Cannabis for medical use: consistent quality to help protect patients

Michael Eisenstein, M.S.,
Science Writer and Editor

Kristi L Muldoon Jacobs, Ph.D.,
USP, Director, Regulatory Science

Americans generally trust that any medication they buy has been subjected to rigorous safety and quality controls and close government oversight. But what happens when that drug remains illegal at the federal level? This is the problem confronting cannabis—a product that is now available for medicinal use under the laws of 33 states, the District of Columbia, and three US territories[1], but still explicitly illegal in the eyes of the federal government.

Different states have adopted their own disparate approaches to oversight of medical cannabis, and the application of inconsistent regulatory frameworks and uneven approaches to quality standards may leave consumers at risk. Consumers and patients expect quality to be inherent in the products they use for good reason; poor quality products and control can lead to adverse events and health risks. For example, a 2018 study[2] from George Thompson of the University of California at Davis and colleagues found that cannabis samples obtained at various California dispensaries tested positive for fungal and bacterial pathogens that could put immunocompromised patients in danger of serious infection. The United States Pharmacopeia (USP) has published scientific work developed by a panel of experts that may serve to provide needed information and guidance to these states and others seeking to address public health risks associated with cannabis used medically under state law, with an article in the *Journal of Natural Products* that outlines core quality attributes and tools that may serve as resources for quality control of this plant.

A complex regulatory landscape

Cannabis plant material containing >0.3% Δ9-tetrahydrocannabinol (THC) is still classified as Schedule I by the US Drug Enforcement Administration (DEA). This means that the agency deems it to be purely a drug of abuse with no accepted medical utility, and this in turn has hindered efforts by researchers to study this plant in safety or clinical trials. Nevertheless, there is mounting evidence that the two primary chemical constituents of cannabis – THC and cannabidiol (CBD) – could help patients manage anxiety, seizures, chronic pain, and the adverse effects of cancer chemotherapy, among other indications[3]. Indeed, the US Food & Drug Administration (FDA) has approved multiple drugs based on cannabis-derived compounds. These include Dronabinol, a synthetic version of THC used to treat nausea and vomiting caused by cancer chemotherapy, and Epidiolex, a solution of CBD that has proven effective in certain forms of epilepsy.

Regulation of the cannabis plant itself remains complicated. The US Farm Bill signed into law in 2018 makes it legal to cultivate and sell hemp[4], a variant of cannabis that produces low levels of THC (< 0.3%). Hemp has no intoxicating effects but is extremely useful as an industrial material and has also become popular as an ingredient in food and cosmetics. The legal future of cannabis for medicinal purposes in the US remains uncertain at present, but the FDA has shown openness to supporting further clinical

testing and development. In June 2018, then-Commissioner Scott Gottlieb issued a statement[5] in which he declared that "the FDA will continue to support rigorous scientific research on potential medical treatments using marijuana and its components that seek to be developed through the appropriate scientific channels." As of February 2020, there were at least 160 active clinical trials exploring the positive and negative medical effects of cannabis.[6]

But the cat is already out of the bag -- cannabis use for medicinal purposes is commonplace in many states, and the advocacy organization Americans for Safe Access estimates that nearly 3 million US citizens currently use cannabis medicinally[7]. When the members of the USP Convention[8] gathered in 2015 to map out the organization's strategic priorities for the next five years, it had already become crystal clear that safety and quality guidelines for medical cannabis represented a critical unaddressed issue. "There was an outcry for standards at that time," says Gabriel Giancaspro, Vice President, Science—Dietary Supplements and Herbal Medicines at USP. "As different states were individually approving legislation, they were doing so in a non-harmonized manner in terms of standards... some states were very stringent, and some were not."

The USP is a scientific nonprofit organization that plays a leading role in developing and formalizing standards for medicines, dietary supplements, and foods based on expert advice from the medical and scientific community. USP standards are enforced by FDA in the U.S. In recognition of the fact that the U.S. federal government, including FDA, does not recognize cannabis as a legal drug product, USP has decided not to create formal compendial standards at this time. As an alternative, USP has opted to publish the findings of its experts in the form of a scientific paper rather than a conventional USP monograph, while still employing a rigorous process similar to the one typically used by the organization to formulate its quality standards.

This began with assembling an expert panel of clinicians, scientists, and industry representatives from around the world. This team included several experts from Canada, where cannabis is currently legal both as a medical and recreational product, as well as Mahmoud ElSohly and Ikhlas Khan, from the University of Mississippi's National Center for Natural Products Research (NCNPR)—the only US institution with federal approval to cultivate cannabis for research use. "USP is drawing key experts from different countries and different areas of expertise so that the work that comes out of it will be truly authoritative and international," says panel member Robin Marles, Senior Scientific Advisor at Health Canada's Food Directorate and Chair of the Botanical Dietary Supplements and Herbal Medicines Expert Committee of USP.

Profiling plants

The USP's guidelines are entirely focused on the inflorescence of the cannabis plant, popularly known as the flower or 'bud'. And as with any plant product, the first challenge was to determine how to classify the various varieties and subtypes that are currently in use. Among the lay community, the plant is generally categorized as belonging to one of two species, Cannabis indica or Cannabis sativa, which are in turn represented by a myriad of evocatively named "strains" with monikers like 'Purple Kush' and 'Sour Diesel', each with its own purported properties and characteristics.

These categorizations don't hold much scientific water, however. Dr. Ethan Russo, a neurologist who has published extensively on his psychopharmacological research on cannabis for medical purposes and served on the USP's expert panel, has described this simplistic notion of the indica versus sativa species dichotomy as "total nonsense."[9] Similarly, the 'brand names' associated with particular strains can be misleading, with considerable variation in the cannabinoid content among different specimens of the same strain.[10] "You could get the same color and the same smell, but actually the THC and the CBD and some of the other compounds could be quite different," says Marles.

USP has elected to recognize cannabis as a single plant species, Cannabis sativa, with different varieties or subtypes that can then be classified based on their THC and CBD content. The former primarily contributes to the 'high' sought by the plant's recreational users, but THC also seems to play a prominent role in the medical benefits of cannabis. CBD, in contrast, has no psychoactive intoxicating effects, but has been shown to prevent seizures in some forms of epilepsy, and may have benefits for certain psychiatric conditions as well. The expert panel therefore opted to classify organize plant material into three 'chemotype' categories: THC-dominant, CBD-dominant, or intermediate varieties that contain physiologically meaningful levels of both. This scheme is intended to give prescribers and consumers greater clarity on the substances they are using. "We're not describing specific products—we're describing cannabis in general," says Marles.

The USP panel recommends the use of science-based analytical procedures to properly identify cannabis varieties. This entails the use of a technology called high-performance liquid chromatography (HPLC) and gas chromatography (GC) to separate out and quantify not just THC and CBD, but also 11 other cannabinoids that are less well-studied clinically but may also have an impact on the plant's therapeutic properties. In order to support these testing approaches, it was necessary for USP to develop trustworthy reference standards for each of these chemical constituents, so that analytical laboratories can validate their test results.

Different cannabis varieties can also vary in terms of their composition of terpenes—a class of aromatic chemicals that can confer distinctive fragrances and flavors such as pine or citrus to a given bud sample. The USP expert panel identified five different terpenes that are especially abundant in cannabis. In many cases, one of these will be present at higher levels than all other terpenes in a given variety, but the panel also identified three common combinations of 'co-dominant' terpenes that occur in roughly equivalent amounts in some varieties. USP recommends profiling these constituents via a separate GC procedure.

Even though terpene compounds have not yet been decisively linked to any clear pharmacological effect, they offer a useful data point for identification and labeling of cannabis varieties, and there is reason to believe that at least some terpenes may modulate the plant's medicinal and psychoactive properties. "More clinical research needs to be done," says Giancaspro, "but if you don't define what are those different types, then you cannot start making those connections." These detailed profiles of cannabinoid and terpene content can also help guide prescribers and ensure that patients are consistently receiving the cannabis varieties that they intended.

Controlling contamination

Routine testing is especially important because the composition of a given chemotype can be profoundly affected by both the cultivation conditions and how the plant is processed and stored prior to sale. Given the known impact of these conditions on total THC and CBD levels, the panel offers specific suggestions for acceptable moisture levels for stored plant material. This is particularly important, as excessive drying can compromise the pharmacological activity of the plant material, while too much moisture can promote the growth of toxic microbes and mold.

This latter aspect represents one of the foremost safety issues for cannabis, as illustrated by the above-mentioned California dispensary study from Thompson and colleagues.

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"The bud itself is very tightly packed and very sticky, and so lots of bacteria and molds can get inside," says Marles, noting that such contamination has already led to multiple recalls in Canada. Similar problems have plagued dispensaries in various US states—for example, Colorado dispensaries received five health alerts about recalls related to mold contamination in late 2019 and early 2020.[11]

Of particular concern are the various species of Aspergillus mold. Marles notes that Aspergillus spores can survive the heat associated with smoking or vaporization and can subsequently infiltrate the lungs of cannabis users. The resulting infection can cause serious respiratory problems and may even be fatal for patients with weak immune systems. This is of particular concern for patients undergoing treatment for cancer, who might turn to cannabis to manage the pain and nausea associated with chemotherapy. Unfortunately, there are no robust, validated tests for Aspergillus at present. Molecular assays based on the polymerase chain reaction (PCR) enable the detection of harmful Aspergillus via the targeted enzymatic amplification of species-specific DNA sequences but are also vulnerable to false positives resulting from detection of non-pathogenic Aspergillus species. USP highlights the development of such tests as an important priority for the scientific community to address moving forward; in the meantime, Marles notes that the organization has been working with other standard-setting groups such as ASTM International, which is developing cultivation practices that limit opportunities for contamination.[12] "By making sure that you have an appropriately sanitized production facility, you can greatly reduce the risk of mold getting into the product," he says.

The panel highlighted several other safety concerns related to cultivation practices, such as pesticides. In Canada, cannabis production is limited to using a relatively small group of known, approved pesticides. US growers are not subject to such limitations. "You might find all kinds of pesticides due to contamination with pesticides by drift from neighboring cultivation sites", says Giancaspro. The U.S. Environmental Protection Agency (EPA) regulates pesticides for food crops, but there is no specific tolerance or exemption from tolerance for cannabis, and the nature and extent of the risk associated with a given chemical could differ considerably for a smoked or vaporized product versus dietary exposure. USP has therefore opted for a cautious approach, with maximum acceptable exposure limits for each pesticide that are 1,000-fold lower than the acceptable daily intake levels established by the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO). USP also cautions growers to be mindful of toxic heavy metals such as lead, cadmium, mercury, and arsenic. Cannabis is known to readily absorb these elements from the ground—indeed, some farmers are even using cannabis plants from the hemp varieties as a means for actively remediating contaminated soil.[13, 14]

Room to grow

The recommendations offered in the *Journal of Natural Products* article provide a valuable foundation for alignment of testing and quality of products derived from cannabis, and Marles notes that the Canadian government may consider these guidelines as legal requirements for medical cannabis.

But this document is also just a first step. Much remains to be learned about the clinical utility of this plant, and it seems likely that future research will introduce greater complexity in terms of cannabis classification, as scientists gain more insights into the specific physiological effects of its diverse cannabinoid and terpene constituents. Indeed, as USP moves into its next strategic planning cycle, Marles anticipates that the next iteration of the cannabis expert panel may feature fewer plant scientists and more pharmacologists and clinical researchers.

Furthermore, these guidelines address the actual plant material itself, rather than the finished product as used by patients. Experts will need to continue to work together to address emerging challenges associated with different routes of administration as well as new risks that might emerge, such as potential exposure to toxic solvents used to prepare cannabis-based extracts. These future investigations will build on the quality standards established in this initial document—for example, the reference standards that USP produces for HPLC or GC analysis should be equally applicable to a CBD lozenge or THC-enriched oil as to a dried bud. "It's a logical progression, so we can work to set up a series of connected standards for quality," says Marles.

The complexity and the challenge of ensuring safe products demand efforts by all concerned organizations. USP encourages all interested stakeholders and organizations committed to quality such as AOAC, AHP and ASTM, to support the exploration of science-based standards to help ensure product quality, and thereby advance our common goals of protecting and promoting public health.

[1] https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx

[2] https://www.journalofinfection.com/article/S0163-4453(18)30032-X/fulltext

[3] https://www.bmj.com/content/365/bmj.l1141

[4] https://www.brookings.edu/blog/fixgov/2018/12/14/the-farm-bill-hemp-and-cbd-explainer/

[5] https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-importance-conducting-proper-research-prove-safe-and

[6] https://clinicaltrials.gov/ct2/results?cond=&term=&type=Intr&rslt=&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&intr=cannabis&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=

[7] https://www.safeaccessnow.org/asa_activist_newsletter_september_2019

[8] https://www.usp.org/about/convention-membership

[9] https://www.liebertpub.com/doi/full/10.1089/can.2015.29003.ebr

[10] https://www.nature.com/articles/s41598-018-22755-2

[11] https://www.westword.com/marijuana/two-more-denver-dispensaries-issue-marijuana-mold-recall-11636152

[12] https://www.astm.org/Standards/D8219.htm

[13] https://www.cbsnews.com/news/cannabis-plant-soil-decontamination-italy-vincenzo-fornaro/

[14] https://link.springer.com/chapter/10.1007/978-981-10-3084-0_10