

# **Cannabis-Derived Botanical Drugs: A Viable Regulatory Pathway for Marketing Medical Edibles?**

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## **ABSTRACT**

There is a belief among some firms in the cannabis industry that cannabis-infused edibles (“edibles”) could be legally marketed under federal law if cannabis were descheduled from the Controlled Substances Act (CSA). Yet, despite this belief, many of these products would remain illegal under current federal law because they would be marketed in violation of the Federal Food, Drug, and Cosmetic Act (FDCA). Some firms in the cannabis industry have further assumed that FDA lacks the authority to regulate edibles under the FDCA when such products are sold and distributed within the confines of a single state. While technically true—FDA’s jurisdiction does generally require a nexus to interstate commerce—this understanding is too simplistic and may leave cannabis firms with a false sense of security over the legal status of their products. This article confirms that the present options for legally marketing edibles in compliance with the FDCA are currently limited and thus proceeds to evaluate an alternative approach: the development of FDA-approved, cannabis-derived botanical drugs. While finding that cannabis-derived botanical drugs are viable from a regulatory perspective, this article concludes that the prospect of competition from recreational cannabis products is likely to discourage many cannabis firms from pursuing this approach. In the end,

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this article predicts that the respective competitive landscapes for CBD- and THC-containing products may evolve somewhat differently and that ultimately Congress may decide to intervene in this space to preserve the integrity of a nationwide market for FDA-regulated products.

## INTRODUCTION

Cannabis-infused edibles (“edibles”) can be broadly defined as products that have been infused with an extract of cannabis and which are generally intended to be consumed by oral ingestion, instead of by smoking or vaping.<sup>1</sup> These products typically resemble conventional foods or dietary supplements and are currently marketed in a variety of forms, including as baked goods, beverages, chocolates, hard candies, “gummies,” and lozenges.<sup>2</sup>

The “cannabis-derived” extracts used to manufacture edibles are typically derived from the flowering heads (“buds”) and leaves of the plant *Cannabis sativa*<sup>3</sup> and generally contain the biologically active phytocannabinoids delta-9-tetrahydrocannabinol (delta-9-THC or “THC”<sup>4</sup>) and/or cannabidiol (“CBD”<sup>5</sup>). These extracts may also contain variable amounts of other cannabis constituents—primarily other phytocannabinoids and terpenoids—depending on the cultivar of cannabis used to produce the extract, the method of extraction, and the degree of purification.<sup>6</sup> Cannabis researchers have posited that such complex “whole plant” extracts may be

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<sup>1</sup> Daniel G. Barrus et al., *Tasty THC: Promises and Challenges of Cannabis Edibles* [hereinafter *Tasty THC*], METHODS REP RTI PRESS, at 2 (Nov. 2016), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5260817/> [<https://erma.cc/KXJ3-FNSB>].

<sup>2</sup> *Id.*

<sup>3</sup> This article adopts the monotypic (single-species) perspective of cannabis taxonomy under which all varieties of cannabis are catalogued as subspecies of *C. sativa*, such as *C. sativa sativa*, *C. sativa indica*, and *C. sativa ruderalis*. See FOOD & DRUG ADMIN., CDER, NDA 210365, PRODUCT QUALITY REVIEW OF EPIDIOLEX 35 (Mar. 29, 2018), [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2018/210365Orig1s000ChemR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000ChemR.pdf) [<https://perma.cc/K5NH-E39C>] (noting that, while “the debate continues about whether all cannabis cultivars are *C. sativa*,” the monotypic perspective “is popular and has strong evidence as *C. sativa* and *C. indica* are commonly crossbred to produce hybrid phenotypes with chosen characteristics”).

<sup>4</sup> Tetrahydrocannabinol (THC) is considered the key psychoactive cannabinoid present in cannabis and predominantly exists in four isomeric forms depending on how it is derived. The main plant-derived stereoisomer is (-)-trans- $\Delta^9$ -THC (delta-9-THC) which for purposes of this article is referred to simply as “THC.” See Jacquelyn Runco et al., *The Separation of  $\Delta^8$ -THC,  $\Delta^9$ -THC, and Their Enantiomers by UPC<sup>2</sup> Using Trefoil Chiral Columns*, WATERS SOLUTIONS, at 1, <http://www.waters.com/webassets/cms/library/docs/720005812en.pdf> [<https://perma.cc/6BKN-4HJG>].

<sup>5</sup> CBD is generally not considered to be psychoactive or to have a significant potential for abuse. See generally DEA, Schedules of Controlled Substances: Placement in Schedule V of Certain FDA-Approved Drugs Containing Cannabidiol, HHS Recommendation, at 1, 4, <https://www.regulations.gov/document?D=DEA-2018-0014-0002> [<https://perma.cc/D6QQ-XPYZ>]. CBD is, however, purported to exhibit potentially therapeutic properties, such as anti-inflammatory, anti-anxiety, anti-psychotic, and anti-convulsant activities. See Brightfield Group, INDUSTRY EXPERT REPORT: UNDERSTANDING CANNABIDIOL (CBD) 4 (2017).

<sup>6</sup> See, e.g., Martin A. Lee, *Sourcing CBD: Marijuana, Industrial Hemp & the Vagaries of Federal Law*, PROJECT CBD, <https://www.projectcbd.org/politics/sourcing-cbd-marijuana-industrial-hemp-vagaries-federal-law> [<https://perma.cc/26Z2-42JX>] (discussing differences between CBD oil derived from hemp and CBD oil derived from marijuana) (last visited Feb. 21, 2019).

therapeutically more efficacious than the isolated compounds THC and/or CBD—a phenomenon coined the “entourage effect.”<sup>7</sup>

The terminology surrounding cannabis and the cannabis-derived extracts used to infuse edibles can at times be confusing and mistakes may have legal consequences.<sup>8</sup> For purposes of this article, the term “cannabis” is used as an umbrella term to refer to both “hemp”<sup>9</sup> and “marijuana”<sup>10</sup> varieties/cultivars of the plant *Cannabis sativa*. Accordingly, the “cannabis-derived extracts” discussed throughout this article include both hemp-derived extracts (e.g., hemp-derived CBD oil) and marijuana-derived extracts (e.g., oils produced from THC-dominant, CBD-dominant, or THC/CBD-balanced cultivars).<sup>11</sup>

In the United States, edibles now account for a meaningful share of total cannabis sales in states where cannabis has been legally marketed for a longer duration.<sup>12</sup> Interestingly, it has been reported that users of medical cannabis are four-times more likely to consume edibles than users of recreational cannabis.<sup>13</sup> Anecdotal evidence suggests that this preference may be a result of several factors. *First*, edibles may offer a more convenient and discreet way of administering cannabis than smoking or vaping.<sup>14</sup> *Second*, the subjective and therapeutic effects achieved by consuming edibles—e.g., their more gradual onset and prolonged effects—may be preferable when used for medical purposes.<sup>15</sup> *Third*, the use of edibles may be a means to avoid

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<sup>7</sup> Ethan B. Russo, *The Case for the Entourage Effect and Conventional Breeding of Clinical Cannabis: No “Strain,” No Gain*, 9 FRONT. PLANT SCI. 4 (Jan. 9, 2019), <https://www.frontiersin.org/articles/10.3389/fpls.2018.01969/full> [<https://perma.cc/44K4-66YL>].

<sup>8</sup> See *infra* Part III.C.1 (noting that, while marijuana-derived CBD oil remains illegal under federal law, hemp-derived CBD oil is no longer a scheduled substance under the Controlled Substances Act).

<sup>9</sup> Hemp is legally defined as a cultivar of *Cannabis sativa* containing low concentrations of the psychoactive phytocannabinoid THC ( $\leq 0.3\%$  THC by dry weight). See Lee, *supra* note 6. These plants are typically grown to produce seed oil, fiber, and food. See Brightfield Group, *supra* note 5, at 4.

<sup>10</sup> Marijuana refers to cultivars of *Cannabis sativa* containing higher concentrations of the psychoactive phytocannabinoid THC and which are traditionally cultivated for their drug-like properties. See Lee, *supra* note 6.

<sup>11</sup> Though marijuana-derived extracts will contain higher concentrations of THC than hemp-derived extracts, the ratio of THC to other phytocannabinoids in these extracts (e.g., CBD) will vary by cultivar. For example, a THC-dominant extract may contain a ratio of 2:1 THC:CBD or higher, whereas a CBD-dominant extract may contain a ratio of 5:1 CBD:THC or higher. See Brightfield Group, *supra* note 5, at 5. THC/CBD-balanced extracts may contain a ratio of approximately 1:1 THC:CBD. See TILRAY PRODUCTS, <https://www.tilray.com/products> [<https://perma.cc/E5DJ-XWCN>] (marketing “THC & CBD Balanced” products that contain equal amounts of THC and CBD).

<sup>12</sup> Jacob T. Borodovsky et al., *Smoking, Vaping, Eating: Is Legalization Impacting the Way People Use Cannabis?*, 36 INT. J. DRUG POLICY 1 (2016); see Ryan Vandrey et al., *Pharmacokinetic Profile of Oral Cannabis in Humans: Blood and Oral Fluid Disposition and Relation to Pharmacodynamic Outcomes*, 41 J. OF ANALYTICAL TOXICOLOGY 2: 83 (Mar. 2017), <https://academic.oup.com/jat/article/41/2/83/2967155> [<https://perma.cc/J9CN-MKXA>] (citing a report finding that edible products comprised an estimated 40% of medical and non-medical retail cannabis sales in Colorado in 2014).

<sup>13</sup> Rosalie Pacula et al., *In the Weeds: A Baseline View of Cannabis Use Among Legalizing States and Their Neighbors*, 111(6) ADDICTION 5 (2016). Note, however, that overall both recreational users and medical users preferred smoking cannabis over consuming edibles. See Vandrey et al., *supra* note 12, at 84 (noting that surveys of medical cannabis users indicate that 16–26% of medical cannabis patients use edible cannabis products).

<sup>14</sup> Barrus, *supra* note 1, at 3.

<sup>15</sup> *Id.*

the perceived harmful toxins and health risks associated with inhaling cannabis.<sup>16</sup> These observations provide a rationale for exploring legal pathways for expanding consumer access to safe, effective, and high-quality forms of edibles, including those suitable for use in the treatment of medical conditions (medical edibles) or to promote general health and well-being (cannabis-derived dietary supplements).

However, despite the therapeutic promise of medical edibles, and efforts at the state-level to increase access to cannabis, uncertainty remains over the legal status of cannabis-derived products under federal law. For example, while firms in the cannabis industry generally recognize that certain cannabis-derived products remain federally illegal under the Controlled Substances Act (CSA), cannabis firms less commonly appreciate that the sale and distribution of these products may also be prohibited under the Federal Food, Drug, and Cosmetic Act (FDCA). That is, even if cannabis were completely descheduled by being removed from the CSA, the sale and distribution of many medical edibles would remain restricted under federal law—at least until these products were otherwise brought into compliance with all applicable provisions of the FDCA.

Further, cannabis firms often operate under a business model that assumes that the risk of FDA enforcement action for violations of the FDCA is remote. This assumption is premised upon a belief that the Agency lacks jurisdiction over cannabis operations that occur entirely within the confines of a single state—e.g., the wholly intrastate sale and distribution of medical edibles. While this may be generally true, this belief underestimates the potential risk of agency enforcement action by overlooking less well-known avenues through which FDA arguably could establish a connection to interstate commerce.<sup>17</sup> To be sure, the Agency has, to date, taken a relatively modest approach to enforcement action against cannabis-derived products that are being marketed in violation of the FDCA—perhaps because the manufacture, sale, and distribution of these products was otherwise prohibited by CSA.<sup>18</sup> But, for this same reason, FDA may, paradoxically, adopt a stronger enforcement posture if cannabis were eventually fully descheduled.

This Article proceeds in three parts. Part I examines two provisions of the FDCA under which FDA arguably could take enforcement action against medical edibles under the Agency's existing authority to regulate food. This part finds that the current options for legally marketing medical edibles—whether as a conventional food or a dietary supplement—are more limited than is often assumed. For example, no edible could contain either THC or CBD as the presence of these substances would violate the FDCA's drug exclusion rule. In response to this prohibition, cannabis firms marketing edibles must attempt to limit the sale and distribution of these products to the confines of a single state—a limitation which could impede the growth of these businesses and which, in some cases, may still not be sufficient to avoid the ambit of FDA's jurisdiction.<sup>19</sup>

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<sup>16</sup> Id.

<sup>17</sup> See *infra* Part I.

<sup>18</sup> See Robert MacCoun & Michelle Mello, *Half-Baked—The Retail Promotion of Marijuana Edibles*, 372 NEW ENG. J. OF MED. 989, 990 (2015) (commenting that “[p]olitically, the agency can’t easily begin regulating marijuana sales while such sales remain federally prohibited”).

<sup>19</sup> See *infra* Part I.B.2. Cannabis firms should also be aware that the legal status of edibles under the laws of some states is tied to the legal status of these products under federal law. See, e.g., Ben Smart, *NC regulators cracking down on CBD-infused products; warning letters coming to businesses starting next*

Part II describes an alternative approach for marketing medical edibles that cannabis firms may wish to consider: the development of cannabis-derived botanical drugs. Importantly, this part finds that FDA's modified approach to developing botanical drugs would make approval of a cannabis-derived botanical drug *possible*, whereas such approval may be impossible under the Agency's conventional drug development approach.

Concluding that it would be possible for a cannabis-derived botanical drug to gain FDA approval, Part III proceeds to critically assess whether this strategy represents an economically viable option for cannabis firms seeking to market medical edibles in compliance with the FDCA. This part finds that the time and cost associated with developing a cannabis-derived botanical drug—while relatively attractive by conventional drug development standards—may still be cost-prohibitive for many cannabis firms. This part also finds that, while barriers to market entry of fully substitutable generics may exist, competition from recreational cannabis and eventually other categories of FDA-regulated products (e.g., cannabis-derived dietary supplements) would likely further discourage firms from using this pathway.

In the final analysis, this article concludes that FDA has sufficient regulatory tools under its existing statutory authorities to ensure that a level playing field exists for certain types of cannabis-derived products (e.g., those containing hemp-derived CBD), but that Congressional action may ultimately be required to strike a similar balance for other types of cannabis-derived products (e.g., those that contain THC). If that is correct, cannabis firms should be aware that new federal laws may be in the works and should continue to actively monitor these developments—particularly if legislative proposals to fully legalize cannabis gain additional traction.

## I. FDA'S AUTHORITY TO REGULATE MEDICAL EDIBLES

Between 2015 and 2017, FDA issued warning letters to multiple cannabis firms asserting that various products containing the cannabinoid, cannabidiol (CBD), were being marketed as unapproved “new drugs” in violation of the FDCA.<sup>20</sup> Included among this group of CBD-containing products were several popular forms of edibles such as “gummies” and hard candies.<sup>21</sup> FDA's conclusion that these products were being marketed in violation of the FDCA flowed from the Agency's initial

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*week* (Feb. 7, 2019), <http://www.wect.com/2019/02/06/nc-regulators-cracking-down-cbd-infused-products-warning-letters-coming-businesses-starting-next-week/> [<https://perma.cc/49DU-RHZC>] (“North Carolina has routinely adopted by reference the federal Food, Drug & Cosmetic Act and implementing regulations. The violation of these federal laws and regulations would equally be a violation of state laws and regulations.”) (last visited Feb. 22, 2019); *see also* Eli Harrington, *Citing FDA, Maine Takes Steps to End Sales of CBD to Public*, HEADY VERMONT BLOG (Feb. 2, 2019), <https://headyvermont.com/citing-fda-position-the-state-of-maine-is-ending-the-sale-of-cbd-foods-tinctures-and-capsules-to-the-public/cannabis/> [<https://perma.cc/X65E-7GRX>] (noting that it is a violation of the Maine Food Code to market food products containing CBD oil because this ingredient is an unapproved food additive *under federal law*) (last visited Feb. 22, 2019).

<sup>20</sup> *See generally* Food & Drug Admin., *Warning Letters and Test Results for Cannabidiol-Related Products*, <https://www.fda.gov/newsevents/publichealthfocus/ucm484109.htm> [<https://perma.cc/777F-8YQ2>] (last visited Dec. 17, 2018).

<sup>21</sup> *Warning Letter to Green Roads of Florida LLC* (Oct. 31, 2017), <https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm583188.htm> [<https://perma.cc/4RCV-A8PZ>].

determination that these products met the statutory definition of “drugs” under section 201(g)(1)(B) of the FDCA.

The Agency’s determination that the CBD products were drugs was based on advertising claims made on the firms’ websites and social media pages which suggested that the products could be used to treat various diseases and medical conditions (“disease claims”). In FDA’s view, the use of such disease claims indicated that the products were “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals” and, accordingly, fell within the statutory definition of “drugs.”<sup>22</sup> Products that FDA determines to be “drugs” are required to comply with the Agency’s “current good manufacturing practices” (cGMP) and labeling regulations.<sup>23</sup> FDA further concluded that these products were “new drugs” because they were not generally recognized as safe and effective for their claimed uses and because the firms had not obtained prior marketing approval from FDA by submitting a new drug application (NDA).<sup>24</sup>

On account of this warning letter campaign, cannabis firms are now relatively more aware that disease claims should be avoided when marketing edibles, lest the product be regulated as a drug. In contrast, firms have much less appreciation for how a failure to comply with other provisions of the FDCA could impact the legal status of their edible products. In particular, there are two provisions of section 301 of the FDCA [21 U.S.C. § 331] that arguably are violated when edibles are sold or distributed in interstate commerce.<sup>25</sup> Broadly speaking, these provisions are triggered when FDA determines, first, that a specific product (e.g., a medical edible) meets the statutory definition of a “food” and, second, that the product fails to comply with the relevant statutory requirements of the FDCA.

Where a violation of the FDCA is identified, and the requisite nexus to interstate commerce exists, FDA can take a range of enforcement actions against the firm marketing the product, including: (i) issuing a warning letter, (ii) initiating a seizure action against the violative product, (iii) seeking an injunction to prevent further violations of the FDCA, and (iv) recommending criminal prosecution.<sup>26</sup> In practice, however, FDA is likely to prioritize enforcement actions that involve violations that pose a risk to public health. Indeed, as FDA recently explained, the Agency intends to take enforcement action against firms selling cannabis-derived products where

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<sup>22</sup> As discussed in Part I.A, *infra*, these products were presumably also introduced into interstate commerce because FDA’s regulatory jurisdiction over drugs does not extend to the purely intrastate sale or distribution of these products.

<sup>23</sup> See Sean M. O’Connor & Erika Lietzan, *The Surprising Reach of FDA Regulation of Cannabis, Even after Descheduling*, AM. U. L. REV. 863 (Forthcoming), [https://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=3242870](https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3242870) [<https://perma.cc/L9PL-YV8L>] (last visited Feb. 21, 2019).

<sup>24</sup> Warning Letter to Green Roads of Florida LLC, *supra* note 21.

<sup>25</sup> For an excellent comprehensive analysis of these provisions, see generally O’Connor & Lietzan, *supra* note 23.

<sup>26</sup> Food & Drug Admin., Types of FDA Enforcement Actions, <https://www.fda.gov/AnimalVeterinary/ResourcesforYou/ucm268127.htm> [<https://perma.cc/2AQW-5WWH>] (last visited Dec. 17, 2018). While FDA is not required to issue a warning letter prior to taking enforcement action, the Agency will often first issue a warning letter to a firm identifying the significant violations of the FDCA that may lead to enforcement action if not promptly and adequately corrected. FOOD & DRUG ADMIN., REGULATORY PROCEDURES MANUAL § 4-1-1 (Sep. 2018), at 3, <https://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074330.pdf> [<https://perma.cc/6GML-D3RW>].

those products “are being marketed in violation of the FDA’s authorities” and “put consumers at risk.”<sup>27</sup>

However, as this part explains, cannabis firms should be aware that FDA’s interpretation of certain provisions of the FDCA can be non-intuitive—and, thus, difficult to apply to a firm’s particular operations—and that the Agency’s view of the types of violations amounting to a public health risk can evolve over time in response to new information and events. Thus, understanding and pursuing voluntary compliance with the provisions set forth in this part is a prudent course of action, especially when considering that a disruption in the supply of a firm’s product due to an enforcement action could create business risk by jeopardizing the firm’s relationships with its customers and ultimately its brand.

#### A. *The Limits of FDA’s Jurisdiction Over Medical Edibles*

FDA’s authority to regulate medical edibles under the FDCA derives, in the first instance, from Congress’ power to regulate interstate commerce under the Commerce Clause. In *Gonzales v. Raich*, the Supreme Court upheld the constitutionality of federal laws prohibiting the possession of home-grown cannabis intended for personal medical use, even though such use was specifically allowed under state law.<sup>28</sup> In reaching its decision, the Court recognized Congress’ broad authority to regulate even “purely local activities that are part of an economic ‘class of activities’ that have a substantial effect on interstate commerce.”<sup>29</sup> The Court also recognized that “when a general regulatory statute bears a substantial relation to commerce, the *de minimis* character of individual instances arising under that statute is of no consequence.”<sup>30</sup>

The *Raich* decision thus places few limitations on Congress’ power to enact laws regulating cannabis-related activities, even where such activities are entirely intrastate and bear no direct connection to interstate commerce.<sup>31</sup>

The *Raich* decision, however, does not necessarily mean that Congress intended to delegate to FDA similarly broad authority over the regulation of food and drugs when it enacted the various provisions of the FDCA. It must be noted, in this regard, that for each of the FDCA provisions discussed in this part—and which represent a potential source of authority under which edibles could be regulated—Congress included a specific interstate commerce nexus.<sup>32</sup> And FDA interprets this language,

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<sup>27</sup> Food & Drug Admin., *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 *Gottlieb Statement on Cannabis Products*], <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm628988.htm> (last visited Feb. 11, 2019) [<https://perma.cc/92U6-X367>].

<sup>28</sup> *Gonzalez v. Raich*, 545 U.S. 1, 32–33 (2005).

<sup>29</sup> *Id.* at 17.

<sup>30</sup> *Id.* (citing *United States v. Lopez*, 514 U.S. 549, 558 (1995) (first emphasis deleted)).

<sup>31</sup> Scholars have criticized the Court’s broad interpretation of the Commerce Clause in *Raich*. See, e.g., Ilya Somin, *Gonzales v. Raich: Federalism as a Casualty of the War on Drugs*, 15 CORNELL JL. & PUB. POL’Y 507, 508 (arguing “that *Raich* represents a major - possibly even terminal - setback for efforts to impose meaningful judicial constraints on Congress’ Commerce Clause powers”).

<sup>32</sup> See 21 U.S.C. § 331(d) (prohibiting “[t]he introduction or delivery for introduction into interstate commerce of any article in violation of [21 U.S.C. § 355]”) (emphasis added); 21 U.S.C. § 355(a) (“No person shall introduce or deliver for introduction into interstate commerce any [unapproved] new drug”) (emphasis added); 21 U.S.C. § 331(l) (prohibiting “[t]he introduction or delivery for introduction into

in related contexts, as an expression of Congress' intent to limit the application of such provisions to only those activities with a *direct* connection to interstate commerce.<sup>33</sup> It is thus reasonable to conclude that FDA's authority to regulate edibles extends only to those products with a *direct* connection to interstate commerce and thus does not reach the purely intrastate sale and distribution of these products. In contrast, where Congress has not included an interstate commerce nexus in a provision of the FDCA, FDA appears to take the position that its jurisdiction is bounded only by the limits of Congress' power under the Commerce Clause and, thus, that the Agency has the authority to regulate certain intrastate activities that fall within the scope of these provisions.<sup>34</sup>

### B. FDA Regulation of Medical Edibles as a Food

As previously discussed, FDA can take enforcement action against a medical edible as a "drug" where disease claims are made about the product. However, even in the absence of disease claims, FDA may still have the authority to regulate a medical edible as a food. The FDCA defines the term "food" to mean any article used for food or drink for man or other animals, including articles used as components (ingredients) of any such food or drink.<sup>35</sup> Case law has interpreted this definition to include any article used by people in the ordinary way most people use food — that is, primarily for taste, aroma, or nutritive value.<sup>36</sup> FDA's authority to regulate food, as relevant here, thus extends to the panoply of forms of medical edibles—e.g., baked goods, beverages, chocolates, gummies, hard candies, and chewing gum—as long as the requisite connection to interstate commerce exists.

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*interstate commerce* of any food to which has been added a drug approved under [21 U.S.C. § 355] . . . or a drug . . . for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public") (emphasis added); 21 U.S.C. § 331(k) (prohibiting "[t]he alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, tobacco product, or cosmetic, if such act is done while such article is held for sale (whether or not the first sale) after shipment in *interstate commerce* and results in such article being adulterated or misbranded") (emphasis added).

<sup>33</sup> See, e.g., Standards for the Growing, Harvesting, Packing, and Holding of Produce for Human Consumption, 80 Fed. Reg. 74,354, 74,361-62 (Nov. 27, 2015). In arguing that Section 301 (vv) of the FDCA does *not* require an interstate commerce nexus, the Agency noted that "other subsections in section 301 of the FDCA . . . demonstrate that Congress has included a specific interstate commerce nexus in the provisions of the FDCA when that is its intent." Accordingly, the Agency argued that, in the absence of such language, "it is reasonable to interpret [such provisions of the FDCA] as not limiting the application of the rule only to those [activities] with a direct connection to interstate commerce."

<sup>34</sup> See, e.g., Current Good Manufacturing Practice, Hazard Analysis, and Risk-Based Preventive Controls for Human Food, 80 Fed. Reg. 55908, 55919-20 (Sep. 17, 2015) (arguing that, where the provision lacks an interstate commerce nexus, the Agency need not establish a direct connection to interstate commerce "given the collective impact on commerce of facilities that manufacture, process, pack, or hold food that is sold in intrastate commerce"); 21 U.S.C. § 331(uu) (prohibiting "[t]he operation of a facility that manufactures, processes, packs, or holds food for sale in the United States if the owner, operator, or agent in charge of such facility is not in compliance with [21 U.S.C. § 350g]," but not requiring food from the facility to be in interstate commerce); 21 C.F.R. § 1.225(b) ("If you are an owner, operator, or agent in charge of a domestic facility, you must register your facility *whether or not the food from the facility enters interstate commerce.*") (emphasis added); 21 C.F.R. § 1.326(b) ("Persons subject to the regulations in this subpart must keep records *whether or not the food is being offered for or enters interstate commerce.*") (emphasis added).

<sup>35</sup> 21 U.S.C. § 321(f).

<sup>36</sup> *Nutrilab, Inc. v. Schweiker*, 713 F.2d 335, 338 (7th Cir. 1983).



*1. Prohibition Against Food to Which a Drug Has Been Added*

Section 301(l) of the FDCA [21 U.S.C. § 331(l)] prohibits the introduction, or delivery for introduction, into interstate commerce of any food to which has been added an approved drug or a drug for which substantial clinical investigations have been instituted and made public. This prohibition is commonly referred to as the “drug exclusion” rule. Accordingly, FDA’s current position is that it is illegal to introduce a food—such as a medical edible—into interstate commerce if it contains THC and/or CBD.<sup>37</sup> This is because THC and CBD are the active ingredients in two FDA-approved drug products: MARINOL (THC) and EPIDIOLEX (CBD).<sup>38</sup> Relying on a similar drug exclusion provision, FDA has taken the same position with respect to dietary supplements that contain THC and/or CBD.<sup>39</sup> As such, many cannabis firms are currently marketing medical edibles in violation of the FDCA and, thus, potentially subject to agency enforcement action.

Until recently, however, FDA has generally declined to exercise its authority over food and dietary supplement products containing THC or CBD, perhaps because sales of such products were federally prohibited under the Controlled Substances Act (CSA).<sup>40</sup> There are now indications, however, that the Agency’s enforcement posture is changing. In 2017, FDA issued a warning letter to a cannabis firm reiterating that section 301(l) of the FDCA (the drug exclusion rule) prohibits the introduction into interstate commerce of any food to which CBD has been added.<sup>41</sup> On that basis, FDA concluded that the introduction or delivery for introduction into interstate commerce of various CBD-containing products sold by the firm—such as gummies and hard candies—was prohibited.<sup>42</sup>

While this warning letter did not describe the evidence that FDA relied upon to establish a nexus to interstate commerce, the act of distributing an edible to a purchaser in another state in response to an online sale would clearly suffice. In contrast, a firm that sells and distributes edibles entirely within the confines of a single state might avoid FDA’s jurisdiction, as such purely intrastate activities would lack a *direct* connection to interstate commerce. It is imperative, however, for cannabis firms to recognize that the types of activities sufficient to create a nexus to interstate commerce are sometimes more attenuated and less intuitive.

For example, in *United States v. Sanders*, the Tenth Circuit held that the language “deliver[ed] for introduction into interstate commerce”—in an analogous provision of the FDCA—encompasses in-person (intrastate) sales to *out-of-state* customers when those sales are made with the knowledge that the product subsequently will be transported across state lines.<sup>43</sup> While it is unclear what quantum of knowledge might be required, it is worth noting that cannabis firms may already have some

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<sup>37</sup> Food & Drug Admin., FDA and Marijuana: Questions and Answers, <https://www.fda.gov/newsevents/publichealthfocus/ucm421168.htm#legal> [<https://perma.cc/4YD3-WM4P>] (last visited Dec. 17, 2018).

<sup>38</sup> *Id.*

<sup>39</sup> *Id.*

<sup>40</sup> See MacCoun & Mello, *supra* note 18, at 990.

<sup>41</sup> Warning Letter to Green Roads of Florida LLC, *supra* note 21.

<sup>42</sup> *Id.*

<sup>43</sup> *United States v. Sanders*, 196 F.2d 895, 898 (10th Cir. 1952).

degree of knowledge regarding their *sales* to out-of-state customers—even in the absence of actual knowledge of interstate transport—through practices such as verifying customers’ ages by requesting state-issued driver’s licenses/IDs, maintaining visitor logs, and perhaps even through surveillance footage of the parking lot areas surrounding a dispensary. That said, the mere in-person (intrastate) sale of a medical edible to an out-of-state customer, without more, is likely insufficient in most instances to create a nexus to interstate commerce for purposes of establishing a violation under the FDCA.<sup>44</sup>

It should be noted, however, that FDA may not initially need evidence of violative activity to establish a connection with interstate commerce. Rather, when taking enforcement action under the FDCA, FDA benefits from a statutory presumption that a nexus to interstate commerce exists.<sup>45</sup> Thus the burden of proof for challenging FDA’s jurisdiction falls on the regulated entity who must establish that the product in question (e.g., the medical edible) had not, in fact, been introduced into interstate commerce.<sup>46</sup> In this regard, it remains to be seen whether the implementation of a certification program under which a cannabis firm’s customers would certify that they will not transport the purchased product across state lines could be a useful approach for mitigating enforcement risk in this particular scenario.<sup>47</sup>

## 2. *Prohibition Against the Adulteration of Food While Held for Sale After Shipment in Interstate Commerce*

Even where a cannabis firm marketing medical edibles seeks to avoid FDA’s jurisdiction by selling and distributing its products within the confines of a single state, FDA potentially could still regulate these products under section 301(k) of the FDCA, given the Agency’s broad interpretation of interstate commerce under this provision. Section 301(k) prohibits any act “with respect to, a food . . . if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded.”<sup>48</sup> Thus, for FDA to regulate a medical edible under this provision, the Agency must establish that the product is (i) adulterated (or misbranded) and (ii) “held for sale . . . after shipment in interstate commerce.” Each of these requirements will be addressed in turn.

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<sup>44</sup> *See id.* (“If [the defendant] knowingly and regularly sold misbranded drugs and delivered them, knowing that they were purchased for transportation in interstate commerce, and solicited customers to return for future purchases and deliveries, he was guilty of a violation of the [FDCA].”).

<sup>45</sup> 21 U.S.C. § 379a.

<sup>46</sup> In practice, the Government is unlikely to rely solely on the statutory presumption. *See United States v. Chung’s Products LP*, 941 F.Supp.2d 770, 795 (S.D. Tex. 2013) (noting that, in addition to relying on the statutory presumption of interstate commerce, “the Government also provided undisputed evidence that Chung’s distributes its products in interstate commerce”); *United States v. Blue Ribbon Smoked Fish, Inc.*, 179 F.Supp.2d 30, 42 (E.D.N.Y. 2001) (same).

<sup>47</sup> FDA has recommended the use of certification programs in other regulatory contexts involving restricted product sales. *See* FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: DISTRIBUTION OF IN VITRO DIAGNOSTIC PRODUCTS LABELED FOR RESEARCH USE ONLY OR INVESTIGATIONAL USE ONLY (Nov. 25, 2013), at 11 <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM376118.pdf> [<https://perma.cc/4BNR-FQAT>] (“User certification programs, where users certify that they will not use RUO/IUO products in a manner inconsistent with the labeling, would be viewed as one factor to consider when assessing [the totality of the circumstances surrounding the distribution and use of the product].”).

<sup>48</sup> 21 U.S.C. § 331(k).

The FDCA provides at least two ways in which a medical edible could be deemed adulterated. First, FDA could deem that a medical edible is adulterated if the product contains an unapproved food additive. The FDCA defines the term “food additive” to mean “any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food.”<sup>49</sup> Thus a food additive, in its broadest sense, is any substance that is added to food—a definition which undoubtedly includes the types of cannabis-derived extracts that are used as ingredients in the manufacture of medical edibles.

Because such ingredients meet the definition of a “food additive,” cannabis-derived extracts—regardless of their source or composition—must obtain premarket approval from FDA in order to be legally used as an ingredient in a food.<sup>50</sup> To obtain premarket approval, a firm must submit a food additive petition to FDA requesting that the agency issue a regulation allowing use of the additive.<sup>51</sup> Otherwise, the FDCA provides that any food containing an *unapproved* food additive is deemed to be unsafe and, thus, adulterated.<sup>52</sup> To date, no cannabis-derived extract has been approved as a food additive and thus many cannabis firms may currently be marketing medical edibles that would be deemed adulterated under the FDCA.

There is, however, an important exception to the requirement for premarket approval of a food additive—one which, in the absence of the drug exclusion rule,<sup>53</sup> would permit medical edibles to avoid FDA enforcement action under section 301(k) if the products were otherwise lawful. Under the FDCA, substances determined to be generally recognized as safe (GRAS) are excluded from the statutory definition of “food additive” and thus from the premarket approval requirement.<sup>54</sup> Instead, it is the firm seeking to use/market the substance (and not FDA) that makes the GRAS determination, although FDA has established a voluntary GRAS notification procedure for firms seeking to obtain the Agency’s position on these self-determinations.<sup>55</sup>

As applied to medical edibles, once a cannabis firm affirms that its cannabis-derived extract is GRAS, the extract could be used as an ingredient to manufacture medical edibles without the final product being deemed adulterated. Indeed, at least one firm has publicly disclosed that it has achieved self-affirmed GRAS status for its hemp-derived CBD oil.<sup>56</sup> The ultimate success of this approach, however, hinges on whether FDA decides to issue a regulation exempting hemp-derived CBD from the scope of the drug exclusion provision.<sup>57</sup>

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<sup>49</sup> 21 U.S.C. § 321(s).

<sup>50</sup> 21 U.S.C. §§ 348; 342(a)(2)(C).

<sup>51</sup> 21 U.S.C. § 348; 21 C.F.R., part 170.

<sup>52</sup> 21 U.S.C. §§ 348; 342(a)(2)(C).

<sup>53</sup> See *supra* Part I.B.1 for a discussion of the drug exclusion rule.

<sup>54</sup> 21 U.S.C. § 321(s).

<sup>55</sup> 21 C.F.R., part 170, subpart E.

<sup>56</sup> Press Release, CV Sciences, Inc. Achieves Industry’s First Hemp Extract GRAS Self-Affirmation (Sep. 10, 2018), <https://ir.cvsciences.com/press-releases/detail/85/cv-sciences-inc-achieves-industrys-first-hemp-extract> [<https://perma.cc/4FP7-Q6WJ>].

<sup>57</sup> See *infra* Part III.C.1.

In addition to being deemed adulterated for containing an unapproved food additive, FDA also could determine that a medical edible is adulterated if the product contains a pesticide chemical residue.<sup>58</sup> This risk is not merely hypothetical: analytical testing has detected the presence of pesticide chemical residues in many cannabis products and these levels appear to be even more concentrated in the types of cannabis-derived extracts commonly used to manufacture edibles.<sup>59</sup> Under the FDCA, a food is deemed adulterated if it bears or contains a pesticide chemical residue that is “unsafe.”<sup>60</sup> A pesticide chemical residue is deemed to be “unsafe” if it exceeds the limits of an established tolerance and no applicable exemption from the requirement of a tolerance is in effect.<sup>61</sup> Because cannabis is not currently considered to be a crop,<sup>62</sup> EPA has not registered any pesticides for use on cannabis or set any tolerances for pesticide residues that may remain on cannabis.<sup>63</sup> Accordingly, the presence of pesticide chemical residues in a cannabis-derived extract used to manufacture a medical edible may technically be sufficient for that product to be deemed adulterated under the FDCA.<sup>64</sup> The actual risk of FDA enforcement action, however, may depend on the potential risk to consumers—that is, the safety profile of the pesticide in question and the level of pesticide chemical residues observed in the product.

As was the case with the previously discussed provision of the FDCA, once FDA has determined that an edible is adulterated, it must still establish a nexus to interstate commerce for the product to fall within the Agency’s jurisdiction. Under the interstate commerce provision of section 301(k), the product must be “held for sale . . . after shipment in interstate commerce.”<sup>65</sup> FDA interprets this language to mean that the prerequisite connection to interstate commerce “is established when one or more components used in the manufacture of the product have crossed state lines . . . [a principle] known as ‘component jurisdiction.’”<sup>66</sup> And courts have upheld

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<sup>58</sup> 21 U.S.C. §§ 342(a)(2)(B) and (a)(1).

<sup>59</sup> See Cannabis Safety Institute, *Pesticide Use on Cannabis* (Jun. 2015) [hereinafter *Pesticide Use on Cannabis*], at 3, 10, <http://cannabissafetyinstitute.org/wp-content/uploads/2015/06/CSI-Pesticides-White-Paper.pdf> (finding that “pesticides can now be found on close to half of the Cannabis sold in Oregon dispensaries” and that “extremely high levels [of pesticides]” can be found in the Cannabis extracts used to make edibles); 60-Day Notice to TKO, <https://oag.ca.gov/system/files/prop65/notices/2017-01928.pdf> (alleging that a medical marijuana product (“Peanute [sic] Butter Cookie”) tested positive for myclobutanol).

<sup>60</sup> 21 U.S.C. § 342(a)(2)(B). A food could also be deemed adulterated if it bears or contains “any poisonous or deleterious substance”: (i) “which may render it injurious to health” (for an “added” substance); or (ii) which would “ordinarily render it injurious to health” (for a “not-added” substance). 21 U.S.C. § 342(a)(1) (emphasis added).

<sup>61</sup> 21 U.S.C. § 346a(a).

<sup>62</sup> See *Pesticide Use on Cannabis*, *supra* note 59, at 13.

<sup>63</sup> See Jenna Hardisty Bishop, *Weeding the Garden Of Pesticide Regulation: When The Marijuana Industry Goes Unchecked*, 65 DRAKE L. REV. 223, 226, 232-33 (2017).

<sup>64</sup> An edible might also be deemed adulterated under 21 U.S.C. § 342(a)(1) if it bears or contains certain levels of other types of contaminants, including heavy metals, residual solvents, microbial contaminants, or adventitious toxins (e.g., aflatoxins).

<sup>65</sup> 21 U.S.C. § 331(k).

<sup>66</sup> See, e.g., Current Good Manufacturing Practice in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements, 72 Fed. Reg. 34752, 34787 (Jun. 25, 2007) [hereinafter *CGMP for Dietary Supplements*] (citing *Baker v. United States*, 932 F.2d 813, 814–15 (9th Cir. 1991); *United States v. Article of Food \* \* \* Coco Rico, Inc.*, 752 F.2d 11, 14 (1st Cir. 1985); *United States v.*

the Agency's interpretation.<sup>67</sup> Thus the procurement of even a single ingredient from across state lines for purposes of manufacturing an edible—e.g., sugar, cacao, food coloring, etc.—may technically be sufficient to establish a nexus to interstate commerce.<sup>68</sup>

The key takeaway for cannabis firms is that FDA has the authority under section 301(k) to take enforcement action against medical edibles (as adulterated food) where such products *contain one or more ingredients that have crossed state lines*. This is the case even for products that are subsequently sold or distributed entirely within the confines of a single state.

## II. FDA'S MODIFIED APPROACH TO DEVELOPING BOTANICAL DRUGS

In light of the limited *legal* marketing options for medical edibles identified in Part I, this part presents a potential solution for cannabis firms seeking to market medical edibles in full compliance with the FDCA: the development of FDA-approved botanical drug products ("botanical drugs"). Though assuredly a more time- and cost-intensive option—particularly when compared to the prevailing non-FDA-regulated approach—gaining FDA approval as a botanical drug would offer significant benefits to a cannabis firm, including (i) the ability to legally market a cannabis-derived product containing THC and/or CBD (ii) for an approved disease indication and (iii) with nationwide distribution.

In addition, obtaining FDA's imprimatur as to the product's safety, efficacy, and quality could be valuable from a marketing perspective, as consumer survey data suggests that safety, efficacy, and quality are key criteria influencing cannabis purchasing decisions.<sup>69</sup> The botanical drug pathway could also result in product innovation and additional options for consumers. For example, while in practice only certain types of commonly marketed edibles may be suitable for botanical drug development (e.g., gummies), other less-commonly marketed dosage forms with potential therapeutic benefits—such as lozenges, chewing gum, and thin films—

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Dianovin Pharmaceuticals, Inc., 475 F.2d 100, 103 (1st Cir.), *cert. denied*, 414 U.S. 830 (1973); *United States v. Cassaro, Inc.*, 443 F.2d 153, 155–56 (1st Cir. 1971); *United States v. Detroit Vital Foods, Inc.*, 330 F.2d 78, 81–82 (6th Cir.), *cert. denied*, 379 U.S. 832 (1964); *United States v. Allbrook Freezing & Cold Storage, Inc.*, 194 F.2d 937, 939 (5th Cir. 1952); *United States v. Varela-Cruz*, 66 F.Supp.2d 274, 277–281 (D.P.R. 1999)) ("The interstate commerce prerequisite under section 301(k) . . . of the act is established when one or more components used in the manufacture of the product have crossed State lines. This principle is known as "component jurisdiction[.]"

<sup>67</sup> See, e.g., *Baker*, 932 F.2d, at 816 (holding that "wholly intrastate manufactures and sales of drugs are covered by [section 301(k)] as long as an ingredient used in the final product traveled in interstate commerce.").

<sup>68</sup> See *CGMP for Dietary Supplements*, *supra* note 66, at 34787 (citing *United States v. Miami Serpentarium Laboratories*, [1981–1982 Transfer Binder] Food Drug Cosm. L.Rep. (CCH) paragraph 38,164 at 38,930 (S.D. Fla. 1982); *United States v. 14 Cases \* \* \* Naremco*, 374 F.Supp. 922, 925 (W.D. Mo. 1974); *Detroit Vital Foods*, 330 F.2d at 81; *United States v. 40 Cases \* \* \* Pinocchio Brand \* \* \* Oil*, 289 F.2d 343, 346 (2d Cir.), *cert. denied*, 368 U.S. 831 (1961)) ("Nor does it matter that the interstate product component comprises only a minute part of the article . . . or if the interstate ingredient combines with others to form a different product.").

<sup>69</sup> Deloitte LLP, 2018 CANNABIS REPORT 11 (2018), <https://www2.deloitte.com/content/dam/Deloitte/ca/Documents/consulting/ca-cannabis-2018-report-en.PDF> [<https://perma.cc/AHP8-WLFN>].

could be further explored. Given these potential benefits, this part discusses the key features of FDA’s botanical drug approval framework and considers how this regulatory pathway might be used by cannabis firms to develop cannabis-derived botanical drugs.

### A. Overview of Botanical Drugs

Botanical drugs are not a defined category of products under FDA’s laws or regulations. FDA describes the term “botanicals” to mean products derived from “*plant materials*, algae, macroscopic fungi, and combinations thereof.”<sup>70</sup> Thus the term “botanical drug” simply means a “botanical” product that is intended to be used as “drug”—that is, a botanical “product intended for use in diagnosing, curing, mitigating, or treating disease.”<sup>71</sup> And the term “cannabis-derived botanical drug” means a “botanical drug” formulated with an extract derived the plant *Cannabis sativa* (“cannabis”), which generally would contain the phytocannabinoids THC and/or CBD, and possibly additional cannabis constituents such as other phytocannabinoids, terpenoids, and flavonoids.

It is important to note here that FDA excludes highly purified substances from its description of botanical drugs.<sup>72</sup> For this reason, FDA recently declined to review EPIDIOLEX as a botanical NDA because it was formulated with a highly purified preparation of CBD.<sup>73</sup> This was the case even though the preparation of CBD was a plant-derived extract from cannabis.<sup>74</sup> In contrast, a less-purified, cannabis-derived extract more closely resembling the natural spectrum of constituents present in the flowering tops of cannabis (e.g., phytocannabinoids and terpenoids) should generally be eligible for development as a botanical drug.<sup>75</sup>

Botanical drugs often have “unique features . . . [that] require special consideration during the review process,” such as “substantial prior human experience . . . [and a] lack of . . . distinct active constituent[s].”<sup>76</sup> Indeed, botanical drugs are typically complex, heterogeneous mixtures that contain “multiple chemical components” whose “biological activities are generally not well characterized.”<sup>77</sup>

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<sup>70</sup> FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: BOTANICAL DRUG DEVELOPMENT 2 (2016) [hereinafter BOTANICAL DRUG DEVELOPMENT GUIDANCE], <https://www.fda.gov/downloads/Drugs/Guidances/UCM458484.pdf> [<https://perma.cc/Z3EM-R3T3>].

<sup>71</sup> *Id.* at 3.

<sup>72</sup> *Id.* at 2. FDA’s description of botanicals also excludes “materials derived from botanical species that are *genetically modified* with the intention of producing a single molecular entity (e.g., by recombinant DNA technology or cloning).” (emphasis added).

<sup>73</sup> PRODUCT QUALITY REVIEW OF EPIDIOLEX, *supra* note 3, at 35.

<sup>74</sup> *Id.*

<sup>75</sup> See, e.g., FOOD & DRUG ADMIN., CDER, NDA 21-902, BOTANICAL REVIEW OF VEREGEN 2 (2006) [hereinafter VEREGEN BOTANICAL REVIEW], [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2006/021902s000\\_botanicalr.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/021902s000_botanicalr.pdf) [<https://perma.cc/H9PZ-U7VW>] (describing the botanical drug substance as “a *partially purified green tea extract with 85-95% catechins*” (emphasis added)).

<sup>76</sup> FOOD & DRUG ADMIN., OFFICE OF PHARMACEUTICAL QUALITY, MAPP 5210.9, REVIEW OF BOTANICAL DRUG PRODUCTS 1 (1st rev. ed. 2016) <https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm079939.pdf> [<https://perma.cc/JDS5-KMCG>].

<sup>77</sup> See Sau Lee, Acting Associate Director for Science & Botanical Review Team Leader, FDA, Presentation at the FDA/PQRI Conference on Advancing Product Quality: Botanical Drug Development and Quality Standards, at slide 5 (Oct. 6, 2015) [hereinafter 2015 FDA Botanical Review Team

Botanical drugs thus differ from chemically synthesized and purified drugs in that they “exhibit batch-to-batch variations” in their chemical composition due to “natural variability at the plant and [botanical] raw material levels.”<sup>78</sup> Due to these unique characteristics, FDA generally considers the entire botanical drug substance (e.g., the cannabis-derived extract) to be the active ingredient (API) of the botanical drug product, as opposed to any specific active constituent(s) present within that extract/mixture (e.g., THC and/or CBD).<sup>79</sup> In 2003, “CDER established a Botanical Review Team (BRT) to help manage the unique features and review issues associated with botanical drug products.”<sup>80</sup>

In 2016, FDA published a revised guidance document for industry on botanical drug development.<sup>81</sup> In the guidance document, FDA set forth a modified approach for drug development intended to facilitate the development of new therapies from botanical sources in two principle ways. First, the guidance provides incentives to encourage early-phase clinical trials by modifying the requirements for an IND.<sup>82</sup> Second, the guidance adopts a flexible “totality-of-evidence” approach to ensure therapeutic consistency of the marketing batches.<sup>83</sup> These incentives are intended to encourage sponsors to conduct clinical trials on products with extensive prior use in alternative medical practice and which otherwise may have been difficult (if not impossible) to develop under the conventional drug development approach.<sup>84</sup>

It must be emphasized, however, that the overall clinical efficacy and safety requirements needed to gain approval of a botanical drug are the same as those for any other drug product.<sup>85</sup>

### *B. Incentives to Encourage Early-Phase Clinical Trials*

Before being permitted to conduct clinical studies on an investigational drug under federal law (including a botanical drug), the product’s sponsor must submit an

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*Presentation*], <http://pqri.org/wp-content/uploads/2015/10/01-PQRI-Lee-Botanicals-20151.pdf> [<https://perma.cc/7G3W-87PM>].

<sup>78</sup> See *id.* at slide 6.

<sup>79</sup> BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 22 (the “entire botanical mixture generally is considered to be the active ingredient”). See also *2015 FDA Botanical Review Team Presentation*, *supra* note 77, at slide 7.

<sup>80</sup> MAPP 5210.9, *supra* note 76, at 2.

<sup>81</sup> See generally BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70.

<sup>82</sup> See Charles Wu, Food & Drug Admin., Presentation at EMA Seminar: Recent developments of marketing authorization of botanical drugs in the USA, at slide 6 (Sep. 14, 2017) [hereinafter *2017 FDA Botanical Review Team Presentation*], [https://www.bfarm.de/SharedDocs/Downloads/DE/Service/Termine-und-Veranstaltungen/dialogveranstaltungen/dialog\\_2017/170914/8\\_Wu.pdf?\\_\\_blob=publicationFile&v=2](https://www.bfarm.de/SharedDocs/Downloads/DE/Service/Termine-und-Veranstaltungen/dialogveranstaltungen/dialog_2017/170914/8_Wu.pdf?__blob=publicationFile&v=2) [<https://perma.cc/GBQ5-2H5Q>]; see also BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 5–6.

<sup>83</sup> See *2015 FDA Botanical Review Team Presentation*, *supra* note 77, at slide 15–16.

<sup>84</sup> VEREGEN BOTANICAL REVIEW, *supra* note 75, at 4–5 (noting that “[r]elatively little attention was paid to the requirements for approval of [a] botanical NDA at the time of drafting the [original Botanical Guidance] document, probably because few were sure that following the Guidance would lead to [a] successful NDA submission and it was hard to imag[in]e what a botanical NDA package would look like”).

<sup>85</sup> BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 28.

investigational new drug (IND) application establishing that the product will not expose humans to unreasonable risks.<sup>86</sup>

The amount of information that must be submitted in an IND is product-specific and depends on several factors, including the extent of prior human experience with the product and the product's known or suspected risks.<sup>87</sup> To encourage botanical drug development, FDA has incentivized sponsors to conduct early-phase clinical trials by (i) reducing the amount of required chemistry, manufacturing, and control (CMC) information and (ii) emphasizing prior human experience as a substitute for preclinical animal toxicology studies.<sup>88</sup>

### 1. *Early-Phase CMC Considerations*

FDA adopts a flexible approach to the CMC information required for INDs submitted for early-phase clinical trials investigating botanical drugs. In contrast to the conventional approach for purified chemical drugs, FDA provides that neither purification nor identification of the active ingredient(s) in a botanical drug is required.<sup>89</sup> This modified approach makes it *possible* for complex, naturally derived mixtures—such as cannabis-derived extracts—to gain FDA approval as new drugs whereas before only highly purified active constituents from such naturally derived mixtures would likely have been approvable under the Agency's conventional drug development approach. This flexibility, however, comes at a price: because botanical drugs are allowed to be approved as complex mixtures, ensuring the consistency of their quality becomes a more complicated issue.<sup>90</sup>

For most botanical drugs, FDA expects that detailed CMC information (e.g., data from comprehensive characterization of the drug substance) may not be warranted for early-phase clinical trials.<sup>91</sup> This may partially reflect the Agency's expectation that many botanical drugs will have a prior marketing history, such as use in a foreign market or as a dietary supplement in the United States.<sup>92</sup> Though submission of detailed CMC information may not be needed to begin early-phase clinical trials, preliminary CMC data must still be submitted prior to initiating Phase 3 studies, and FDA recommends that sponsors initiate such data collection during the earlier phases of clinical development.<sup>93</sup>

### 2. *Prior Human Experience with the Investigational Botanical Drug*

Under FDA's modified approach to the development of botanical drugs, information on prior human experience with the investigational botanical drug may,

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<sup>86</sup> Food & Drug Admin., *Investigational New Drug (IND) Application*, <https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm> [<https://perma.cc/6GHF-2427>] (last visited Dec. 17, 2018).

<sup>87</sup> BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 5–6.

<sup>88</sup> See 2017 FDA Botanical Review Team Presentation, *supra* note 82, at slide 6.

<sup>89</sup> VEREGEN BOTANICAL REVIEW, *supra* note 75, at 2; see also 2017 FDA Botanical Review Team Presentation, *supra* note 82, at slide 6.

<sup>90</sup> VEREGEN BOTANICAL REVIEW, *supra* note 75, at 2.

<sup>91</sup> BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 6.

<sup>92</sup> *Id.* at 6, 8.

<sup>93</sup> *Id.* at 6.



in some cases, substitute for preclinical animal toxicology studies.<sup>94</sup> This approach could allow an investigational botanical drug to enter Phase 1 and Phase 2 clinical trials more quickly. While standard toxicological studies in animals would still be needed to support late-phase clinical trials,<sup>95</sup> these studies could potentially be delayed until the early-phase clinical trials had begun, resulting in an abbreviated clinical development program.

As previously discussed, FDA expects that many investigational botanical drugs will have been previously marketed or tested in clinical studies, whether in the U.S. or a foreign market.<sup>96</sup> Thus, when relying on an investigational botanical drug's marketing history, FDA requests documentation of the annual sales volume of the product, an estimate of the size of the exposure population, and the rates of adverse effects.<sup>97</sup> Examples of relevant marketing history would include use of the investigational botanical drug as a dietary supplement (United States), an herbal medicine (Europe), or a traditional medicine (China).<sup>98</sup> However, for prior marketing history to be considered relevant, a sponsor must establish a "bridge" between such prior human experience with the botanical and the investigational botanical drug under development, by comparing, among other things, the identity of the two preparations and the doses at which they are intended to be used.<sup>99</sup>

For an investigational botanical drug containing an extract of cannabis, FDA would likely allow the proposed product to proceed to early-phase clinical trials without further preclinical toxicology testing *if the investigational botanical drug was currently lawfully marketed as a dietary supplement in the United States*.<sup>100</sup> However, as previously discussed, FDA's current position is that it is illegal to market a dietary supplement containing THC or CBD due to the drug exclusion rule and, thus, arguably no relevant prior human experience with a cannabis-derived dietary supplement in the United States currently exists.<sup>101</sup> For a botanical drug that is *not* currently lawfully marketed in the United States, FDA may still allow the product to proceed to early-phase clinical trials without additional preclinical toxicology testing if there is "extensive human experience" with the route of administration and the method in which the product is prepared, processed, and used.<sup>102</sup>

Regardless, FDA would require additional preclinical toxicology testing if the anticipated exposure in the proposed clinical trials exceeded that in the prior human

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<sup>94</sup> FOOD & DRUG ADMIN., CDER, NDA 202292, SECONDARY BOTANICAL REVIEW MEMORANDUM OF MYTESI (Aug. 8, 2012) [hereinafter MYTESI SECONDARY BOTANICAL REVIEW MEMORANDUM], at 2–3, [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2012/202292Orig1s000BotanicalR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202292Orig1s000BotanicalR.pdf) [<https://perma.cc/BP3S-33NN>]; see also BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 13.

<sup>95</sup> BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 18.

<sup>96</sup> *Id.* at 8 (noting that "[t]he use of botanical drugs in foreign markets may provide useful human experience").

<sup>97</sup> *Id.* at 7.

<sup>98</sup> 2015 FDA Botanical Review Team Presentation, *supra* note 77, at slide 6.

<sup>99</sup> BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 7–8.

<sup>100</sup> *Id.* at 13 (emphasis added).

<sup>101</sup> See *supra* Part I.B.1.

<sup>102</sup> BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 13.

uses.<sup>103</sup> FDA could also require additional toxicology testing if the investigational botanical drug is proposed to be used for a nontraditional route of administration.<sup>104</sup> For example, in the context of an investigational cannabis-derived botanical drug, this potentially could occur where a sponsor pursued a transmucosal or sublingual route of administration (e.g., by developing a lozenge or a thin film) but prior human experience with the cannabis-derived extract was limited to oral administration or inhalation.

### *C. Recommendations for Late-Phase Clinical Trials and NDA Submission*

One of FDA's primary concerns regarding late-phase clinical development and NDA submission of an investigational botanical drug is ensuring the therapeutic consistency of the marketing batches.<sup>105</sup> Because a conventional CMC approach based on analytical testing is generally insufficient for quality control of a botanical drug—given the complex nature of such naturally derived mixtures—FDA has adopted a flexible “totality-of-evidence” approach to ensure that the marketed product batches are therapeutically consistent with the product batches tested during clinical development.<sup>106</sup>

In essence, FDA's “totality-of-evidence” approach expands the “identity” of the botanical drug—which typically would be established by conventional CMC chemical testing—to include both “pre-CMC” steps (botanical raw material control) and “post-CMC” approaches (biological assays and clinical data).<sup>107</sup> FDA evaluates these different aspects of quality control (pre-CMC, CMC, and post-CMC) collectively, such that the amount of data needed from, e.g., botanical raw material control (pre-CMC) and/or a biological assay (post-CMC) would depend on the extent to which the different constituents (e.g., phytocannabinoids and terpenoids) in the investigational botanical drug substance (cannabis-derived extract) had been characterized by conventional CMC chemical testing.<sup>108</sup> For botanical NDAs, FDA recommends that applicants present an integrated evaluation of these quality data in a botanical-drug specific section of the NDA entitled “Assurance of Therapeutic Consistency” under Module 2.3.P.2 (Pharmaceutical Development).<sup>109</sup>

The remainder of this part discusses each of the three components of FDA's “totality-of-evidence” approach as applied to botanical drugs. Together these components provide an integrated framework for evaluating the quality of an investigational botanical drug at each step of the manufacturing process and clinical development, including at the stage of the botanical raw material (e.g., dried cannabis flower), the botanical drug substance (e.g., a partially purified cannabis-derived extract), and the botanical drug product (the finished dosage form, such as a lozenge).

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<sup>103</sup>*Id.*

<sup>104</sup>*Id.*

<sup>105</sup>*Id.* at 4.

<sup>106</sup>See 2015 FDA Botanical Review Team Presentation, *supra* note 77, at slide 15–16.

<sup>107</sup>MYTESI SECONDARY BOTANICAL REVIEW MEMORANDUM, *supra* note 94, at 2–3; see also BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 4.

<sup>108</sup>BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 29.

<sup>109</sup>*Id.*

### 1. Conventional CMC Approach

As complex, naturally derived mixtures, botanical drug substances can rarely have CMC specifications as precise as those of pure chemical drugs.<sup>110</sup> Although the complexity of botanical drugs limits the utility of the conventional CMC approach, analytical characterization of the botanical drug substance (e.g., a partially purified extract of cannabis) remains the most important approach to ensuring quality and therapeutic consistency of a botanical drug.<sup>111</sup> And, in practice, analyses using multiple analytical chemical techniques should be conducted as extensively as the technology and practical considerations allow.<sup>112</sup>

Specifically, FDA recommends that quality control tests be performed on each batch of the botanical drug substance (cannabis-derived extract) and include, as relevant here, tests for the following attributes: (i) strength (by dry weight); (ii) chemical identification and quantification of active constituents (if known) or chemical constituents; (iii) biological assay (if the active constituents are not known or quantifiable); and (iv) tests for residual pesticides, heavy metals, microbiological contamination, and adventitious toxins (e.g., aflatoxins).<sup>113</sup> FDA also recommends analytical quantification of other classes of compounds that contribute to the mass balance of the botanical drug substance (cannabis-derived extract), such as lipids, amino acids, carbohydrates, and vitamins.<sup>114</sup> In addition to quality control tests, FDA recommends implementing manufacturing process controls.<sup>115</sup>

Consistent with the rationale underlying the Agency's totality-of-evidence approach, data collected on the typical profile of cannabis constituents indicates that a minimally purified extract derived from cannabis would indeed be a complex mixture, as research has identified (in total) around 150 cannabinoids, 140 terpenoids, and 20 flavonoids in cannabis.<sup>116</sup> Thus, as in the case of other botanicals, it may not be feasible (or practical) to completely characterize cannabis-derived extracts by chemical testing as would typically be done under the conventional CMC approach. Nonetheless, an adequate biochemical profile for a cannabis-derived extract might be obtained by monitoring only a subset of the constituents—e.g., the nine cannabinoids known to be pharmacologically active along with the 17 most

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<sup>110</sup>MYTESI SECONDARY BOTANICAL REVIEW MEMORANDUM, *supra* note 94, at 4.

<sup>111</sup>*Id.*

<sup>112</sup>*Id.*

<sup>113</sup>BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 10–11.

<sup>114</sup>*Id.* at 26. Although not related to the development of a cannabis-derived botanical drug, a similar approach was recently taken to characterize an extract of hemp. Tennille K. Marx et al., *An Assessment of the Genotoxicity and Subchronic Toxicity of a Supercritical Fluid Extract of the Aerial Parts of Hemp*, JOURNAL OF TOXICOLOGY 2 (June 7, 2018) (“Edible fatty acids comprise 61% of this concentrated extract, while phytocannabinoids are present at 26% (of this, approximately 96% is CBD and less than 1% is THC); the remaining 13% include fatty alkanes, plant sterols, triterpenes, and tocopherols and thus approximately 100% of the extract constituents are accounted for.”).

<sup>115</sup>*See* BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 10.

<sup>116</sup>Matthew W. Giese et al., *Development and Validation of a Reliable and Robust Method for the Analysis of Cannabinoids and Terpenes in Cannabis*, 98 JOURNAL OF AOAC INTERNATIONAL 1503 (July 2015) [hereinafter *Analytical Method for Cannabinoids and Terpenes*], <https://phytofacts.info/resources/methods.pdf> [<https://perma.cc/QA9Z-UNXZ>]; Christelle M. Andre et al., *Cannabis sativa: The Plant of the Thousand and One Molecules*, 7 FRONT. PLANT SCI. 6 (Feb. 4, 2016), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4740396/> [<https://perma.cc/K5SL-DKL3>].

common terpenoids.<sup>117</sup> Monitoring this characteristic profile of marker constituents could be useful when performing quality control tests on batches of the botanical drug substance (conventional CMC) and, as discussed below, on the botanical raw material itself (pre-CMC control).

## 2. *Pre-CMC Control*

The pre-CMC component of the totality-of-evidence approach extends quality control upstream in the manufacturing process to include the botanical raw material (e.g., dried cannabis flower) with the goal of reducing the variability at the plant and raw material levels.<sup>118</sup> FDA recommends several steps a botanical drug manufacturer should take to control the botanical raw material. These include (i) implementation of Good Agricultural and Collection Practices (GACP) to control the growing and harvesting of medicinal plants and (ii) characterization of the botanical raw material by relying on a combination of chemical identification and authentication approaches.<sup>119</sup> With respect to the second recommendation, chemical identification of the botanical raw material could rely on similar types of chemical testing to those used to characterize the botanical drug substance under the conventional CMC approach, whereas authentication might be accomplished by DNA fingerprinting.<sup>120</sup>

Also consistent with the rationale underlying the Agency's totality-of-evidence approach, the content of cannabis constituents (e.g., phytocannabinoids and terpenoids) in cannabis-derived botanical raw material (dried cannabis flower) has been found to be variable, even across plants tested from the same lot.<sup>121</sup> For a cannabis-derived botanical drug, such variability in the botanical raw material may be particularly important to control where the botanical drug substance is intended to be a minimally purified extract—such as a “whole plant” or “broad-spectrum” cannabis extract—because the composition of the finished extract will more closely approximate the actual composition of the botanical raw material.

When compared to other firms developing botanical drugs, at least some cannabis firms may be particularly well-positioned to implement the recommended pre-CMC controls given their prior experience with consistently producing high-quality cannabis at commercial scale for consumer use and because the pre-CMC controls are generally consistent with certain industry best practices. Indeed, sophisticated cannabis operations are already embracing the use of comprehensive analytical testing to identify and characterize their products. For example, strain identification can now be accomplished by genetic testing,<sup>122</sup> and chemovars can be identified by their biochemical profiles (or “fingerprints”).<sup>123</sup> Moreover, newer approaches to

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<sup>117</sup>See *Analytical Method for Cannabinoids and Terpenes*, *supra* note 116.

<sup>118</sup>See 2015 FDA Botanical Review Team Presentation, *supra* note 77, at slide 19.

<sup>119</sup>BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 17.

<sup>120</sup>*Id.*

<sup>121</sup>See *Analytical Method for Cannabinoids and Terpenes*, *supra* note 116, at 1520.

<sup>122</sup>See e.g., PHYLOS BIOSCIENCE, *Genotype Test: Genetic identification and insights for hemp and cannabis*, <https://phylos.bio/genotype-test> [<https://perma.cc/AL5Q-U4JT>] (last visited Dec. 17, 2018); see also MEDICINAL GENOMICS, *StrainSEEK® Strain Identification and Registration*, <https://www.medicinalgenomics.com/strainseek-strain-identification-and-registration/> [<https://perma.cc/2TFP-TGBZ>] (last visited Dec. 17, 2018).

<sup>123</sup>See e.g., NAPRO RESEARCH, *PhytoFacts®*, [https://phytofacts.info/phytofacts/test/PGND-150323\\_104](https://phytofacts.info/phytofacts/test/PGND-150323_104) [<https://perma.cc/9XPM-YG5M>] (last visited Dec. 17, 2018).

authentication and supply chain traceability have been developed, including the use of molecular tagging coupled with blockchain technology.<sup>124</sup> Thus cannabis firms with sophisticated grow operations are expected to be well-positioned to implement the types of pre-CMC controls required for the production of pharmaceutical-grade botanical raw material (dried cannabis flower) such as that which is needed for the manufacture of cannabis-derived botanical drugs.

### 3. *Post-CMC Approaches*

Like the pre-CMC controls, the post-CMC approaches are also intended to supplement the conventional CMC approach by providing additional quality information, although here the focus is on the botanical drug substance (cannabis-derived extract) and the botanical drug product (the finished dosage form, such as a lozenge)—and not the botanical raw material (dried cannabis flower). The two approaches to post-CMC quality control recommended by FDA are: (i) the use of clinically relevant biological assays (bioassays) and (ii) the collection of certain clinical data (dose-response data and multiple-batch data).

Bioassays are “an important method for measuring a botanical drug’s potency and activity to ensure quality[.]”<sup>125</sup> In cases where chemical testing alone may not be sufficient to ensure quality—and thus therapeutic consistency—FDA recommends that applicants use a bioassay in the release specifications and stability protocols for the botanical drug substance (cannabis-derived extract) and/or the botanical drug product (e.g., a lozenge).<sup>126</sup> FDA also suggests that bioassays could be used in bridging studies—both during botanical drug development and when making post-approval manufacturing changes—to determine whether different batches of a botanical drug substance (cannabis-derived extract) are similar.<sup>127</sup> Where the same botanical drug is intended for multiple indications (e.g., chronic pain and PTSD), FDA recommends that the applicant consult with the Agency regarding whether it is necessary to develop a separate bioassay for each indication.<sup>128</sup>

In addition, FDA recommends that bioassays be closely related to the drug’s presumed mechanism of action (MOA).<sup>129</sup> This could potentially present an obstacle in the context of a cannabis-derived botanical drug as the MOA(s) for complex cannabis-derived extracts—and even for particular constituent cannabinoids such as CBD—is not fully defined.<sup>130</sup> In contrast, for botanical drugs with an established

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<sup>124</sup>Press Release, Applied DNA Sciences, Applied DNA Awarded Multi-Year Contract to Develop Molecular Tracking Systems for Legal Cannabis Worldwide (Jan. 25, 2018), <https://www.businesswire.com/news/home/20180125005100/en/Applied-DNA-Awarded-Multi-Year-Contract-Develop-Molecular> [<https://perma.cc/RD3S-VC3H>].

<sup>125</sup>2017 FDA Botanical Review Team Presentation, *supra* note 82, at slide 24.

<sup>126</sup>See BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 25.

<sup>127</sup>*Id.* at 16; see also 2015 FDA Botanical Review Team Presentation, *supra* note 77, at slide 19.

<sup>128</sup>BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 25.

<sup>129</sup>*Id.*

<sup>130</sup>See, e.g., FOOD & DRUG ADMIN., FDA BRIEFING DOCUMENT, PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE MEETING (NDA 210365 (CANNABIDIOL)) 6 (Apr. 19, 2018), <https://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/peripheralandcentralnervoussystemdrugsadvisorycommittee/ucm604736.pdf> [<https://perma.cc/G7RJ-JFPA>] (“The exact mechanism of the anticonvulsant effect of CBD is unknown, but does not appear to involve an interaction with cannabinoid receptors.”).

MOA—as was the case with the FDA-approved botanical drug MYTESI—a clinically relevant bioassay could play an important role in approval.<sup>131</sup> Nonetheless, cannabis researchers have developed *in vitro* bioassays for use in evaluating the activity of cannabinoids and such assays potentially could provide useful information regarding the quality of cannabis-derived extracts.<sup>132</sup> Indeed, FDA has indicated that “other less [clinically] relevant bioassays” may also be considered and evaluated in individual cases.<sup>133</sup>

With respect to clinical considerations, “Phase 3 clinical [trials] of botanical drugs have the same purpose as Phase 3 clinical [trials] of nonbotanical drugs” (i.e., to establish whether the product provides a treatment benefit for the studied indication and to monitor for adverse reactions).<sup>134</sup> However, on account of variations in the chemical composition of different batches of a botanical drug substance (cannabis-derived extract), FDA recommends that sponsors generate evidence that the observed variations in the batches do not cause any meaningful differences in the botanical drug product’s therapeutic effect.<sup>135</sup> One approach FDA recommends is “to use *multiple* batches of the botanical drug product (i.e., each manufactured by using a *different* batch of the drug substance) in the Phase 3 clinical studies and to examine the clinical effects across these drug product batches” (emphasis added).<sup>136</sup> The objective of this approach is “to quantify potential heterogeneity in clinical outcomes for subjects who receive different batches in the study”—an approach analogous to other types of subgroup analyses.<sup>137</sup> An observed “lack of significant interaction” between the clinical outcome and the different batches would “provide confidence” that the botanical drug’s therapeutic effects would be consistent across the marketed batches.<sup>138</sup>

Another approach FDA recommends “to show that [the] clinical response to a botanical drug will not be affected by variations” in the chemical composition of different batches is for the sponsor to generate dose-response data.<sup>139</sup> The objective of this approach is “to demonstrate that the drug’s effect on clinical outcomes is not sensitive to dose, while also demonstrating that the studied doses are more effective than placebo or control, or not inferior to active treatment.”<sup>140</sup>

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<sup>131</sup> See, e.g., FOOD & DRUG ADMIN., CDER, NDA 202292, SUMMARY REVIEW OF MYTESI 3 (Dec. 14, 2012), [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2012/202292Orig1s000SumR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202292Orig1s000SumR.pdf) [<https://perma.cc/PS54-4MXB>] (“The current application decision is approval in light of the establishment of final details of a suitable clinically relevant bioassay that had previously hindered the initial approval of this application.”).

<sup>132</sup> See, e.g., Afeef S. Husni, *Evaluation of Phytocannabinoids from High-Potency Cannabis Sativa using In Vitro Bioassays to Determine Structure–Activity Relationships for Cannabinoid Receptor 1 and Cannabinoid Receptor 2*, 23 MED CHEM RES. 4295–4300 (Sept. 1, 2014), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4235762/> [<https://perma.cc/GP23-M68R>].

<sup>133</sup> BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 29.

<sup>134</sup> *Id.* at 20.

<sup>135</sup> *Id.* at 15–16.

<sup>136</sup> *Id.* at 16.

<sup>137</sup> *Id.* at 21.

<sup>138</sup> 2017 FDA Botanical Review Team Presentation, *supra* note 82, at slide 25.

<sup>139</sup> BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 21.

<sup>140</sup> *Id.*

If the clinical effects are not sensitive to dose (but are still superior to the placebo control group), it can reasonably be assumed that any variations within the established specification will probably not affect the therapeutic consistency of the marketed batches.<sup>141</sup> However, it is unclear whether this approach would be useful in the context of a cannabis-derived botanical drug where interpreting the dose-response may be complex and vary by setting.<sup>142</sup>

### III. COMPETITIVE LANDSCAPE FOR CANNABIS-DERIVED BOTANICAL DRUGS

The conclusion from Part II is that FDA's modified approach to the development of botanical drugs could make the approval of a cannabis-derived botanical drug *possible* whereas approval may have been precluded under the Agency's conventional drug development approach. However, the mere possibility of gaining FDA approval as a cannabis-derived botanical drug does not, of course, mean that this regulatory pathway represents an economically viable strategy for the development of medical edibles. That determination instead would be a function of the time and costs associated with developing the drug as well as the potential landscape of products against which the drug would have to compete following FDA approval.

To further assess the question of economic viability, this part begins by discussing the estimated time and cost associated with developing a cannabis-derived botanical drug. This part next discusses the potential regulatory hurdles a competitor may face when pursuing FDA approval of a generic version of the original cannabis-derived botanical drug. This part concludes with a discussion of potential regulatory and legislative actions that could influence the competitive landscape of products against which a cannabis-derived botanical drug would compete.

#### A. *Projected Time and Cost Associated with Developing a Cannabis-Derived Botanical Drug*

It takes at least 10 years on average to take a new drug from the drug discovery stage through FDA approval.<sup>143</sup> However, the length of the development program is

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<sup>141</sup> 2017 FDA Botanical Review Team Presentation, *supra* note 82, at slide 25.

<sup>142</sup> See Med & Healthcare Prod. Regulatory Agency, *Public Assessment Report Decentralised Procedure of Sativex Oral Mucosal Spray* at 19, <http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con084961.pdf> [<https://perma.cc/FAX3-EE4H>] (observing that "there is no dose response relationship in the occurrence of adverse events or efficacy"); see also Vandrey et al., *supra* note 12, at 83 ("Subjective drug and cognitive performance effects were generally dose dependent, peaked at 1.5-3 h post-administration, and lasted 6–8 h. Whole blood cannabinoid concentrations were significantly correlated with subjective drug effects.").

<sup>143</sup> See PhRMA, *Research & Development: Clinical Trials*, <https://www.phrma.org/advocacy/research-development/clinical-trials> [<https://perma.cc/ZZU2-EQXC>] ("From drug discovery through FDA approval, developing a new medicine takes at least 10 years on average and costs an average of \$2.6 billion.") (last visited Feb. 11, 2019); see Bruce Booth, *A Billion Here, A Billion There: The Cost Of Making A Drug Revisited*, LIFE SCI VC, <https://lifescivc.com/2014/11/a-billion-here-a-billion-there-the-cost-of-making-a-drug-revisited/> [<https://perma.cc/GM6J-XRZ6>] (reporting that the average duration of a new drug development program is 10.9 years from discovery through registration based on inputs used by the Tufts CSDD 2014 Model) (last visited Feb. 11, 2019).

likely to be shorter in the case of a cannabis-derived botanical drug for several reasons. First, a firm developing a cannabis-derived botanical drug is expected to benefit from publicly available data and information from prior studies on cannabis and cannabis-related compounds. By eliminating parts of the drug discovery and nonclinical phases of development, this preexisting information could reduce the time required to develop a cannabis-derived botanical drug to approximately 8.5 years—1.5 years for the preclinical stage,<sup>144</sup> six years for the clinical trials,<sup>145</sup> and approximately twelve months for FDA review of the new drug application (NDA).<sup>146</sup>

Second, FDA's modified approach to developing botanical drugs could further shorten the development timeline if the required preclinical animal toxicology studies could be conducted concurrently with the early stage clinical trials (i.e., the Phase 1 and Phase 2 trials). While this may not be possible for all cannabis-derived botanical drugs (as discussed below), this incentive could further reduce the development timeline to approximately seven years by eliminating the preclinical stage.<sup>147</sup> However, the actual length of the drug development program for a given cannabis-derived botanical drug would also depend on the particular indication that was pursued. For example, the timeline might be shorter for a sleep-related indication (with an average clinical testing period of 4.5 years) but longer for a pain indication (with an average clinical testing period of 6.4 years).<sup>148</sup> Thus it is reasonable to project that it could take between six and eight years to develop a cannabis-derived botanical drug.<sup>149</sup>

In terms of cost, it is estimated that the average cost of developing and gaining FDA approval for a new drug is around \$2.6 billion.<sup>150</sup> This figure, however, includes, among other things, the cost associated with paying for the development of other drugs that failed to demonstrate safety or efficacy in clinical trials.<sup>151</sup> For a

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<sup>144</sup>See Booth, *supra* note 143 (reporting that the average duration of the preclinical phase of drug development is 1.5 years based on inputs used by the Tufts CSDD 2014 Model).

<sup>145</sup>Erika Lietzan, *The Drug Innovation Paradox*, 83 MO. L. REV. 88 (2018).

<sup>146</sup>See FOOD & DRUG ADMIN., PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022 4, <https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM511438.pdf> [<https://perma.cc/K7MT-NXM6>] (committing to review ninety percent of standard NME NDAs within ten months of the sixty day filing date).

<sup>147</sup>See Booth *supra* note 143.

<sup>148</sup>Lietzan, *supra* note 145, at 100.

<sup>149</sup>To date, FDA has approved only two products as botanical drugs: VEREGEN (2006) and MYTESI (2012). Based on this limited experience, it is difficult to draw meaningful conclusions about the average time and cost that might be associated with the development of a cannabis-derived botanical drug. However, using the regulatory review period calculated for patent term extension and the preclinical stage input used in this article, it is estimated that the development of VEREGEN took about ten years, while MYTESI—which experienced several challenges and product changes during development—took about twenty-three years.

<sup>150</sup>Tufts Center for the Study of Drug Development, *Background: How the Tufts Center for the Study of Drug Development Pegged the Cost of a New Drug at \$2.6 Billion* (2014), [https://static1.squarespace.com/static/5a9eb0c8e2ccd1158288d8dc/t/5ac66aeb0e2e7280a329b092/1522952939855/cost\\_study\\_background.pdf](https://static1.squarespace.com/static/5a9eb0c8e2ccd1158288d8dc/t/5ac66aeb0e2e7280a329b092/1522952939855/cost_study_background.pdf) [<https://perma.cc/EHM7-7MTP>].

<sup>151</sup>See Matthew Herper, *The Cost Of Developing Drugs Is Insane. That Paper That Says Otherwise Is Insanely Bad*, FORBES (Oct 16, 2017), <https://www.forbes.com/sites/matthewherper/2017/10/16/the-cost-of-developing-drugs-is-insane-a-paper-that-argued-otherwise-was-insanely-bad/#3bc010272d45> [<https://perma.cc/QYL3-8G3U>] (“The \$2.7 billion figure includes the cost not only of these [other drug



company with only a single drug product, it has been estimated that the median cost of developing a new drug is around \$350 million.<sup>152</sup> Moreover, because cannabis and cannabis-related compounds have been previously studied, it might be expected that the actual cost of developing a cannabis-derived botanical drug would more closely approximate the direct costs associated with the preclinical and clinical phases of the drug development program. Thus, for more cost-intensive therapeutic areas, such as pain, the cost of gaining FDA approval is estimated to be around \$135 million—\$10 million for the preclinical studies<sup>153</sup> and \$125 million for the clinical trials (assuming two Phase 3 trials would be required).<sup>154</sup> In contrast, for the central nervous system therapeutic area, the cost could be around \$65 million.<sup>155</sup> Other estimates suggest that the cost of botanical drug development could be \$80 million<sup>156</sup> or \$100 million.<sup>157</sup> Thus it is reasonable to project that it could cost around \$100 million to develop a new cannabis-derived botanical drug.

While the time and cost associated with developing a cannabis-derived botanical drug appear relatively attractive when compared with those associated with developing a conventional new drug, they likely would still be cost-prohibitive for many cannabis firms. That said, this regulatory pathway could be attractive for cannabis firms that decide to partner with pharmaceutical firms, although anticipated competition from other cannabis product may ultimately discourage pharmaceutical firms from entering the space. Thus, FDA may need to take additional steps within the Agency's existing authority to ensure the economic viability of this regulatory option.

One step FDA could consider taking is to adopt a more flexible view of prior human experience with cannabis-derived products in the United States when determining the amount of preclinical data required to support early phase clinical

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development] failures, but also of not putting the money spent on them into something that would give a more reliable return.") (last visited Feb. 11, 2019).

<sup>152</sup>See Matthew Herper, *The Cost Of Creating A New Drug Now \$5 Billion, Pushing Big Pharma To Change*, FORBES (Aug 11, 2013), <https://www.forbes.com/sites/matthewherper/2013/08/11/how-the-staggering-cost-of-inventing-new-drugs-is-shaping-the-future-of-medicine/#f95d4dc13c33> [https://perma.cc/QT33-EXTA] ("A company hoping to get a single drug to market can expect to have spent \$350 million before the medicine is available for sale.") (last visited Feb. 11, 2019).

<sup>153</sup>See Booth, *supra* note 143 (reporting that the average cost per preclinical phase is \$10 million based on inputs used by the Tufts CSDD 2014 Model).

<sup>154</sup>See DEP'T OF HEALTH AND HUMAN SERV., ASSISTANT SECRETARY FOR PLANNING AND EVALUATION (ASPE), EXAMINATION OF CLINICAL TRIAL COSTS AND BARRIERS FOR DRUG DEVELOPMENT (Jul. 25, 2014), <https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development> [https://perma.cc/3S2J-ZJ2M] (reporting that the total per-study costs for the pain and anesthesia therapeutic area are: \$1.4 million (Phase 1), \$17.0 million (Phase 2), and \$52.9 million (Phase 3)).

<sup>155</sup>*Id.* (reporting that the total per-study costs for the central nervous system therapeutic area are: \$3.9 million (Phase 1), \$13.9 million (Phase 2), and \$19.2 million (Phase 3)).

<sup>156</sup>Kevin Kinsella, *Global Markets for Botanical and Plant-Derived Drugs to Reach \$35.4 Billion by 2017*, BCC RESEARCH, <http://blog.bccresearch.com/global-markets-for-botanical-and-plant-derived-drugs-to-reach-35.4-billion-by-2017> [https://perma.cc/UK2Q-Y6NA] ("In contrast to traditional drug development, botanical drug development is approximately \$80 million over 10 years with potential average sales of \$1 billion.") (last visited Feb. 11, 2019).

<sup>157</sup>Coco Feng, *U.S. Approval Offers Shot in the Arm to China's Traditional Medicine*, CAIXIN (Jan. 26, 2018), [https://www.wangvisioninstitute.com/forms/drwang\\_caixin\\_jan2018.pdf](https://www.wangvisioninstitute.com/forms/drwang_caixin_jan2018.pdf) [https://perma.cc/TUF7-AMKW].

trials.<sup>158</sup> Under the Agency's current approach, early-phase clinical trials may be allowed to proceed without further preclinical pharmacological/toxicological testing where an investigational botanical drug is currently marketed in the United States as a dietary supplement *and* such marketing is lawful.<sup>159</sup> Because the marketing of cannabis-derived dietary supplements remains illegal under federal law, FDA is unlikely to attribute *any* weight to prior human experience with such products when determining the amount of preclinical data required to support early-phase clinical trials of investigational cannabis-derived botanical drugs. This position could increase the time associated with the development of cannabis-derived botanical drugs by requiring preclinical studies to be conducted prior to—instead of in tandem with—the early-phase clinical trials.

However, there are arguably scenarios where the Agency should attribute at least some weight to prior human experience with unlawfully marketed cannabis-derived products. One such scenario is where a cannabis firm seeks to develop a cannabis-derived botanical drug using the same cannabis-derived extract that it currently legally markets in medical edibles or cannabis-derived dietary supplements under state law. This may especially be true where the firm's products are legally marketed within states with comprehensive cannabis laws and regulations and where the firm has conducted the types of safety studies FDA generally recommends for dietary supplements.<sup>160</sup> In this scenario, the prior human experience with consuming the cannabis-derived extract may be relevant to the Agency's IND safety determination.

### *B. Competition from Generic Cannabis-Derived Botanical Drugs*

Because it could take six to eight years and \$100 million to develop a cannabis-derived botanical drug, the projected period of exclusive marketing without generic competition could be a key determinant of a firm's ability to recoup its drug development costs and to earn a profit.

In order to gain FDA approval as a fully substitutable, generic version of a drug (including a botanical drug), a generic manufacturer must submit an abbreviated new drug application (ANDA) to FDA under section 505(j) of the FDCA.<sup>161</sup> An ANDA relies on the Agency's previous findings of safety and effectiveness for the original brand-name drug and, as a result, may be approved without submission of the same type and extent of information as required when submitting a stand-alone new drug application (NDA) under section 505(b)(1) of the FDCA.<sup>162</sup> Thus section 505(j) of the FDCA, together with its implementing regulations, generally requires that an ANDA contain information to demonstrate that the proposed generic drug and the applicable brand-name drug are the "same" with respect to active ingredient(s),

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<sup>158</sup> See BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 13.

<sup>159</sup> *Id.*

<sup>160</sup> See generally FOOD & DRUG ADMIN., DRAFT GUIDANCE: DIETARY SUPPLEMENTS: NEW DIETARY INGREDIENT NOTIFICATIONS AND RELATED ISSUES 67-87 (Aug. 2016) [hereinafter NDIN DRAFT GUIDANCE].

<sup>161</sup> 21 U.S.C. § 355(j).

<sup>162</sup> FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: NDA SUBMISSIONS—CONTENT AND FORMAT 2 (Sep. 2018).

dosage form, route of administration, strength, previously approved conditions of use, and—with certain exceptions—labeling.<sup>163</sup>

Accordingly, a manufacturer seeking approval of a generic version of a cannabis-derived botanical drug through the ANDA approval pathway would have to demonstrate, among other things, that its product contains the “same” active ingredient as the previously approved cannabis-derived botanical drug whose data it intends to rely on for approval. Thus, if FDA determined that the proposed generic contained a *different* active ingredient than the originally approved cannabis-derived botanical drug, the generic manufacturer may need to submit a stand-alone 505(b)(1) NDA—a significantly longer and more costly approval process because additional clinical data would need to be generated to support the product’s safety and efficacy. In the present context, the key question that arises concerns the identity of the active ingredient in a cannabis-derived botanical drug—more specifically, whether the active ingredient is one or more of the individual, active constituents present in the cannabis-derived extract (e.g., THC and/or CBD), or whether it is the entire cannabis-derived extract itself (i.e., all active and inactive ingredients)?

FDA’s current position appears to be that the entire botanical drug mixture is *generally* considered to be the active ingredient.<sup>164</sup> Thus, as applied to a cannabis-derived botanical drug, this likely means that the entire cannabis-derived extract would be considered the drug’s active ingredient and not a particular active constituent of the extract such as THC and/or CBD. Under this approach, each subsequent cannabis-derived botanical drug—assuming it contained a cannabis-derived extract with a somewhat different composition<sup>165</sup>—would be considered to contain a different active ingredient than the original cannabis-derived botanical drug and, thus, would not be approvable through the ANDA pathway.<sup>166</sup> In these situations, generic applicants would likely consider seeking approval through the 505(b)(2) NDA pathway—an alternative abbreviated-approval pathway that is a hybrid of the ANDA and 505(b)(1) NDA pathways.<sup>167</sup>

On the other hand, it should be noted that FDA has broad discretion to determine whether a proposed generic’s active ingredient is the same as the active ingredient in

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<sup>163</sup>*Id.*

<sup>164</sup>BOTANICAL DRUG DEVELOPMENT GUIDANCE, *supra* note 70, at 22.

<sup>165</sup>The biochemical profile of a cannabis-derived extract could vary because different cultivated varieties (“cultivars”) were used as the botanical raw material and/or because different extraction processes were used to produce the extract. Indeed, should cannabis-derived botanical drugs prove economically viable, it may be the case that a variety of cannabis-derived extracts with different therapeutic properties are produced by using conventional selective breeding approaches to generate a diverse spectrum of cultivars (botanical raw materials) with different biochemical profiles. And the different properties of these extracts could enable some degree of product differentiation.

<sup>166</sup>An application for a generic botanical drug may also not be approvable through the ANDA pathway if there are unjustified differences in the proposed generic’s formulation (i.e., the identity and quantity of all active and inactive ingredients in the product). *See* FDA, DRAFT GUIDANCE: DETERMINING WHETHER TO SUBMIT AN ANDA OR A 505(B)(2) APPLICATION 8–9 (Oct. 2017) [hereinafter ANDA AND 505(B)(2) DRAFT GUIDANCE], <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM579751.pdf> [<https://perma.cc/U7CQ-5PTU>]. This could occur, for example, where there are differences in the identity and quantity of inactive ingredients in the proposed generic (e.g., certain inactive phytocannabinoids and/or terpenoids), and the applicant fails to demonstrate that these differences do not adversely affect the safety and effectiveness of the proposed generic. *Id.*

<sup>167</sup>This Article reserves a more fulsome discussion of the abbreviated approval pathway described in section 505(b)(2) of the FDCA [21 U.S.C. § 355(b)(2)] for another occasion.

the original brand-name drug.<sup>168</sup> For example, in the context of cannabis-derived botanical drugs, FDA could adopt a flexible, “totality-of-evidence” approach to evaluating the sameness of a proposed generic’s active ingredient (cannabis-derived extract) as the Agency previously has done when evaluating generic versions of other complex active ingredients.<sup>169</sup> Indeed, the totality-of-evidence approach already set forth in the *Botanical Drug Development Guidance* could be a useful starting point for establishing criteria to compare the similarity of the active ingredients contained in different botanical drugs, similar to how this approach is currently used to compare the similarity of different manufacturing batches of the same botanical drug substance (cannabis-derived extract) during product development. Moreover, FDA could consider formalizing the criteria for demonstrating active ingredient sameness in a product-specific guidance for cannabis-derived botanical drugs as the Agency previously has done for other products with complex active ingredients.<sup>170</sup>

However, it remains unclear how the criteria in any such approach would be weighed in specific situations. For example, it is possible that two cannabis-derived botanical drugs could appear to have the “same” activity when evaluated with a clinically relevant *in vitro* or *in vivo* bioassay, yet appear quite “different” when the botanical raw materials (dried cannabis flowers) and botanical drug substances (cannabis-derived extracts) were chemically characterized.<sup>171</sup> In this situation, clinical data directly comparing the two products might be required to resolve the conflicting criteria.<sup>172</sup> And where the clinical data demonstrated that the two botanical drugs were the “same,” FDA could decide to approve the proposed generic product under the ANDA pathway.

Nonetheless, at least in the near-term, it seems more likely that any subsequently filed cannabis-derived botanical drug will be considered to contain a different active ingredient than the original botanical drug and, thus, generic entry through the ANDA pathway would be blocked. If so, the original cannabis-derived botanical drug could potentially benefit from an extended period of exclusive marketing without competition from a fully substitutable generic drug under state pharmacy law<sup>173</sup>—conditions which could help the firm recoup its drug development costs and

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<sup>168</sup>ANDA AND 505(B)(2) DRAFT GUIDANCE, *supra* note 166, at 8.

<sup>169</sup>*See, e.g.,* Sau Lee et al., *Scientific considerations in the review and approval of generic enoxaparin in the United States*, 31 NATURE BIOTECHNOLOGY 220 (2013).

<sup>170</sup>*See, e.g.,* FOOD & DRUG ADMIN., DRAFT GUIDANCE ON GLATIRAMER ACETATE (rev. 2018), <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495029.pdf> [<https://perma.cc/LX5N-AMGD>].

<sup>171</sup>This result might occur where the “differences” observed between the two cannabis extracts consisted mostly of inactive ingredients that did not meaningfully contribute to the activity of the extracts. For an argument to this effect in a relevant (but distinct) regulatory context, *see* FDA, RE: VASCEPA (ICOSAPENT ETHYL) CAPSULES (NDA 202057) EXCLUSIVITY DETERMINATION (2016), <http://www.fdalawblog.net/wp-content/uploads/archives/docs/VASCEPA%20-%20Exclusivity%20Determination%20on%20Remand.pdf> [<https://perma.cc/TL5A-JVMX>].

<sup>172</sup>As previously mentioned, to reduce uncertainty as to how these situations would be resolved in practice, FDA could consider issuing a product-specific draft guidance document providing criteria for demonstrating active ingredient sameness when seeking generic approval of a cannabis-derived botanical drug. *See, e.g.,* FOOD & DRUG ADMIN., DRAFT GUIDANCE ON ENOXAPARIN SODIUM (2011), <https://www.fda.gov/downloads/guidances/ucm277709.pdf> [<https://perma.cc/S536-2HM7>].

<sup>173</sup>It is possible, however, that these products would still face competition from branded generics approved under the section 505(b)(2) pathway.

to earn a profit. Further, other commonly used incentives for recouping drug development costs—such as patent-related incentives and regulatory exclusivity—would also apply to botanical drugs, although the practical value of these incentives for a *cannabis-derived* botanical drug remains to be determined.<sup>174</sup>

In the longer term, however, FDA's position could evolve as scientific understanding of the mechanism of action of cannabis-derived extracts further develops, especially if the activity of these extracts is found to result from only a limited number of active constituents (e.g., THC and/or CBD).<sup>175</sup>

### C. Competition from Recreational Cannabis and (Non-Drug) Cannabis-Derived Products

While the prior analysis suggests that a cannabis-derived botanical drug might be able to avoid generic drug competition for a period of time, the product may nonetheless have to compete with non-FDA-regulated products (e.g., recreational cannabis) and eventually with other FDA-regulated cannabis-derived products (e.g., THC- and/or CBD-containing dietary supplements). And this competitive landscape of products against which a cannabis-derived botanical drug would have to compete will be influenced, to a large extent, by policy decisions made by FDA and Congress in the upcoming years.

#### 1. FDA Regulatory Actions That Could Impact the Cannabis Market

While immediate competition from non-FDA-regulated cannabis products—such as recreational cannabis—may be sufficient in some cases to discourage a firm from developing a cannabis-derived botanical drug, the competitive landscape could become even more crowded in the near future if cannabis were entirely descheduled from the CSA and FDA subsequently took steps to except THC and CBD from the drug exclusion rule. As previously discussed, the drug exclusion rule (section 301(ii) of the FDCA) prohibits firms from introducing a food, such as a medical edible, into interstate commerce if the product contains THC and/or CBD because these substances are active ingredients in previously approved drug products.<sup>176</sup> However, section 301(ii) creates an exception for situations where “the Secretary, in the Secretary's discretion, has issued a regulation, after notice and comment, approving the use of such drug . . . in the food.”<sup>177</sup> And FDA has indicated—when discussing

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<sup>174</sup>See O'Connor & Lietzan, *supra* note 23, at 43.

<sup>175</sup>See ANDA AND 505(B)(2) DRAFT GUIDANCE, *supra* note 166, at 8 (“In some instances, current limitations of scientific understanding and technology may preclude approval of an ANDA with the data permitted for submission in an ANDA, including, for example, with respect to establishing active ingredient sameness of a given product. As scientific understanding and technology evolve, though, FDA may be able to receive, review, and approve ANDAs where it previously lacked the scientific basis to do so.”).

<sup>176</sup>See *supra* Part I.B.1.

<sup>177</sup>21 U.S.C. § 331(ii)(2) (2012). Note that the Secretary of Health and Human Services (the “Secretary”) has delegated to the Commissioner of FDA all authority vested in the Secretary under the FDCA under 21 U.S.C. § 301. FOOD & DRUG ADMIN., FDA STAFF MANUAL GUIDE 1410.10 (DELEGATIONS OF AUTHORITY TO THE COMMISSIONER OF FOOD AND DRUGS) (2016), <https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffManualGuides/UCM273771.pdf> [<https://perma.cc/3NTM-Z68E>].

the drug exclusion rule applicable to dietary supplements—that such a regulation may be requested by filing a citizen petition under 21 C.F.R. § 10.30.<sup>178</sup>

There are clear signs that FDA may begin the process of notice-and-comment rulemaking for at least certain cannabis-derived substances in the near future. On December 20, 2018, the Agriculture Improvement Act of 2018 (the “2018 Farm Bill”) was signed into law.<sup>179</sup> Among other changes, the 2018 Farm Bill descheduled hemp-derived extracts (e.g., hemp-derived CBD oil) by removing these products from the CSA.<sup>180</sup> On the same day, FDA released a statement explaining that the Agency was currently evaluating whether to pursue a rulemaking process that would potentially culminate in the allowance of hemp-derived CBD in foods and dietary supplements.<sup>181</sup> Because pursuing such a process appears consistent with Congress’s intent in passing the hemp-related provisions of the 2018 Farm Bill, it seems more likely than not that a regulation will eventually be issued, although the details of any such proposal remain to be determined.<sup>182</sup>

If FDA were to issue a regulation effectively carving out hemp-derived CBD from the scope of the drug exclusion rule, it would likely result in a proliferation of CBD-containing products—such as food, beverages, and dietary supplements—that could compete with CBD-only<sup>183</sup> cannabis-derived botanical drugs. Even so, it is possible that any such rule would restrict the level at which CBD could be used in these non-drug products and that this could enable these products to be effectively differentiated from FDA-approved drugs in the cannabis market. This approach appears reasonable in the case of CBD because there is information suggesting that the effective dose of CBD when used in products such as dietary supplements may be at least an order of magnitude lower than the therapeutic dose of CBD recommended in the FDA-approved drug product EPIDIOLEX.<sup>184</sup> Thus it may be possible for CBD-containing dietary supplements to coexist in the marketplace with CBD-only cannabis-derived botanical drugs without resulting in product substitution.

It should be noted, however that, if all cannabis products were eventually descheduled, the process for issuing a regulation to waive the drug exclusion rule for

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<sup>178</sup>NDIN DRAFT GUIDANCE, *supra* note 160, at 42.

<sup>179</sup>Agriculture Improvement Act of 2018, Pub. L. No. 115-334 (2018) [hereinafter *2018 Farm Bill*].

<sup>180</sup>*Id.* at 529, 419.

<sup>181</sup>*Gottlieb Statement on Cannabis Products, supra* note 27.

<sup>182</sup>*See* Letter from Sen. Ron Wyden and Sen. Jeffrey Merkley to Scott Gottlieb, M.D., Comm’r, U.S. Food and Drug Admin. (Jan. 15, 2019), <https://www.wyden.senate.gov/download/hemp/cbd-letter-to-fda> [<https://perma.cc/KZQ7-MW9Z>] (requesting that FDA “immediately begin updating regulations for hemp-derived CBD and other hemp-derived cannabinoids, and give U.S. producers more flexibility in the production, consumption, and sale of hemp products”).

<sup>183</sup>“CBD-only” products are those that contain CBD—whether derived from hemp or marijuana—and *negligible amounts of THC*. *See* Brightfield Group, *supra* note 5, at 5 (emphasis in original).

<sup>184</sup>*See* Miles Sarill, *Researching safety and efficacy of CBD, hemp extracts*, NATURAL PRODUCTS INSIDER (Oct. 29, 2018), <https://www.naturalproductsinsider.com/ingredients/researching-safety-and-efficacy-cbd-hemp-extracts> [<https://perma.cc/8NN4-8W3Y>] (explaining that CBD-containing dietary supplements are reported to be effective in servings between 5 and 15 mg of active CBD when presented with a broad spectrum of other phytocannabinoids, terpenes and flavonoids, whereas the recommended dose of the FDA-approved drug EPIDIOLEX for an adult would be 700 to 1400 mg).

THC-containing<sup>185</sup> cannabis-derived extracts would likely be more complicated. First, unlike CBD, THC is a psychoactive compound with the potential for abuse. Second, also unlike CBD, the effective doses of THC used in recreational cannabis-derived products are similar to the recommended doses used in FDA-approved drugs. For example, currently marketed edibles generally contain between 10-50 mg of THC per dose,<sup>186</sup> whereas the recommended daily dose for the FDA-approved drug MARINOL is generally between 2.5-50 mg of THC.<sup>187</sup> As such, it is reasonable to expect that a THC-containing cannabis-derived botanical drug would face significant competition from state-level sales of recreational cannabis and other THC-containing products, even if FDA declined to issue a regulation allowing THC to be used in foods, beverages, and dietary supplements introduced into interstate commerce. Thus, the respective competitive landscapes for THC- and CBD-containing cannabis-derived botanical drugs may ultimately evolve somewhat differently.

## 2. *Congressional Actions That Could Impact the Cannabis Market*

There is currently solid public support in the United States for the legalization of cannabis with 62% of U.S. adults now in favor—double the support that existed in 2000.<sup>188</sup> With pressure building to legalize cannabis, it is not surprising that a recent bill was introduced in Congress proposing to deschedule cannabis by removing all cannabis products from the CSA.<sup>189</sup> The passage of such legislation could greatly impact the economic viability of cannabis-derived botanical drugs by increasing competition from recreational cannabis and cannabis-derived products. Indeed, pharmaceutical firms developing THC-containing drug products have acknowledged that the legalization of cannabis could significantly limit the commercial success of their drug product candidates by placing them in competition with recreational cannabis and cannabis-derived products.<sup>190</sup>

The legalization of cannabis may have a disproportionate impact on the economic viability of THC-containing cannabis-derived botanical drugs. As previously

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<sup>185</sup>For purposes of this article, the term “THC-containing” cannabis-derived extracts means extracts containing non-negligible amounts of THC (>0.3% THC), including THC-dominant, CBD-dominant, and THC/CBD-balanced extracts. *See supra* notes 9, 11.

<sup>186</sup>*See* Vandrey et al., *supra* note 12, at 95.

<sup>187</sup>PRESCRIBING INFORMATION FOR MARINOL, DOSAGE AND ADMINISTRATION, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/018651s029lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018651s029lbl.pdf) [<https://perma.cc/ALG9-2U2T>]; *see* SUMMARY OF PRODUCT CHARACTERISTICS FOR SATIVEX, POSOLOGY AND METHOD OF ADMINISTRATION, <https://www.medicines.org.uk/emc/product/602/smpc> [<https://perma.cc/DN33-QY4W>] (“Doses of greater than 12 sprays per day [~30 mg of THC) are not recommended.”) (last visited Feb. 12, 2019).

<sup>188</sup>Hannah Hartig and Abigail Geiger, *About six-in-ten Americans support marijuana legalization*, PEW RESEARCH CENTER (Oct. 8, 2018), <http://www.pewresearch.org/fact-tank/2018/10/08/americans-support-marijuana-legalization/> [<https://perma.cc/6PEK-7NUA>].

<sup>189</sup>S. 420, 116th Cong. § 201(a) (2019).

<sup>190</sup>*See* Insys Therapeutics, Inc., FORM S-1 REGISTRATION STATEMENT 19 (2007), <https://www.sec.gov/Archives/edgar/data/1409532/000119312507185285/ds1.htm> [<https://perma.cc/P4SR-8GW7>] (“If marijuana or non-synthetic cannabinoids were legalized in the United States, the market for dronabinol product sales would likely be significantly reduced and our ability to generate revenue and our business prospects would be materially adversely affected.”).

discussed, it may be more complicated for FDA to issue a regulation allowing THC to be used in food, beverages, and dietary supplements in interstate commerce because, among other things, these THC-containing products may be more easily substituted for THC-containing FDA-approved drugs. If so, the inability to market such THC-containing products in the absence of a regulation could increase the attractiveness of developing cannabis-derived botanical drugs, as there would be fewer FDA-regulated products to compete with such as THC-containing dietary supplements. Nonetheless, the mere prospect of competing with state-level sales of recreational cannabis and other THC-containing products might be enough to discourage firms from developing THC-containing cannabis-derived botanical drugs, especially if recreational cannabis were legalized and these products became more accessible to consumers. And, of course, FDA may ultimately decide to issue a regulation allowing THC to be used in foods, beverages, and dietary supplements in interstate commerce—a development that would result in another source of competition for THC-containing cannabis-derived botanical drugs.

Assuming *arguendo* that policymakers will eventually conclude that FDA’s drug approval pathway represents the most responsible approach for increasing consumer access to safe, effective, and high-quality THC-containing non-recreational cannabis products, it is worth briefly considering the steps Congress might take under its power to regulate cannabis to preserve the integrity of the nationwide market for FDA-approved cannabis-derived drugs.

As previously discussed, the Supreme Court’s decision in *Raich* confirmed—if not expanded—Congress’ power “to regulate purely local activities that are part of an economic ‘class of activities’ that have a substantial effect on interstate commerce.”<sup>191</sup> As the *Raich* Court explained, “Congress can regulate purely intrastate activity that is not itself ‘commercial,’ in that it is not produced for sale, *if it concludes that failure to regulate that class of activity would undercut the regulation of the interstate market in that commodity.*”<sup>192</sup> For purposes of the present discussion, the situation is even more clear than in *Raich* as there is no question that the sale and distribution of recreational cannabis and cannabis-derived products would amount to commercial activity. Thus, it would be squarely within Congress’ power to regulate recreational cannabis products should it find that the marketing of such products distorts the nationwide market for related goods and services, even if the products themselves did not enter interstate commerce.

In this regard, it is noteworthy that FDA has previously argued that certain prohibited acts under the FDCA can affect the nationwide market for FDA-regulated products. In *U.S. v. Regenerative Sciences*, FDA argued that the defendant’s decision to market an unapproved drug product “affects the market for out-of-state products that are approved by FDA to treat the same [] conditions defendants treat.”<sup>193</sup> FDA further argued that the “*availability* of defendants’ drug product . . . [would] affect patient treatment choices and thus the interstate market.”<sup>194</sup> If Congress were to adopt a similar line of reasoning, it is possible that it would find that the marketing of

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<sup>191</sup> *Gonzales v. Raich*, 545 U.S. 1, 17 (2005).

<sup>192</sup> *Id.* at 18.

<sup>193</sup> Initial Brief for Appellee at 48, *United States v. Regenerative Scis., LLC*, 741 F.3d 1314 (D.C. Cir. 2014) (No. 12-5254).

<sup>194</sup> *Id.* at 48–49.



recreational cannabis and cannabis-derived products disrupts the integrity of the nationwide market for FDA-approved drug products (e.g., THC-containing cannabis-derived botanical drugs) and potentially other FDA-regulated products (e.g., THC-containing cannabis-derived dietary supplements). If so, Congress could decide to impose additional restrictions on how recreational cannabis and cannabis-derived products are marketed.

As one example, Congress could, in conjunction with the legalization of cannabis, adopt measures to establish a more meaningful boundary between the recreational and non-recreational<sup>195</sup> segments of the cannabis market. These measures might include prohibiting state-regulated cannabis dispensaries from selling or distributing any non-recreational cannabis-derived products (e.g., medical edibles and THC- or CBD-containing dietary supplements). These measures might also include providing federal regulators with additional authority to police the intrastate advertising and promotion of recreational cannabis products to further ensure that these products are not being marketed for non-recreational uses.

In tandem with these steps, Congress could also require that all non-recreational cannabis-derived products containing THC (e.g., dietary supplements and non-prescription drugs) be exclusively sold in bona fide pharmacies—that is, in the same locations where FDA-approved cannabis-based drugs would normally be dispensed. Congress could further require that all such sales of non-recreational cannabis-derived products containing THC be limited to “behind the counter” and be subject to controls similar to those imposed on the sale of cold medicine containing pseudoephedrine under the Combat Methamphetamine Epidemic Act of 2005.<sup>196</sup> Last, to maintain consistency with this approach to THC-containing cannabis products, Congress could also prohibit the sale of other non-recreational cannabis-derived products (e.g., CBD-only dietary supplements and beverages) in state-regulated dispensaries serving the recreational cannabis market but permit the sale of these products in other consumer retail locations, including pharmacies.

## CONCLUSION

The current options for *legally* marketing medical edibles in compliance with the FDCA—whether as a conventional food or a dietary supplement—are more limited than is often assumed. *First*, no disease claims (whether express or implied) could be made about an edible—otherwise the product would be regulated by FDA as a drug. *Second*, no edible could contain either THC or CBD as the presence of these substances would violate the FDCA’s drug exclusion rule. To avoid these prohibitions, cannabis firms must attempt to limit the sale and distribution of medical edibles to the confines of a single state—a limitation which could impede the growth of these businesses. *Third*, any edible that contained a cannabis-derived extract (e.g., hemp-derived CBD oil) could be deemed adulterated under the FDCA unless the

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<sup>195</sup>For purposes of this article, the “non-recreational” segment of the cannabis market refers to the following categories of cannabis-derived products: (i) foods, beverages, and dietary supplements intended for nutritional use or to promote general health and well-being; and (ii) FDA-approved drugs.

<sup>196</sup>FOOD & DRUG ADMIN., LEGAL REQUIREMENTS FOR THE SALE AND PURCHASE OF DRUG PRODUCTS CONTAINING PSEUDOEPHEDRINE, EPHEDRINE, AND PHENYLPROPANOLAMINE (2017) <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm072423.htm> [https://perma.cc/2NVU-Z2A6].

extract was an FDA-approved food additive or had been self-affirmed GRAS. And, when considering taking enforcement action against adulterated edibles, FDA could rely on the principle of component jurisdiction to establish a connection to interstate commerce, even where only a single ingredient used to manufacture the product had been shipped across state lines.

To avoid these prohibitions, cannabis firms wishing to market medical edibles could consider developing cannabis-derived botanical drugs. FDA's modified approach to developing botanical drugs would make approval of such products *possible* whereas, before, approval may have been precluded under the Agency's conventional drug development approach. However, the time and cost required to develop a cannabis-derived botanical drug would be significant—at least relative to the existing non-FDA-regulated approach. It nonetheless could be an attractive option for cannabis firms partnering with experienced pharmaceutical firms, especially when considering that market entry of fully substitutable generic products may be limited in the near term. Notwithstanding these benefits, an FDA-approved cannabis-derived botanical drug could face competition from both recreational cannabis products as well as from other categories of FDA-regulated products such as cannabis-derived dietary supplements. And the real prospect of such a crowded landscape of competing—and in some cases substitutable—cannabis products may discourage most firms from developing these products.

In the final analysis, this article concludes that FDA has sufficient regulatory tools under its existing statutory authorities to ensure that a level playing field exists for certain types of cannabis-derived products (e.g., those containing hemp-derived CBD), but that Congressional action may ultimately be required to strike a similar balance for other types of cannabis-derived products (e.g., those that contain THC). While it remains to be seen what, if any, measures Congress may ultimately decide to take to regulate cannabis and cannabis-derived products, cannabis firms should be aware that new federal laws may be in the works and should continue to actively monitor these developments—particularly if legislative proposals to fully legalize cannabis gain additional traction.