CBD flies off shelves, fosters uncertainty in tox lab

Anne Paxton

May 2019—If a futurist had forecast 10 years ago that, in 2019, a compound of the cannabis plant would be sold over the counter and online and consumed for health reasons by an estimated quarter of the U.S. adult population, most people would have scoffed at the suggestion.

Cannabidiol (CBD), however, is just such a compound. It has become hugely popular and seemingly ubiquitous. For clinical laboratories, the trend should be concerning, some toxicology experts say. They worry that CBD's skyrocketing use poses risks and may not be justified by the scientific knowledge base about the compound, how it should be tested, and what the results should be used for.

"It's not apparent that everybody in the laboratory industry appreciates how hard the questions that CBD creates really are," says Gregory Janis, MS, scientific director of MedTox Laboratories, one of LabCorp's specialty testing labs, and associate vice president of research and development at LabCorp.

CBD, which like THC (delta-9-tetrahydrocannabinol) is one of more than 100 natural compounds of marijuana, was an unlikely prospect for such meteoric growth, Janis says. "CBD kind of went from being the redheaded stepsister of THC and gained its own following outside of the marijuana community."

That new standing has made CBD a research focus of pharmaceutical companies and one of the hottest products in the retail and direct-to-consumer markets. Market research company Brightfield Group forecasts that CBD or "cannabis wellness" sales will run about $22 billion by 2022.

CBD earned its high profile, in part, because of two little-known diseases, says Marilyn Huestis, PhD, a senior fellow and member of the steering committee of the Lambert Center for the Study of Medicinal Cannabis and Hemp at Thomas Jefferson University. "Both in vitro studies of cells and in vivo studies in animals have shown that CBD has properties that may be very helpful therapeutically, including anti-inflammatory and anti-epileptic properties." It was the latter that led to development of the drug Epidiolex, which the Food and Drug Administration approved in June 2018 to reduce seizures in individuals with Lennox-Gastaut syndrome or Dravet syndrome.

"Lennox-Gastaut and Dravet syndromes are literally what moved the entire country toward medical cannabis and then legal cannabinoids," says Dr. Huestis, who is also president of Huestis and Smith Toxicology, Severna Park, Md. Epidiolex was the first approved medicinal marijuana product directly from the hemp plant, not synthetic. "They took the plant and purified, purified, purified it so it is 98 percent CBD," she explains. That not only eased Epidiolex's approval but also further stoked the nationwide spread of legal CBD.

As a 2017 study by the National Academy of Medicine reported, there is enough evidence to affirm that both THC and CBD are relatively safe. But the issue with CBD specifically is that very little is known about whether it works to treat chronic pain as many users claim. "There is no strong data saying CBD is efficacious," Dr. Huestis points out.

This lapse is enormously troubling, in her view, because people across the board are taking the drug every day in large amounts, and that includes vulnerable populations such as children and pregnant women. And manufacturers of CBD oil are not regulated at all, she adds. A recent survey of all CBD oils sold in the U.S. and Canada, for example, found that 74 percent of the bottles did not contain what was said on their labels.

Regulation of CBD runs across the spectrum, Janis says. Some states don't allow CBD sales at all, while others allow a wide variety. In Minnesota, for example, "If you have a medical condition allowing marijuana use, you can get a product very high in THC and low in CBD or you can go to the other extreme—get high CBD and low THC—and anything in between in different blends, different ratios." This has occurred despite awareness that some of the medical uses associated with CBD have been driven more by popular culture than by scientific evidence, he says.

“Murky” is the best word to describe CBD’s legal status as a result. In fact, “incredibly murky,” according to Janis. Cannabis comes in different forms, he explains. “We have what we call marijuana and what we call hemp. They are essentially the same plant but bred to be different. Marijuana is bred to be very high in THC while hemp is bred to be very low.” A long time ago, in fact, “smoking rope” was considered a means, if you did enough of it, of getting high because there is a tiny bit of THC in hemp, he points out. CBD does not have an intoxicating effect on users. Under the 2018 farm bill, production of hemp, the source of most CBD now being produced, was legitimized at the federal level as long as it contains less than 0.3 percent THC.

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The Drug Enforcement Administration still classifies CBD as schedule I material (comparable to heroin and LSD; prohibited for use as a drug), with the exception of Epidiolex, which is FDA-approved only for the two epilepsy conditions. FDA’s approval of Epidiolex forced the DEA to reschedule any approved pharmaceutical preparation of CBD as a schedule V drug (comparable to cough syrup with codeine; having a currently accepted medical use and low potential for abuse). “That is a sort of low-risk scheduling. But the DEA kept anything that was not an approved pharmaceutical preparation as a schedule I,” Janis says. Now some 33 states have medical marijuana laws, 14 have laws specifically about CBD, and “it seems like CBD is sold everywhere regardless of the laws.”

So the big picture is complicated. Since the FDA has an approved pharmaceutical agent that is CBD, that gives the agency authority to regulate CBD as a drug. “The FDA has the ability to say something is a drug product,” Janis points out. “You can’t have drug products in food; you can’t have them in supplements without a review; a drug product has to be proven to be an effective medicine. For example, you don’t find Lipitor mixed in with cheese at the grocery store. You’re just not allowed to do that.” Could the FDA control CBD that way? Some state and city governments have acted in anticipation of such a move, he notes. In New York City and in Maine, CBD edibles were recently pulled out of storefronts by city or state health boards based on guidance from the FDA.

MedTox Laboratories runs drug tests to look for a metabolite of THC, THC-COOH, which can linger in the body for days and weeks, as an indicator of marijuana use. But consumers’ rampant, unregulated use of CBD has added a new level of complexity to testing for THC, Janis says. “We need to ensure that Grandma who is taking CBD, which has a small amount of THC in it most of the time, is not reported as being a marijuana user. She’s a CBD user. But on the flip side, the people who interpret the tests such as physicians, medical review officers, and parole officers hear from clients that ‘I don’t actually smoke marijuana. I take CBD and that’s why I have positive tests.’” That may be a true statement, he says, or claiming CBD use may be a coverup, a way of hiding marijuana use.

At MedTox, “When we do a test for marijuana use, we report concentrations of the marijuana metabolite carboxy THC in ng/mL above a certain threshold. That threshold is designed to indicate whether a sample is positive depending on why the test was being done,” Janis says. “And currently we cannot differentiate marijuana use from CBD use.”

MedTox is now testing improved methods. “We recently developed a method that will let us differentiate most CBD use from marijuana use,” Janis says. “There will always be a gray area where test results are inconclusive. But there are certainly the extremes where it can be said that someone is probably exclusively using CBD or is using marijuana and is using CBD as a cover story.”

The precedents were set when testing for codeine was developed, he says. “They set the levels pretty high to indicate a positive opiate user. That lets them avoid having codeine from poppy seeds give a person a positive result just because they like Eastern European foods.”

The plethora of unregulated CBD products is the source of the problem, in his view. “There are usually quality controls on medical marijuana products. But outside state-run facilities, CBD products are unregulated. They generally have a small amount of THC in them, it’s usually measurable, and that’s where the issue arises. It’s far too small a level to get high, but it’s still exposure.”

Knowledge of the metabolites that indicate CBD use has only recently been developed, Janis says. “How these metabolites would behave in many testing paradigms was kind of unknown. It raises concerns. One group did an in vitro test, in which they put CBD in artificial gastric fluid and reported it was converted into THC. THC and CBD are so closely related that it is feasible that would happen. But other evidence and the FDA don’t consider CBD a pro-drug converting into THC.”

Dr. Huestis rejects the idea that THC can be formed from CBD; in vivo studies have not demonstrated this effect. “In studies where we gave up to 800 mg of CBD orally to someone, there was no THC present at all,” she reports.

The challenge, Janis says, is the trace amounts of THC that are in CBD products. “It actually depends on how long you’ve been using a product and in what form you take it. If you use a CBD cream and put it on your skin, there’s very little chance that those levels would ever reach a point where a THC test would show positive. If you smoke or orally take large doses for a very long period, then it becomes a hard question to answer. THC metabolites stick around in the body for a very long time. CBD metabolites would be expected to stick around for not as long. It is an unknown. We don’t know for sure.”

Since unregulated CBD products contain a small percentage of THC, it’s unclear what exposures people are getting, he adds. “Typically people will buy CBD in the form of 10-mg gummies, but they may be taking lots of them to self-medicate for whatever reason they deem it benefits them.” In Washington state, where marijuana for recreational use was legalized in 2012, a single THC dose is 10 mg, he notes. “It would take a lot of CBD to get to that intoxicating level of THC from contamination—maybe a whole bottle of gummies at one time. But the current tests for THC are designed to pick up trace levels of THC metabolites, which could be reached without intoxication, so that’s where we have to be careful.”

With CBD oils the most common of the CBD products sold, and 74 percent of oils not containing what is on the label, the CBD oils could contain THC that could produce positive tests, Dr. Huestis says.

“We don’t have the studies in CBD that we do in THC. I did a study of cannabis users who were dependent and trying to quit use in treatment. They were getting a lot of CBD to see if it would help them not crave THC. When they relapsed and smoked, I could see a difference in the THC-to-CBD ratios. When they smoked cannabis, their THC concentration went way up—but only for an hour. So there was no way you could tell if they were only using CBD or occasionally THC.”

Other studies she has helped conduct have shown that heavy users of marijuana can show a significant buildup of THC in the body. “We published our work on how chronic frequent users build up a large body burden of THC,” Dr. Huestis says. “I sent two of these users home after 30 days residence on a closed unit, where they had no access to any drugs. And they still had low but measurable THC.” It makes sense that the same buildup would occur for CBD, she adds, but as yet there are no data to show that.

Labs will need many more studies of THC and CBD levels, she says. “I think labs should consider that in the future,

not today, there will be many reasons to monitor CBD and THC as part of therapeutic drug monitoring when patients are on medications. Right now we don't know what those levels are. There are no studies yet documenting that different cannabinoid drugs are efficacious. For therapeutic drug monitoring, you would monitor the parent drug and its metabolites. We don't have a commercial source for the 7-hydroxy or carboxy CBD metabolites. And what will make the big difference is if the 7-hydroxy is found to be active. Then we need to be measuring it."

The Lambert Center at Thomas Jefferson University is now doing a lot of work with physicians interested in testing the efficacy of THC or CBD. "I'm trying to help them design the studies appropriately so in the end you could have data to take to the FDA for drug approval." The pharmaceutical companies are also developing CBD metabolite tests. "A number of them have produced synthetic CBD, and if they can synthesize that, they should be able to synthesize metabolites. I know they have the 7-hydroxy and carboxy to use as standards or controls," Dr. Huestis says.

Typically, mass spectrometry to test urine for THC metabolites is available in laboratories, but CBD is not run in many places. More labs are starting to perform their own laboratory-developed tests commercially. "But the lab, of course, has to have a schedule I license because both THC and CBD are schedule I compounds," she notes.

The FDA's decision, when approving Epidiolex, to move it from a schedule I to schedule V drug was surprising, Dr. Huestis says, because the agency did not take CBD itself out of schedule I. "So they are waiting to see if there are more compounds, either cannabis extracts or synthetic drugs, that have proven medical indications, and then they will move the drugs to a different schedule."

Some hoped-for indications have not been borne out in trials. GW Pharmaceuticals, the manufacturer of Epidiolex, also made Sativex, a cannabis plant extract that is 50 percent THC and 50 percent CBD, for example. "It was tested in the U.S. for chronic pain associated with cancer as an adjunct to opioids and it failed," Dr. Huestis says. "It was not efficacious at reducing the pain of cancer in an adjunctive situation. But it is a plant extract, and many people believe those natural compounds are essential—that they contribute to the efficacy."

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Marilyn Huestis, PhD

That may have been true of Epidiolex, but plant extracts also have a significant downside, Dr. Huestis says. "It's really difficult to control the percentages of not only CBDs and THCs but many other components like flavonoids and terpenes when you are growing plants. So being able to produce something reproducible time after time to get an application through the FDA is probably going to be difficult to achieve."

The general public seems to believe there are no dangers from ingesting large quantities of CBD, Dr. Huestis says. But that notion is incorrect. In an article she wrote about CBD's adverse effects, she notes that in children with intractable epilepsy, high doses were necessary to reduce seizures. The dosage of Epidiolex recommended by the FDA for these pediatric patients is a very specific regimen, she says. "You start at 2.5 mg per kilogram of body

weight, then after two days you go to 5, then to 10. Twenty mg/kg is the recommended dosage by the FDA. Some may need higher doses to control seizures." For this use, "CBD is effective and it's a totally new mechanism of action. However, 20 mg/kg is a lot."

Some children receiving high doses of CBD in Epidiolex can experience serious effects on the liver, causing inhibition of some enzymes and induction of other enzymes. "If you are taking any other medication," she says, "it could affect the amount of drug available." A number of pediatric patients have had serious elevations in their transaminases "and had to be withdrawn from the drug in order to get the liver to return to normal."

"So CBD is not a benign drug. People's liver function needs to be carefully monitored," Dr. Huestis warns. Another effect is somnolence, sedation, or lethargy, which has been noted in controlled trials with Epidiolex. This makes it especially hazardous, she says, to have CBD sold without controls.

These potential risks plus the surge in cannabis legalization, the patchwork of laws governing CBD's legal status, the lack of product regulation, changing DEA and FDA classifications, still-evolving drug test cutoffs, and the shortage of research on efficacy are showing that laboratories have many CBD issues yet to confront as the "home remedy du jour," as Janis puts it, shoots to stardom in the wellness products market.

Anne Paxton is a writer and attorney in Seattle.