992 for treatment of anorexia associated with weight loss in patients with AIDS.⁵⁵⁰

The other synthetic cannabinoid faced challenges in the market as well. The FDA approved Eli Lilly's Cesamet (nabilone) at the end of 1985, the same year it approved Marinol.⁵⁵¹ Nabilone is a synthetic cannabinoid similar to Δ^9 -THC,⁵⁵² and it was similarly approved for treatment of nausea and vomiting associated with cancer chemotherapy.⁵⁵³ Lilly withdrew the drug from the market in 1989 for "commercial reasons," but Valeant purchased the drug from Lilly in

548. *Glaxo's Zofran (Ondansetron) Approved for Prevention of Chemotherapy-Induced Nausea and Vomiting with "1-B" Rating After 27-Month Review at FDA*, PINK SHEET (Jan. 7, 1991), <https://pink.pharmaintelligence.informa.com/ps018594/glaxos-zofran-ondansetron-approved-for-prevention-of-chemotherapy-induced-nausea-and-vomiting-with-1b>. The FDA had initially approved Reglan (for a different use) in 1979. *Biocraft, Quantum Pharmics and Colmed Labs Clear Metoclopramide Generics*, PINK SHEET (Aug. 5, 1985), <https://pink.pharmaintelligence.informa.com/PS008721/biocraft-quantum-pharmics-and-colmed-labs-clear-metoclopramide-generics>.

549. MACK & JOY, *supra* note 81, at 144.

550. *Id.* The new use was protected by seven years of orphan exclusivity. *Id.*; see also 21 U.S.C. § 360cc (2012) (providing seven years of exclusivity for an approved drug that was designated under § 360bb for a rare disease or condition). Unimed supported this new use with the results of a randomized, double-blind placebo-controlled study involving treatment of 139 patients for six weeks. MARINOL PACKAGE INSERT, *supra* note 531, § 14.1; see also *Unimed's Marinol (Dronabinol) Gains Indication for Anorexia in AIDS Patients*, PINK SHEET (Jan. 4, 1993), <https://pink.pharmaintelligence.informa.com/PS021983/unimeds-marinol-dronabinol-gains-indication-for-anorexia-in-aids-patients>.

551. *Lilly's Cesamet (Nabilone) Launch Awaits DEA Scheduling*, PINK SHEET (Jan. 6, 1986) [hereinafter *Cesamet Awaits Scheduling*], <https://pink.pharmaintelligence.informa.com/PS009486/lillys-cesamet-nabilone-launch-awaits-dea-scheduling>. The FDA took more than two years to approve the NDA. See *id.* (indicating an advisory committee meeting in April 1983). Through a series of corporate transactions, Cesamet is now marketed by Mylan. *Cesamet*, INFORMA: PHARMA INTELLIGENCE, http://drugprofiles.informa.com/drug_profiles/5266-cesamet (last visited Feb. 5, 2019).

552. The structural formula for dronabinol is $C_{21}H_{30}O_2$. See MARINOL PACKAGE INSERT, *supra* note 531, § 11. The structural formula for nabilone is $C_{24}H_{36}O_3$. *Cesamet Label, NDA 18-677/S-011*, U.S. FOOD & DRUG ADMIN. 3 (May 15, 2006), https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018677s011lbl.pdf.

553. *Cesamet Awaits Scheduling*, *supra* note 551.

2004 and relaunched in 2006.⁵⁵⁴ Its failure in the marketplace may have been attributable to its narrow therapeutic window.⁵⁵⁵

Recently, the FDA approved a quasi-generic dronabinol in a new dosage form. Generally, a generic drug must have the same route of administration, dosage form, and strength as the innovative drug it copies.⁵⁵⁶ The FDA has approved four generic dronabinol products presented in oral capsules at the same strength as Marinol.⁵⁵⁷ Insys Development Company chose to pursue an oral solution, however, which it believed would allow it to “convert a large portion of the market” from the generic dronabinol capsules to its product.⁵⁵⁸ The FDA concluded a “human abuse liability study” would be needed,⁵⁵⁹ however, which meant the company could not use the generic approval pathway. Thus Insys Development Company submitted its application under a statutory provision that permitted the company to rely on the Marinol NDA and add its own data.⁵⁶⁰ The company’s data revealed that its oral solution had a higher potential for misuse, and there were more psychiatric adverse events in the oral solution group

554. *Valeant Returns Synthetic Cannabinoid to USA*, PHARMATIMES (May 17, 2006), http://www.pharmatimes.com/news/valeant_returns_synthetic_cannabinoid_to_usa_996830. The FDA refused to approve the Valeant labeling until the company added “class-related” safety information—regarding psychotomimetic effect—to the package insert. Lee Szilagyi, *Valeant Cesamet Slated to Hit Market in ‘Next Several Weeks’*, PINK SHEET (May 16, 2006), <https://pink.pharmaintelligence.informa.com/PS064159/Valeant-Cesamet-Slated-To-Hit-Market-In-Next-Several-Weeks?vid=Pharma&process>.

555. Di Marzo, *supra* note 133, at 2.

556. 21 U.S.C. § 355(j)(2)(A)(iii) (2012).

557. See FDA, CTR. FOR DRUG EVALUATION & RES., ANDA No. 078292, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=078292> (last visited Feb. 5, 2019); FDA, CTR. FOR DRUG EVALUATION & RES., ANDA No. 078501, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=078501> (last visited Feb. 5, 2019); FDA, CTR. FOR DRUG EVALUATION & RES., ANDA No. 079217, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=079217> (last visited Feb. 5, 2019); FDA, CTR. FOR DRUG EVALUATION & RES., ANDA No. 201463, <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppNo=201463> (last visited Feb. 5, 2019).

558. Bridget Silverman, *Keeping Track: FDA Nixes Medicare’s Aggrastat for STEMI, Approves Insys’ Syndros*, PINK SHEET (July 10, 2016), <https://pink.pharmaintelligence.informa.com/PS118719/Keeping-Track-FDA-Nixes-Medicures-Aggrastat-For-STEMI-Approves-Insys-Syndros>.

559. FDA, CTR. FOR DRUG EVALUATION & RES., APPLICATION NO. 05525ORIG1s000, CROSS DISCIPLINE TEAM LEADER REVIEW 5–6 (May 20, 2016) [hereinafter INSYS GENERIC DRONABINOL TEAM LEADER REVIEW], https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/205525Orig1s000CrossR.pdf.

560. See 21 U.S.C. § 355(b)(2).

than in the oral capsule group.⁵⁶¹ These findings could make the agency more cautious about differences in dosage form and route of administration as other companies move forward with cannabinoid drug products. The FDA approved Syndros in July 2016, and DEA scheduled the drug in March 2017.⁵⁶² It is not clear whether the sales have lived up to the company's expectations.⁵⁶³

2. *Naturally derived CBD*

On June 25, 2018, the FDA approved an NDA for Epidiolex[®] (CBD) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) in patients two years of age and older.⁵⁶⁴ Both are extremely rare seizure disorders that can lead to developmental delays and intellectual disabilities.⁵⁶⁵ Epidiolex's approval marked the first FDA approval of a new drug derived directly from the cannabis plant and attracted attention in the popular press.⁵⁶⁶

561. INSYS GENERIC DRONABINOL TEAM LEADER REVIEW, *supra* note 559, at 52–53. This led to placement in Schedule II instead of Schedule III. *Id.* at 53.

562. Schedules of Controlled Substances: Placement of FDA-Approved Products of Oral Solutions Containing Dronabinol in Schedule II, 82 Fed. Reg. 14,815 (Mar. 23, 2017) (to be codified at 21 C.F.R. pt. 1308).

563. Initially, many insurer formularies did not include the drug. The company has also faced unrelated legal challenges, including suits relating to its marketing of a fentanyl spray and the arrest of its former Chief Executive Officer. *See* Todd Campbell, *Why this Marijuana Stock Crashed 18.5% in August*, MOTLEY FOOL (Sept. 5, 2017, 9:31 AM), <https://www.fool.com/investing/2017/09/05/why-this-marijuana-stock-crashed-185-in-august.aspx>. At the end of 2017 the company characterized the roll-out of Syndros as “controlled,” and its first quarter 2018 reports indicated sales had been flat. *Insys Therapeutics Reports First Quarter 2018 Results*, GLOBENEWSWIRE (May 8, 2018), <https://globenewswire.com/news-release/2018/05/08/1498834/0/en/INSYS-Therapeutics-Reports-First-Quarter-2018-Results.html>; *Insys Therapeutics Reports Fourth Quarter and Full Year 2017 Results*, FINANZEN.NET (Mar. 8, 2018), <https://www.finanzen.net/nachricht/aktien/insys-therapeutics-reports-fourth-quarter-and-full-year-2017-results-6020165>.

564. FDA, EPIDIOLEX PACKAGE INSERT §1 (June 25, 2018), https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/2103651bl.pdf.

565. Shelly B. DeAdder, *The Legal Status of Cannabidiol Oil and the Need for Congressional Action*, 9 BIOTECHNOLOGY & PHARMACEUTICAL L. REV. 68, 68–69 (2016); Michael Cipriano, *Epidiolex Advisory Committee Appears to Be Covering U.S. FDA's Bases, but Liver Injury Concerns Persist*, PINK SHEET (Apr. 17, 2018), <https://pink.pharmintelligence.informa.com/PS122921/Epidiolex-Advisory-Committee-Appears-To-Be-Covering-US-FDAs-Bases-But-Liver-Injury-Concerns-Persist>.

566. *See, e.g.*, Debra Goldschmidt & Susan Scutti, *FDA Approves First Cannabis-Based Drug*, CNN (June 25, 2018, 2:02 PM), <https://www.cnn.com/2018/06/25/health/fda-approves-first-cannabis-drug-bn>; John Hudak, *Opinion, The FDA Just Opened the Door to Transforming Marijuana Policy*, WASH. POST (June 27, 2018), <https://www.washingtonpo>

Although approving a drug derived from cannabis was unprecedented, it is important to understand what the approval does and does not represent. Because the FDA had already approved a drug containing synthetic Δ^9 -THC and a drug containing a THC-like ingredient, the primary significance of Epidiolex's approval was the natural, rather than synthetic, origins of the ingredients.⁵⁶⁷ Nor was it new for the FDA to approve a drug with botanical origins. The agency had approved numerous new drugs with highly-processed active ingredients that derived from natural sources, as well as two botanical NDAs made from less-processed botanical raw materials.⁵⁶⁸ The active ingredient of Epidiolex is a highly purified extract produced from the cannabis plant.⁵⁶⁹ The FDA did not deem this drug substance a botanical.⁵⁷⁰ Consequently, it did not treat the application as a botanical NDA, nor did it exercise the flexibility with respect to chemistry, manufacturing, and controls that botanical drugs have needed in the past.⁵⁷¹ Thus, the precedent is not as significant as it might seem at the surface.

In many respects, the Epidiolex application was unremarkable. CBD shares almost none of the pharmacological features of dronabinol,⁵⁷² and the FDA's controlled substances staff concluded—on the basis of preclinical and clinical data—that it does not have misuse potential.⁵⁷³

st.com/opinions/the-fda-just-opened-the-door-to-transforming-marijuana-policy/2018/06/26/aeb9b628-7978-11e8-aece-4d04c8ac6158; Matthew Perrone, *Medical Milestone: U.S. Ok's Marijuana-Based Drug for Seizures*, CHI. TRIBUNE (June 25, 2018, 4:19 PM), <http://www.chicagotribune.com/business/ct-biz-fda-epidiolex-marijuana-seizure-drug-20180625-story.html>.

567. See *supra* Section IV.B.1.

568. See *supra* Section III.A.2.

569. EPIDIOLEX PACKAGE INSERT, *supra* note 564, § 11.

570. FDA, CTR. FOR DRUG EVALUATION & RES., APPLICATION NO. 210365ORIG1s000, SUMMARY REVIEW 9 (June 22, 2018), https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000SumR.pdf (noting the FDA Office of Product Quality described the drug "as a highly-purified drug substance from a plant source").

571. See generally FDA, CTR. FOR DRUG EVALUATION & RES., APPLICATION NO. 210365ORIG1s000, PRODUCT QUALITY REVIEW(S) (June 4, 2018) [hereinafter EPIDIOLEX PRODUCT QUALITY REVIEW(S)], https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000ChemR.pdf.

572. FDA, PERIPHERAL & CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMM., FDA ADVISORY COMMITTEE BRIEFING DOCUMENT 12 (Apr. 19, 2018) [hereinafter FDA BRIEFING DOCUMENT], <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM604738.pdf>.

573. FDA, PERIPHERAL & CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMM., FDA BRIEFING DOCUMENT: NDA 210365 CANNABIDIOL 55 (Apr. 19, 2018) [hereinafter NDA

It does not attach to cannabinoid receptors or other neural receptors associated with misused drugs, and it did not induce overt behaviors like those induced by drugs like dronabinol.⁵⁷⁴ The NDA contained exactly what one would expect to see in any application for a drug intended to treat a serious but rare condition.⁵⁷⁵ The applicant demonstrated effectiveness through two randomized placebo-controlled studies in LGS and one single randomized placebo-controlled study in DS, together enrolling 516 patients.⁵⁷⁶ A signal of drug-induced liver injury emerged in the clinical trials and expanded access program, which necessitated a more detailed evaluation of liver safety prior to approval.⁵⁷⁷ The reviewers found that administration of the drug to the target population in controlled clinical trials, as well as in the expanded access program, was causally associated with elevations in liver enzymes consistent with drug-induced injury to liver cells.⁵⁷⁸ Actual cases of severe hepatocellular injury, however, did not occur.⁵⁷⁹ They were therefore unable to reach a conclusion on the risk for chronic liver injury.⁵⁸⁰ The advisory committee voted unanimously that the benefit-risk ratio of cannabidiol was favorable for treating

210365 BRIEFING DOCUMENT], <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM604736.pdf>; see also *supra* notes 559–61 and accompanying text (noting research that found potential for abuse in dronabinol oral solution).

574. NDA 210365 BRIEFING DOCUMENT, *supra* note 573.

575. The company also benefitted from fast-track status and rolling review. See FDA BRIEFING DOCUMENT, *supra* note 572, at 42. Fast track is meant to “facilitate development and expedite review of drugs to treat serious and life-threatening conditions” so that drugs that meet unmet medical needs can more quickly reach consumers. FDA, GUIDANCE FOR INDUSTRY: EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS—DRUGS AND BIOLOGICS 9 (2014), <https://www.fda.gov/downloads/Drugs/Guidances/UCM358301.pdf>. The designation entitles the company to more frequent meetings with the agency to discuss the development plan and may allow the company to submit its application piecemeal as it completes each section (thus, a “rolling” submission). *Id.* at 9–10. The FDA will review the pieces as they arrive, rather than waiting for a complete application, which allows the applicant to address issues earlier and should, in theory, allow for earlier approval. In this case, the agency agreed to fast track designation in June 2014, agreed to the rolling submission in July 2016, and received the final pieces of the NDA from the applicant in October 2017. FDA BRIEFING DOCUMENT, *supra* note 572, at 42.

576. FDA BRIEFING DOCUMENT, *supra* note 572, at 43.

577. NDA 210365 BRIEFING DOCUMENT, *supra* note 573, at 7.

578. *Id.* at 51.

579. *Id.*

580. *Id.* at 52.

seizures associated with LGS and DS,⁵⁸¹ and the FDA approved the NDA on June 25, 2018.⁵⁸²

Three aspects of this approval nevertheless hold lessons for other companies. First, even though the Office of New Drug Products concluded that the drug substance was not a botanical, it invited the Botanical Review Team to provide a review of the quality control process for the botanical raw material.⁵⁸³ Although this could have been an anomaly, it is also possible BRT will be involved in review of other drugs containing highly purified extracts from cannabis. As a general rule, and as suggested in Part III, the BRT's involvement will work in an applicant's favor as these reviewers are more familiar with the complexity of botanically sources and more inclined to be flexible.⁵⁸⁴ Further, the written memorandum from the review officer reflects the team's current understanding of the cannabis plant (as well as its history of medical use).⁵⁸⁵ Among other things, the memorandum acknowledges the "competing schools of thought on cannabis taxonomy" and seems to adopt the monotypic (single species, with subspecies) perspective.⁵⁸⁶ The memorandum, though brief, now constitutes a sort of informal "precedent" within the agency, which subsequent new applicants should review.

Second, a substantial expanded access program involved more active patients than had enrolled in the pivotal trials.⁵⁸⁷ The FDA began to

581. FDA, CTR. FOR DRUG EVALUATION & RES., SUMMARY MINUTES OF THE PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEETING 4 (Apr. 19, 2018), <https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/UCM606745.pdf>. FDA's advisory committees are composed of outside experts from the scientific community, as well as industry and consumer representatives. *What is an FDA Advisory Committee?*, FDA, <https://www.fda.gov/AboutFDA/Transparency/Basics/ucm222191> (last visited Feb. 5, 2019). They provide the agency with independent advice on issues relating to drugs, food, and other products, but their recommendations are not binding on the agency. *Id.* See generally Erika Lietzan, *Advisory Committees at FDA: The Hinchey Amendment and "Conflict of Interest" Waivers*, 39 J. HEALTH L. 415, 419–24 (2006) (providing an overview of the development of FDA advisory committees).

582. FDA, CTR. FOR DRUG EVALUATION & RES., NDA APPROVAL: NDA 210365 (June 25, 2018), https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2018/210365Orig1s000Ltr.pdf.

583. See EPIDIOLEX PRODUCT QUALITY REVIEW(S), *supra* note 571.

584. See *Botanical Review Team (BRT)*, FDA, <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm090946> (last visited Feb. 5, 2019).

585. EPIDIOLEX PRODUCT QUALITY REVIEW(S), *supra* note 571, at 8–10.

586. *Id.* at 9 (noting the polytypic (multi-species) perspective, a competing school of thought).

587. FDA BRIEFING DOCUMENT, *supra* note 572, at 52–53.

authorize physician-initiated expanded access programs in May 2013, more than a year before the company began its clinical trials.⁵⁸⁸ Although the company “exerted no control over these programs” (and “site physicians were responsible for specific treatment plans and actions”), it submitted, and the agency considered, the safety data as part of new drug approval.⁵⁸⁹ These data related to “684 patients with DS, LGS, and a variety of severe epilepsy conditions.”⁵⁹⁰ The adverse events in the expanded access program were generally consistent with those from the controlled trials, but interpretation of safety results from expanded access is always complicated by the lack of controls and the variability in investigators.⁵⁹¹ Because cannabis-based drugs are likely to be studied in a variety of serious and life-threatening conditions, requests for expanded access are likely to be a feature of many premarket programs, and the safety data from this use will be an important part of the agency’s review of any resulting NDAs.⁵⁹²

Third, it is unclear how the approval of Epidiolex will affect companies already marketing CBD, and the uncertainty points to one of the most difficult challenges that companies and policymakers would face if cannabis were descheduled. The FDCA does not permit the marketing of a dietary supplement containing the active ingredient of a new drug.⁵⁹³ So it is a federal crime to market dietary supplements containing cannabidiol, and it was already a federal crime when GW Pharmaceuticals was testing its product in clinical trials. The agency has cited violation of the drug exclusion rule in warning letters to companies marketing cannabidiol, and it specifically points to the clinical trials of Epidiolex.⁵⁹⁴ But many of these products remain on

588. *Id.* at 12, 42–43. The company submitted its IND in March 2014 and started clinical trials in October 2014. *Id.* at 42.

589. NDA 210365 BRIEFING DOCUMENT, *supra* note 573, at 14–15.

590. *Id.* at 33.

591. FDA BRIEFING DOCUMENT, *supra* note 572, at 99–100.

592. The new “Right to Try” law will not affect the FDA’s ability to consider the safety data from expanded access programs, if the data are material to the benefit-risk ratio of the drug. *See* Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, Pub. L. No. 115-176, 132 Stat. 1372 (codified at 21 U.S.C. § 360bbb-0a (2012)). The Act provides that the FDA “may not use a clinical outcome associated with the use of an eligible investigational drug pursuant to this section” *unless* it finds that use of the clinical outcome “is critical to determining the safety of the eligible investigational drug.” § 360bbb-0a(c)(1).

593. *See supra* Section III.C.

594. *See* Warning Letter from FDA to Green Roads of Florida LLC (Oct. 31, 2017), <https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm583188>; Warning Letter from FDA to Natural Alchemist (Oct. 31, 2017),

the market. Epidiolex received orphan drug exclusivity, which precludes the FDA from approving cannabidiol for the same uses for seven years.⁵⁹⁵ This is intended to provide GW Pharmaceuticals an opportunity to recoup its research and development costs in the marketplace through exclusive sales.⁵⁹⁶ If the company loses sales to inexpensive cannabidiol dietary supplements, however, it may not be able to recoup the research and development costs. The manufacturers and distributors of the dietary supplements could not make claims about treatment of seizures associated with LGS and DS, but consumers could nevertheless purchase the products, particularly if the price differential is substantial.⁵⁹⁷

GW Pharmaceuticals could reasonably urge the FDA to act against unlawfully marketed dietary supplements, which compete directly with its product and undermine its orphan exclusivity. But when KV Pharmaceuticals effectively did the same thing—secured approval and orphan exclusivity for a treatment that had previously been available to patients in a cheap unapproved form and asked the FDA to take action against the unapproved versions—outraged insurers, patients, and physicians went to the Federal Trade Commission and Congress for relief.⁵⁹⁸ So it is unclear whether the manufacturer of Epidiolex will press the FDA to take action. The FDA might take more formal action on its own initiative, but it would likely be concerned about the same backlash.⁵⁹⁹ Perhaps the parents of children with DS and LGS

<https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm583205>; Warning Letter from FDA to Stanley Brothers Social Enterprises, LLC (Oct. 31, 2017), <https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm583192>; Warning Letter from FDA to That's Natural! Marketing & Consulting (Oct. 31, 2017), <https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm583197>.

595. See FDA, APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS: 38TH EDITION A-11 (Cumulative Supp. 2018), <https://www.fda.gov/downloads/Drugs/InformationOnDrugs/UCM086233.pdf>.

596. See 21 U.S.C. § 360aa(b) (noting “there is reason to believe that some promising orphan drugs will not be developed unless changes are made . . . to provide financial incentives to develop such drugs”).

597. See *supra* Section III.A.1 (explaining that a product will be deemed a drug if it is associated with drug claims).

598. Cathy Kelly, *Makena Pricing Prompts Multi-Pronged Appeals: FDA, FTC—Bayh Dole?*, PINK SHEET (Mar. 21, 2011), <https://pink.pharmaintelligence.informa.com/PS053233/Makena-Pricing-Prompts-MultiPronged-Appeals-FDA-FTC-ndash-BayhDole>.

599. The agency is most likely to act if companies make claims that present a public health risk, for instance, claims about treatment of serious or life-threatening conditions that might cause patients to forego proven therapies. See, e.g., Michael

will prefer the assurance of safety and effectiveness that comes with FDA approval, but others may not. Other companies considering cannabis-based drug products will watch GW's pricing and sales closely. Whether these companies move forward will depend in part on the complexity and burden of the NDA approval process for the particular drug they are developing and on the likely market conditions after approval. If cannabis is descheduled, these companies will also need to consider the risk of investing hundreds of millions of dollars into a new drug product only to find that their target patient population self-medicates with recreational cannabis.

3. *Current conventional drug research and development*

The descheduling of cannabis and THC could lead to a rapid growth in research to develop new drugs from cannabis simply because researchers would no longer struggle to obtain raw materials.⁶⁰⁰ A review of the medical literature from 1948 through March 2015 uncovered twenty-eight randomized clinical trials for uses other than those for which Marinol and Cesamet are approved, including chronic pain, neuropathic pain, multiple sclerosis, Parkinson's disease, Crohn's disease, amyotrophic lateral sclerosis (ALS), and neurogenic symptoms.⁶⁰¹ Today, a review of the Clinical Trial Registry on the National Institutes of Health indicates more than a dozen ongoing clinical trials examining the therapeutic potential of cannabis.⁶⁰² The

Cipriano, *Gottlieb: Epidiolex Approval Covers One Specific Cannabidiol Medication, Not Marijuana*, PINK SHEET (June 25, 2018), <https://pink.pharmaintelligence.informa.com/PS123363/Gottlieb-Epidiolex-Approval-Covers-One-Specific-Cannabidiol-Medication-Not-Marijuana> (quoting the FDA Commissioner saying that the agency will "prioritize enforcement going forward" by focusing on situations where patients face "particularly significant harm because there's otherwise effective, available therapy for those patients").

600. As discussed in Part I, researchers are currently limited to NIDA cannabis from the University of Mississippi. *See supra* notes 161–65 and accompanying text. Many trials on the NIH website are taking place in other countries, however, which may enable them to use other strains depending on the laws in those countries. *ClinicalTrials.gov*, U.S. NAT'L INST. HEALTH: U.S. NAT'L LIBR. MED., <https://clinicaltrials.gov/ct2/home> (last visited Feb. 5, 2019) (listing, in a search for "cannabis," 294 studies completed or active studies outside of the United States).

601. Kevin P. Hill, *Medical Marijuana for Treatment of Chronic Pain and Other Medical and Psychiatric Problems: A Clinical Review*, 313 J. AM. MED. ASS'N 2474, 2474 (2015).

602. *See ClinicalTrials.gov, supra* note 600. This search captured trials that are currently recruiting or enrolling, or active but no longer recruiting. *Id.* The clinical trial registry on the NIH website must include any clinical trial of a new drug that occurs in the United States or under an IND (including under an IND but in a foreign country) and that is not a phase 1 trial. 42 C.F.R. § 11.22 (2017). In practice, it

ongoing trials generally focus on CBD and THC, presumably Δ^9 -THC, rather than other cannabinoids.⁶⁰³ And, like the trials uncovered in the historical literature review, current research focuses primarily on treatment of pain or neurological or psychiatric conditions.⁶⁰⁴ For instance, many are examining the effectiveness of cannabis-based products in treating pain associated with cancer, low back pain, or osteoarthritis of the knee.⁶⁰⁵ Some are considering use of cannabis-based products for treatment of Tourette Syndrome,⁶⁰⁶ tremor associated with Parkinson's Disease,⁶⁰⁷ and multiple sclerosis.⁶⁰⁸ Others

includes many phase 1 trials as well. This Article discusses the ongoing clinical trials that relate to new therapeutic uses. Many other trials listed on the registry relate to cannabis—for instance, examining its safety and pharmacology, and its effect on driving, on sperm production, or breast milk. See *ClinicalTrials.gov*, *supra* note 600.

603. See *ClinicalTrials.gov*, *supra* note 600. Other cannabinoids are, however, being studied. For example, Schrot and Hubbard reported in 2016 that a mixture of cannabidiol and tetrahydrocannabivarin was being tested for treatment of diabetes and metabolic syndrome. Richard J. Schrot & John R. Hubbard, *Cannabinoids: Medical Implications*, 48 ANNALS OF MED. 128, 137 (2016).

604. See Hill, *supra* note 601.

605. See, e.g., NCT02460692, *Trial of Dronabinol and Vaporized Cannabis in Neuropathic Low Back Pain*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/show/NCT02460692> (last updated Oct. 19, 2018) (describing a Phase 2 trial of vaporized cannabis or dronabinol in patients with low back pain associated with nerve injury to determine whether these drugs reduce spontaneous and evoked pain more than placebo); NCT02324777, *Cannabinoid Profile Investigation of Vaporized Cannabis in Patients with Osteoarthritis of the Knee (CAPRI)*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/show/NCT02324777> (last updated Apr. 5, 2018) (describing a Phase 2 trial of vaporized finely ground herbal cannabis to assess analgesic dose response in patients with osteoarthritis of the knee); NCT03339622, *Safety and Efficacy of Smoked Cannabis for Improving Quality of Life in Advanced Cancer Patients*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/show/NCT03339622> (last updated Feb. 8, 2018) (describing a Phase 3 trial of an inhaled cannabis product (dried pellet smoked with a titanium pipe) to improve quality of life and reduce pain intensity in patients with uncontrolled cancer pain and incurable malignancy).

606. See, e.g., NCT03247244, *Safety and Efficacy of Cannabis in Tourette Syndrome*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/show/NCT03247244> (last updated Oct. 19, 2018) (describing a Phase 2 trial considering the safety and effectiveness of vaporized medical cannabis in treatment of adults with Tourette Syndrome).

607. See, e.g., NCT02818777, *A Study of Tolerability and Efficacy of Cannabidiol on Tremor in Parkinson's Disease*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/show/NCT02818777> (last updated Apr. 28, 2017) (describing a Phase 1/2 trial assessing the tolerability and efficacy of cannabidiol oral solution in patients with tremor from Parkinson's Disease).

608. See, e.g., NCT03186664, *The Role of Sativex® in Robotic-Rehabilitation (SARR)*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/show/NCT03186664> (last updated June 14, 2017) (detailing a trial of Sativex (nabiximols) to assess its role in improving

are studying cannabis in treatment of psychiatric conditions such as obsessive-compulsive disorder⁶⁰⁹ or post-traumatic stress disorder.⁶¹⁰ Several trials are examining its use in treatment of agitation associated with dementia,⁶¹¹ and one is considering oral cannabinoid formulations in the treatment of behavioral problems in children and youth with autism spectrum disorder.⁶¹²

Where this research would lead, however, remains to be seen. Descheduling will make it easier to develop drug candidates in the laboratory and to conduct clinical trials. But much of the current research is sponsored by academic researchers rather than biopharmaceutical companies, and this could remain true after descheduling. And in any case, whether the results would lead experienced companies to invest in full blown premarket clinical

motor outcome when coupled with robotic neurorehabilitation training in multiple sclerosis patients).

609. See, e.g., *NCT03274440, Effects of Marijuana on Symptoms of OCD (ECOS)*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/show/NCT03274440> (last updated Nov. 9, 2018) (discussing a Phase 1/2 trial of smoked marijuana in differing concentrations of CBD and THC in patients with obsessive-compulsive disorder (OCD)); *NCT02911324, Cannabinoid Medication for Adults with OCD*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/show/NCT02911324> (last updated Feb. 7, 2018) (explaining a Phase 1 /2 trial of nabilone in patients with OCD).

610. See, e.g., *NCT02759185, Study of Four Different Potencies of Smoked Marijuana in 76 Veterans with PTSD*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/show/NCT02759185> (last updated Nov. 7, 2018) (describing a Phase 2 trial of smoked cannabis in four variations with differing levels of THC and CBD in military veterans with post-traumatic stress disorder (PTSD)); *NCT02517424, Evaluating Safety and Efficacy of Cannabis in Participants with Chronic Posttraumatic Stress Disorder*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/show/NCT02517424> (last updated Apr. 18, 2018) (describing a Phase 2 trial of different potencies of vaporized cannabis to evaluate its safety and effectiveness in treatment of chronic treatment-resistant post-traumatic stress disorder).

611. See, e.g., *NCT03328676, The Effect of Cannabis on Dementia Related Agitation and Aggression*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/show/NCT03328676> (last updated Feb. 23, 2018) (reporting a Phase 2 trial of oral cannabis oil to investigate its effectiveness and safety for treatment of subjects with agitation related to dementia); *NCT02351882, Safety and Efficacy of Nabilone in Alzheimer's Disease*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/show/NCT02351882> (last updated Aug. 10, 2018) (evaluating a Phase 2/3 trial of nabilone to assess its safety and effectiveness in treating agitation in patients with moderate to severe Alzheimer's Disease).

612. See *NCT02956226, Cannabinoids for Behavioral Problems in Children with ASD (CBA)*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/ct2/show/NCT02956226> (last updated Aug. 7, 2018) (describing a Phase 2 trial of two oral cannabinoid formulations to assess their safety, tolerability, and effectiveness for behavioral problems in children and youth with autism spectrum disorder).

programs, in light of the likely challenges maintaining an exclusive position in the marketplace to recover research and development costs, remains to be seen.

C. Dietary Supplements

The prospects for marketing medical cannabis in dietary supplement form are more complex, and the pathway is riskier. It is a misimpression that dietary supplements are mostly unregulated and that labeling a product as a “supplement” is enough to mostly bypass the FDA framework. The most important restriction is that no dietary supplement may contain a constituent of cannabis that already appears in an approved drug or in a drug that is the subject of clinical trials. Although it is theoretically possible to avoid this by proving the substance was marketed (overtly) in dietary supplements or food earlier, the FDA takes such a conservative approach to this exception that, in our view, pursuing the exception is unlikely to be productive.

A company that chose to move forward with another constituent (in a dosage form for ingestion) would need to submit information and data to satisfy the statutory safety standard. It would also need to wait for seventy-five days or (if it was risk averse) wait for the agency to issue a “no objection” letter. The catch, however, is that time is of the essence; once a clinical trial of the same constituent has begun and is made public, the dietary supplement route is legally foreclosed—even if the supplement company is in the middle of its safety tests or waiting for the FDA’s response. Once the seventy-five days lapse or the agency issues a no objection letter, the company could market the dietary supplement nationally, including with structure/function claims. But the agency polices structure/function claims vigorously, and we believe it would be especially vigilant with respect to cannabis-derived dietary supplements. Finally, the full scope of the drug exclusion may be the subject of some dispute with the agency. That CBD is excluded is clear, but whether the FDA would attempt to treat all THCs as the same for purposes of drug exclusion remains to be seen. The dietary supplement pathway would be much less expensive than the new drug pathway, but its availability is much less clear.

The competitive landscape for a dietary supplement would also be very different. Although expensive to develop, an approved new drug would benefit from exclusivity in the marketplace, because the FDA would be precluded from approving generic copies for a time. Depending on the disease being treated, the agency might also be precluded from approving other versions that were not generic copies.

A dietary supplement containing a constituent of cannabis, by way of contrast, could very rapidly become one of many in the marketplace. And without the ability to make disease-related claims, it could be difficult for one company to differentiate its product from others.

CONCLUSION

After descheduling, all three pathways should be available for medical cannabis products. The relative distribution of products among these three pathways will turn on a variety of factors.⁶¹³ Fully exploring those factors and the likely distribution is beyond the scope of this Article, but this Article makes a few preliminary observations here based on the discussion in Parts III and IV.

Given the approval of Epidiolex, the Authors would expect smaller pharmaceutical companies to explore the development of highly purified cannabis constituents for rare diseases that are poorly treated today. This will be particularly true if insurance coverage and protection from competing drug approvals will ensure a profitably exclusive market position for some time. The Authors also expect the pharmaceutical pathway would be pursued for any cannabis constituent that (based on preliminary research) seemed likely to be highly effective, particularly for a chronic or common condition because robust clinical evidence and the imprimatur of FDA approval could lead in this scenario to blockbuster status.

At the same time, some patient groups and caregivers have a strong preference for products that they perceive as more “natural” and “holistic,” which is likely to maintain a market base for traditional cannabis dispensaries. Thus, particularly in states that have legalized medical marijuana and that have patient populations accustomed to the availability of cannabis from dispensaries, intrastate-only medical cannabis operations might flourish. Intrastate dispensaries might also emerge in areas where consumers embrace complementary and alternative medicine, as well as areas where consumers are more suspicious of federal regulation.

Use of the dietary supplement pathway is harder to predict. It is possible this pathway will be commercially advantageous only when structure-function claims can be made. The challenge is that the constituents must be new (not yet tested in drug trials), and yet claims

613. See, e.g., Lester Black, *Legal Weed Isn't the Boon Small Businesses Thought It Would Be*, FIVETHIRTYEIGHT (Dec. 29, 2017, 6:00 AM), <https://fivethirtyeight.com/features/legal-weed-isnt-the-boon-small-businesses-thought-it-would-be>.

must be substantiated with competent and reliable scientific evidence. Time to market will be of the essence, because of the drug exclusion rule, so these dietary supplements may reach the market first without claims. This pathway might be more common in situations where the physiological benefits are uncertain. Concerns about the pricing of prescription drugs and consumer preferences for self-medication with products perceived to be more “natural” could also drive up usage of this pathway.