Brief report

The legalization of cannabinoid products and standardizing cannabis-drug development in the United States: a brief report

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This brief report covers recent advances in cannabis and cannabinoid regulation and drug approval. The popularity of cannabis and cannabinoid products continues to rise, and these products are available for the majority of the population in the United States to purchase as easily as alcohol. Although many states have approved programs and research licenses, these activities and products all remain federally illegal. The solution may be for the United States to offer multiple pathways for product approval that adapt to the diversity of the products and the needs of the consumer. Multiple pathways for market approval would protect public health, whether the public is using cannabis and cannabinoids as a medicine, a wellness product, or as a recreational substance.

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New hope for an old medicine

Cannabis and cannabinoid-containing products are increasingly being accepted as both legitimate consumer goods and as mainstream medical treatments.[1] Many states have enacted their own programs for cultivation, manufacturing, safety testing, and distribution of a wide variety of products from the cannabis plant, yet these products remain Schedule I substances, the most restricted federal classification for a drug in the United States.[2] Because of the conflict between state and federal law, federal agencies do little to regulate the cannabis industry and protect consumers. For example, federal limits on heavy metals or pesticide use cannot be issued or enforced for a Schedule I product; a product that is federally illegal. As such, the future of cannabis legalization in the United States appears to be one both of great promise and associated with significant risk.[3-5]

Although legislative actions (ie, new laws allowing states to issue licenses for cannabis operations, laws allowing cultivation and distribution, etc) have allowed a majority of cannabis and cannabidiol (CBD)-containing products to be available direct to consumers, a lack of cohesive regulation and oversight has left many alarming gaps concerning product quality and patient safety. For example, reports show that non–US Food and Drug Administration (FDA)-approved CBD products available to consumers are often inaccurately labeled, containing varying amounts of active ingredient, and lack evidence for their safety and effectiveness. Indeed, federal regulation and pharmaceutical drug development of cannabis, hemp, and cannabinoid products is an often complex and poorly understood issue.[6,7] The current state and federal cannabinoid and medical cannabis laws are surely overdue for an overhaul, as cannabis is shackled by its Schedule I status in the United

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States, which places the highest possible limitations and restrictions on access to this plant for research and product development. All cannabis products sold at state-licensed facilities are federally illegal, a conflict between state laws and federal laws that has persisted for decades. Hence, patients who use medical cannabis often have limited legal protections from federal laws, which can result in the loss of child custody, eviction from homes, and the loss of a job or health care insurance, among other issues.

The US Drug Enforcement Agency (DEA) made history in April of 2020 by descheduling (removal from the controlled substances regulatory requirements and classifications) Epidiolex—a purified cannabis-derived prescription form of CBD.[8] This is the first time in history that a plant-derived compound from cannabis (Schedule I; no accepted medical value) received FDA approval, and it was then promptly descheduled (the specific preparation of CBD, Epidiolex, no longer appears in any drug-scheduling category). This may be a sign of things to come, as the descheduling of CBD occurs at a time when Δ^9- tetrahydrocannabinol (THC) appears in no less than *three* US scheduling categories. THC from the cannabis plant is considered to be a Schedule I drug, pharmacologically identical to the synthetic preparations of THC that have been FDA approved as Schedule II (as THC pill) and III (as a THC liquid suspension) substances. According to GW Pharmaceuticals' accompanying press release, "Descheduling [of Epidiolex] will enable prescribing free of the previous Schedule V requirements in the United States."[8] In other words, their CBD product would be available without a prescription or could be prescribed for a wide variety of conditions other than the orphan diseases Epidiolex was originally approved to treat (Lennox-Gastaut and Dravet syndromes) and would be covered by insurance; no other cannabis extract or CBD product is covered by health insurance in the United States.

There is no doubt that Epidiolex blazed the trail for prescription cannabinoids, but an additional pathway (or more) will surely be needed for market approval of products that are *not* being developed into prescription drugs. As regulations continue to evolve, there will be many emergent benefits, concerns, and implications associated with cannabinoid-drug development, especially if cannabis and/or THC were to be descheduled as well. A clear, multipath federal regulatory framework may be needed to effectively protect the public's health by ensuring patient safety, product quality, and market access. By simultaneously offering multiple pathways to generating safe, legal medicine and wellness products, while implementing public health policies to control risk, the federal government has an opportunity to systematically examine the potential therapeutic benefits of medical cannabinoid products while protecting patient safety. Legalizing both whole cannabis and cannabinoid products would allow traditional research and drug development processes to occur, and may indeed be the only possible way to quiet the allure of illicit markets. The unregulated or illicit market offers consumers increased ease of access, delivery, and typically, a lower price point, irrespective of quality—something that is unachievable under the current regulatory framework. History tells us that in markets rife with severe access issues and product restrictions, including states with policies for generalized bans on certain types of administration forms and potency restrictions, unregulated markets will fill the gaps.[2]

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Arguably, it may not be fiscally responsible to throw tens of millions of dollars into developing a federally approved prescription cannabis product for such a narrowly targeted orphan disease (ie, as done with Epidiolex)—especially in light of the fact that the *exact same drug* is already widely available without a prescription requirement.[9] This concept is discussed below along with the benefits and implications of legalizing cannabis and cannabinoid products and where it might be helpful to have two (or perhaps more) regulatory pathways designed to facilitate market approval.

Implications for cannabis and cannabinoid product developments

In the words of one researcher:

"…[studying cannabis] takes a lot more energy than it should. The energy should go to more productive endeavors.

If anything, the government should ease [restrictions on] research in an area in which research is so urgently needed."[10]

The restrictions associated with Schedule I drugs, the most restrictive controlled-substances category, have proved a barrier to approval of large-scale studies on cannabis and cannabinoids in the United States; such studies have never been approved. Indeed, by virtue of this regulatory designation, cannabinoids are deemed dangerous and to have no medical value. Numerous case reports and phase 1 studies have been published by US-based researchers, but cannabis drug development has largely occurred outside of this country, such as with the recently approved Epidiolex. For more information about the complexities of this issue, please see the lengthy review by Russo, entitled "Current Therapeutic cannabis Controversies and Clinical Trial Design Issues."[11]

Indeed, pursuing new drug approvals for cannabis-derived products through traditional pathways would probably cost *hundreds* of millions of dollars. It can easily take 10 to 12 years for a single new chemical entity to be approved, with costs exceeding 1 *billion* dollars.[7] These exorbitant costs can be substantially higher for botanical products, given their complexity. Following CBD's movement through the gold-standard drug-approval process, other nonintoxicating cannabinoids found in the cannabis plant could follow similar pathways. For example, cannabigerol (CBG), a major constituent of both medicinal cannabis strains and hemp, may have a similar safety profile to CBD.[12]

Beyond these exorbitant costs, however, there is a clear benefit to legalizing cannabis-based products while regulating the drug-development process for market approval, as it leads inevitably to more standardized products with more consistent availability to consumers. Federal approval pathways for product development, coupled with descheduling efforts concerning cannabis, THC, and other cannabinoids, may lead to a rapid, much-needed growth in cannabis research and development. Investigators would no longer face as many inherent barriers to conducting research, including the frustrating difficulty in obtaining raw materials or the substantial, suffocating regulatory burden.[7]

Legalization might also create the same low levels of abuse and risk as seen with other standardized cannabis-based drugs.[13] For example, the cannabis-based drugs Marinol, Epidiolex, and Sativex each have generated a low substance-abuse risk profile and very little, if any, evidence of diversion.[13] Available data suggest that standardized preparations are both safer and have less risk associated with them than products with unknown potency and provenance. Such standardized pharmaceutical-grade cannabinoid preparations simply have not demonstrated a significant resale value in illicit markets.[13]

Beyond Epidiolex, cannabinoid drug development may also lead to the creation of nonprescription regulatory standards, including (but surely not limited to): guidelines for prescription cannabinoids that are unavailable or not covered by insurance, conditions and symptoms that involve the endocannabinoid system (ECS) but have no corresponding FDA-approved treatment, and tracking potential for cannabis/cannabinoid allergies or drug-drug interactions.[14] Additionally, having both prescription and nonprescription cannabinoid product standards would help to promote a standard of care across clinical practice and research.

There are, however, regulatory approaches and considerations that may have unintended consequences. Here is a short list of often oversimplified-but-contentious issues surrounding cannabis: epidemiology of use (adolescents, children, and maternal); acute intoxication and effects on driving; pregnancy and breastfeeding; later childhood outcomes, from use, abuse, or exposure; social and racial context of cannabis policy; risk behavior in adolescence vs use; adolescent learning and mental health sequelae; potential medical uses in minors; and cannabis-use behaviors and cannabis-use disorders.[15]

Current production and distribution of medical cannabinoid products, approved at the state level, requires neither clinical trials nor federal regulatory approval.[6] This undermines the rigorous approval process required of standardized, pharmaceutically available cannabinoid preparations.[13] Pharmaceutical grade cannabis products face significant challenges for meeting the expectations of regulators, investors, and customers.[7] These myriad issues would *probably* be mitigated by providing market access to properly standardized products, since each of these national public health issues tends to cling to associations with illicit cannabis produced and consumed outside of state legal programs.

Overall, however, the legalization of adult-use cannabis and medical cannabis does *not* seem to have resulted in large increases in the prevalence of past-year cannabis use among adolescents and young adults.[16,17] It should in no way be surprising that there have been increases in cannabis use among adults of legal age. This fact is the rationale for creating regulated commercial and medical markets for cannabis, to provide legal, convenient access for adults who choose to use it.[12] In reality, we know that nearly any regulated system is probably better for public and global health than prohibition.[4] Gray- and black-market users of cannabis are exposed to an illicit commodity marketplace where product safety is not a priority.[18] Reducing the harm associated with recreational use should be a priority, as well as a pathway for cannabis products to be FDA approved as prescription medicine, and to receive market approval to allow interstate commerce.

Some may argue that we have enough data to draw lessons from past, albeit questionable, cannabis policies, and that we surely possess the data to develop better ones, with federal-level regulation being not only necessary but inevitable.[16] Others argue we are in a policy infancy and cannot yet use these data to inform public policy. It can surely be argued that it is unclear as to the early benefits of increasing access to regulated forms of cannabis, and perhaps these perceived benefits may be short lived.[10,15,16] On one hand, we have decades of cannabis policy and data of outcomes related to prohibition, with a gradual liberalization/decriminalization of medical and adult use. On the other hand, we are only just beginning to see the true impact of laws enacted over the last several years. Lessons are being learned about cannabis policy, and those intricacies weave around the implications of any federal or national approval pathways. A detailed review article comparing different countries' cannabis programs is sorely needed, as well as a review article on the history of international hemp and cannabis-product regulation.

Dedicated federal pathways for cannabinoid drug and product development would immediately result in increases in the perceived safety of cannabis products, and FDA/federal approval would lend credibility to approved cannabis products. Insurance coverage or federal market approval would inevitably follow, and allowing interstate commerce would cause huge, beneficial (but volatile) shifts in the cannabis and hemp economy. With clear federal approval pathways, expectations, and banking services (legislation in process), partnerships in this industry with other sectors—such as research institutions, food and beverage manufacturers, and pharmaceutical companies—will be key for success; companies such as Tilray and Canopy have already gone this route.[1] Without federal guidelines to support a strong scientific and product-safety foundation in companies that manufacture and sell cannabinoids (whether it's a prescription drug or a consumer product), many companies will not stand a chance of pivoting to adapt to new regulatory environments.[6,19,20] ■

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