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Clinical Brief

Medicinal Uses of Cannabis-Derived Products

Rapidly evolving state and federal cannabis policies present countless challenges for employers across the country. Frequent changes in state law have significant impact on employers' day-to-day operations, including substance and drug use policies, employee training, and hiring and firing practices. Just as employers address one challenge, another seems to surface.

This clinical brief provides an overview of the legal status of cannabis in the United States, the Food and Drug Administration's (FDA) approved uses for cannabis-derived products in medical treatment, as well as employer workplace policy considerations regarding non-FDA approved cannabis-derived products that may be available.

What is cannabis?

Cannabis sativa L., or marijuana as it's commonly called, is a flowering plant, that has been cultivated for centuries and used for a variety of purposes, including textile fiber, food, and recreation. Cannabis is also the source of more than 100 plant-derived chemical compounds called cannabinoids. The two most well-known and commonly occurring cannabinoids are tetrahydrocannabinol (THC) and cannabidiol (CBD). THC causes the "high" associated with cannabis use. CBD does not produce an intoxicating effect and is increasingly used in products with purported health and wellness benefits.

What is the legal status of cannabis in the United States?

At the federal level, most cannabis and cannabis derivatives are classified as Schedule I substances under the Controlled Substances Act (CSA), and it remains a federal offense to distribute, purchase, possess or use these substances. Schedule I status means a substance is considered to have no currently accepted medical use, high potential for abuse, and lacks accepted safety for use even under medical supervision.

However, the 2018 Farm Bill changed how certain types of low-THC cannabis are classified under the CSA, removing "hemp" from the CSA's definition of marijuana, and therefore from the schedules of controlled substances. Hemp is the cannabis plant and derivatives that contain no more than 0.3% THC on a dry weight basis. The Farm Bill also preserved the authority of the FDA to regulate products containing cannabis or cannabis derivatives, regardless as to whether they are classified as marijuana or hemp. This is important because it is unlawful under

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the Federal Food, Drug & Cosmetic Act, enforced by the FDA, to include either THC or CBD in any food or dietary supplement.

At the state level, legalization of cannabis for medical and recreational purposes has accelerated over the past decade. Today, 33 states and the District of Columbia have legalized cannabis for medical use, and 11 of those states and the District have legalized recreational cannabis. These developments do not affect the legal status of cannabis at the federal level, which, as described above, imposes criminal penalties for the distribution, purchase, possession or use of cannabis, and explicitly preserves FDA's authorities to regulate all products containing cannabis or cannabis-derived compounds.

Cannabis-derived medical therapies

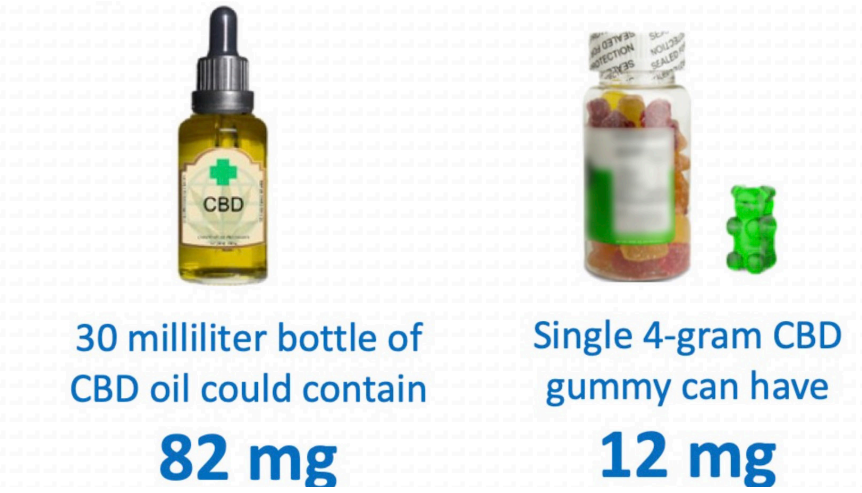
The FDA has approved several pharmaceutical cannabis-based medicines for the treatment of specific medical indications. One of these medicines, a highly purified CBD, is plant-derived, and approved for use in treatment of two forms of childhood onset epilepsy, Dravet Syndrome, and Lennox Gastaut Syndrome. These rare, severe conditions comprise about 5%-10% of epileptic patients and 1%-2% of all childhood epilepsies. The other three medicines, which are synthetic THC, are used in the treatment of anorexia associated with weight loss in patients with AIDS, and nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

Each of these cannabis formulations has been subject to rigorous medical and scientific review. Based on safety and efficacy data derived from extensive preclinical and clinical evaluation, the FDA has determined that these drugs are effective for treatment of these specific medical indications, and that their expected benefits outweigh potential risks to patients. On this point, the FDA has been very clear:

> *Cannabis and cannabis-derived products claiming in their marketing and promotional materials that they're intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases (such as cancer, Alzheimer's disease, psychiatric disorders, and diabetes) are considered new drugs or new animal drugs and must go through the FDA drug approval process for human or animal use before they are marketed in the US. Selling unapproved products with unsubstantiated therapeutic claims is not only a violation of the law, but also can put patients at risk, as these products have not been proven to be safe or effective.*

While the current eligible population for FDA-approved cannabis-derived medications is quite small, there are currently more than 200 clinical trials evaluating cannabinoids for treatment of a broad array of conditions including autism, pain, behavioral health disorders, irritable bowel syndrome, cognitive disorders, and multiple sclerosis. In the face of expanding availability of recreational cannabis and associated CBD and THC-containing products, and the necessary time delays for rigorous evaluation of cannabis-derived pharmacotherapies to secure FDA approval, employers already face challenges with the potential workplace consequences of cannabinoid-containing products purchased at dispensaries or online.

Figure 1. CBD Oil and CBD Gummies



Despite high THC content, these products qualify as hemp under federal law, i.e., THC content is at or below 0.3%.

Cognition and safety concerns of THC/CBD products

Worker safety

THC in cannabis has an intoxicating effect that can affect an individual's motor skills, reaction time, and coordination at low levels (as little as 2.5 to 5 mg). As a result, certain states with recreational cannabis laws prohibit more than 5 mg of THC in a serving of recreational cannabis edible products. THC intoxication can have serious consequences for employees with safety-focused roles such as operating machinery or driving a vehicle.

Studies indicate a link between cannabis use and adverse workplace consequences, including increased risk for injury or accidents. According to a study from the National Institute on Drug Abuse, postal workers who tested positive for THC use had 55% more industrial accidents, 85% more injuries, and 75% greater absenteeism compared with those who tested negative.

It is important for employers to understand that CBD products may also contain significant levels of THC, enough to cause intoxication, without the consumer's awareness.

It is important for employers to understand that CBD products may also contain significant levels of THC, enough to cause intoxication, without the consumer's awareness. The 2018 Farm Bill de-scheduled hemp-derived products containing no more than 0.3% THC. A 30-ml bottle of CBD oil (Figure 1), which is a common retail unit, could contain 82 milligrams of THC and still fall below the 0.3% THC limit established in the Farm Bill. A single 4-gram CBD gummy, commonly sold in packages of 30, could contain 12 mg of THC and remain below the 0.3% THC limit (remember, it may take only 2.5 to 5 mg of THC to cause impairment). As a point of comparison, smoking an entire marijuana joint delivers only about 17 mg of THC.

Finally, due to the varying and inconsistent state-level regulation of non-FDA approved cannabis products, such products often go to market without assurances of standardization for strength, identity, quality, and consistency. In certain cases, cannabis products have been marketed containing harmful contaminants, such as synthetic cannabinoids (e.g., "spice"), pesticides, and heavy metals. And products frequently go to market mislabeled (e.g., products labeled as THC-free contain high levels of THC; or products contain significantly lower levels of CBD than indicated on the product label). In some cases, such quality deficiencies have serious consequences for consumers.

Implications for patients

Why does FDA approval matter?

In the US, the FDA drug approval process is the only way to clarify questions about a drug's efficacy, the conditions it is intended to treat, and safety considerations unique to the patients who will take the drug. It is also the only way to assure standardization, quality control, and batch to batch consistency; establish a reliable dosing range; and identify drug interactions.

A benefit-risk assessment is the cornerstone of the FDA approval process. Before a medicine can be approved for marketing, the FDA must determine that it is effective and that its expected benefits outweigh its potential risks to patients. This assessment is informed by a body of evidence derived from comprehensive preclinical and clinical study.

Regarding cannabis products, most studies cited to support the therapeutic value of non-FDA approved cannabis products are preclinical laboratory or animal studies, observational studies that do not control for bias or confounding factors, or surveys of people self-medicating with cannabis. While such studies can help in generating hypotheses, there are important questions that must be addressed to reach conclusions regarding the safety and efficacy of these products as medicine. FDA approval of specific cannabis formulations is necessary before employers can have confidence a cannabis-derived product is safe and effective for treating specific medical conditions.

For FDA-approved cannabis-derived medicines, rigorous scientific and medical review demonstrates that the benefits of a specific formulation outweigh its known and potential risks for each approved use. That is not the case with non-FDA approved cannabis products (Figure 2).

Employer considerations:

- Be mindful of current state regulations pertaining to availability and use of non-FDA approved cannabis products. These products are subject to varying and inconsistent quality assurance standards, and therefore vary in identity, purity and consistency.
- Because certain companies have invested in the comprehensive research necessary to obtain drug approval from the FDA, there are FDA-approved cannabis-derived medicines currently available. However, due to permissive state cannabis laws, most cannabis businesses have no need to pursue FDA approval, thus potentially manufacturing and distributing unsafe and/or ineffective products.
- Acknowledge potential employee pressures for plan coverage for non-FDA approved products.
- Understand that there are critical differences between FDA-approved cannabis-derived medicines and state-authorized, unapproved cannabis-derived products such as differences in federal legality levels of scientific and medical rigor and quality. For these reasons, coverage for non-FDA approved cannabis derived products is not appropriate.
- Understand workplace implications for use of cannabis-derived products, particularly non-FDA approved products. These products often contain high levels of THC,

Figure 2. FDA-approved versus non-FDA Approved Cannabinoid Products

	Food & Drug Administration (FDA)-Approved Cannabinoid Products Plant-Based and Synthetic Medicines	**Non-FDA Approved Cannabinoid Products** Hemp-Derived Dispensary Products and Medical Marijuana
Study Evidence & Requirements	Placebo-controlled, publicly disclosed clinical trials with large patient samples to determine efficacy, safety, and recommended dosing	Randomized clinical studies have not been conducted. Public disclosure of smaller, informal studies not required.
Manufacturing	FDA inspects to ensure adherence. Produced according to regulated current good manufacturing practices (cGMP). FDA-approved medications must adhere to strict specifications that ensure batch consistency and stable shelf life.	No federal testing standards, and variable from state to state; some states require no testing. FDA does not inspect manufacturing sites for adherence to cGMP.
Quality Standards	Testing methods must be agreed upon with FDA. Meets FDA standards for quality, stability, consistency Tested toe ensure they contain the consistent concentrations of cannabinoids and other products ingredients listed on the label.	Non-prescription, non-FDA approved cannabinoid products are subject to inconsistent regulation at the state level. There are non federal standards for testing to ensure accuracy and consistency.
Legality	Only FDA-approved medicines with CBD or THC (e.g. Epidiolex) is federally legal under the Food, Drug and Cosmetic Act.	Healthcare providers can "recommend" but not prescribe help-derived dispensary products or marijuana, as they are illegal at the federal level
Coverage	Eligible	Not eligible

which can compromise employees' safety and productivity.

- Ensure existing policies related to employee use of mood-altering substances take into consideration cannabis-derived products.

Employer Resources

1. CannabinoidClinical.com is an educational resource where readers can learn more about research on cannabinoids. Representative content includes articles, information leaflets, videos, policy statements, and more.
2. United States Surgeon General's Advisory: Marijuana and the Developing Brain https://www.hhs.gov/about/news/2019/08/29/surgeon-general-releases-advisory-marijuana-damaging-effects.html
3. Aimed Alliance (infographic). Reading the Tea (or Hemp) Leaves: Post FDA Hearing. https://aimedalliance.org/wp-content/uploads/2019/07/FDA-Hearing-Reading-the-Tea-or-Hemp-Leaves-Flyer_v13.pdf or https://aimedalliance.org/aimed-alliance-submits-a-comment-to-the-fda-regarding-the-regulation-of-hemp-derived-cbd-products/
4. If Weed Is Medicine, So Is Budweiser https://www.wsj.com/articles/if-weed-is-medicine-so-is-budweiser-11547770981
5. The Atlantic: The Pitfalls of Weed Legalization (video) https://www.theatlantic.com/video/index/581044/marijuana-use/?utm_source=eb
6. TakeOnEpilepsy.com is a unique online community created by and for caregivers. The site provides expert advice and valuable resources to help this resilient community.

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