Clinical researchers in the US are unable to study the safety and efficacy of cannabis products purchased from legal, state-authorized dispensaries because cannabis is illegal under federal law.

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NATURAL PRODUCTS

Cannabis research stalled by federal inaction

US scientists face numerous barriers to studying health effects of cannabis

BRITT E. ERICKSON, C&EN STAFF

Researchers in the US who want to investigate the medical benefits and risks of cannabis are frustrated. They would like to evaluate the wide array of cannabis products sold in states where cannabis is legal, but federal law prohibits them from doing so because cannabis is still illegal at the federal level.

Most studies on the therapeutic effects of cannabis have relied on synthetic formulations of specific chemicals made by cannabis plants, such as the cannabinoids tetrahydrocannabinol (THC)—the psychoactive component of cannabis—and cannabidiol (CBD). A few researchers have looked at the efficacy of whole cannabis plants to treat chronic pain, but no clinical studies have been conducted on cannabis products purchased from state-authorized dispensaries. US researchers can only study the effects of cannabis using plant material grown by the University of Mississippi under contract with the National Institute on Drug Abuse (NIDA).

In March, the US Drug Enforcement Administration released a new rule intended to allow more organizations to grow more varieties of cannabis, but the cannabis research community says the proposal is still too restrictive. Additionally, cannabis researchers face the need to get approval from three federal agencies, and funding is limited. All these obstacles hinder cannabis research, the community says, leaving medical providers and consumers in the dark about the benefits and risks of cannabis products.

Mississippi monopoly

Researchers have complained for years about the quality and potency of the cannabis grown by the University of Mississippi. In general, it has lower levels of THC than products that are available in legal state markets, says Morgan Fox, media relations director of the National Cannabis Industry Association (NCIA), a trade group for the cannabis industry. Researchers have reported that the cannabis is moldy. Additionally, the material is "basically like powder," Fox says. "So it is not really representative of what people are actually consuming," he says.

The cannabis grown by the University of Mississippi has the appearance of being poor quality because it is highly processed. It is dried immediately after harvesting and stored for long periods of time, sometimes years, in a walk-in freezer at –20 °C. It is also irradiated to kill off any yeasts and molds, following complaints about mold received by the US Food and Drug Administration, says Mahmoud ElSohly, a research professor who oversees the marijuana research facility at the University of Mississippi. Before it is shipped out to researchers, the cannabis is typically ground up into particles of uniform size.

ElSohly claims that the cannabinoids in the plant material are stable over time. "We have the appropriate stability studies" to show that, he says. But the flavor compounds in cannabis, known as terpenes, are destroyed during the drying process. Terpenes may have beneficial health effects and enhance the effects of THC and CBD. It is hard to study such effects, however, when cannabis provided for medical research doesn't contain terpenes.

Terpenes aside, there is a good reason why cannabis grown at the University of Mississippi contains much less THC than that of cannabis sold in state dispensaries, ElSohly says. Cannabis cigarettes made for research all have to be the same size

The University of Mississippi typically harvests about 10 kg of cannabis grown indoors and about 500 kg grown outdoors—enough material to supply researchers for several years. The cannabis is ground into small particles of uniform size to be standardized for clinical research.

CREDIT: UNIVERSITY OF MISSISSIPPI (BOTH)

and shape, he says. When experienced cannabis users were asked to smoke a cigarette with 8% THC, they could not finish it, he says. So the highest THC content in cannabis cigarettes provided for clinical research is 6%, he notes. For comparison, cannabis sold in state dispensaries often contains as much as 30% THC.

"Our charge is not to make material similar to what is out there on the illicit market or in the state-authorized medical marijuana programs," ElSohly says. "We are here to prepare standardized material for research that is given to all investigators so the outcome for one study can be easily compared with the outcome of another study."

Expanding sources, the DEA's way

The DEA acknowledges that the quality and potency of the cannabis supplied by the University of Mississippi is not representative of the cannabis that people are actually consuming in the real world. But the agency has yet to approve any of the dozens of applications from organizations who want to provide more realistic cannabis products to researchers for medical studies.

Many of those applications have been pending since 2016, when the DEA announced that it would adopt a new approach to increase the number of entities registered to grow cannabis for legitimate US researchers.

In August 2019, the DEA released the names of 33 applicants who requested to grow cannabis as bulk manufacturers for research. Many of the applicants requested approval to supply cannabis extract, which can be used in vaping products, edibles, and oral tinctures. Since then, the DEA has received a few additional applications.

The agency claims, however, that because "the size of the applicant pool is unprecedented," it does not plan to make decisions about the applications until it changes the policies and practices that govern the bulk marijuana growers program.

The DEA provided details about those changes in the proposed rule released on March 23. The agency did not respond to a request from C&EN asking about the timeline for the regulation, but the process is likely to take several more months, if not years.

Under the proposed rule, potential growers of cannabis for research have to satisfy a list of public interest criteria spelled out in the US Controlled Substances Act (CSA).

The criteria include having effective controls against diversion of cannabis from research to illicit uses. The DEA interprets that to mean restricting the amount grown by limiting the number of registered manufacturers "to that which can produce an adequate and uninterrupted supply of marihuana under adequately competitive conditions." It is unclear whether the DEA will cap the number of registered manufacturers to satisfy the diversion control criteria.

In addition, growers must have a supply agreement with a researcher who has the appropriate DEA license to study cannabis. Alternatively, growers who plan to supply cannabis for their own research purposes must register with the DEA to study cannabis and can only grow the amount authorized in their research protocol.

Potential growers also must be able to consistently produce and supply cannabis "of a high quality and defined chemical composition." The DEA has yet to define exactly what that means. Moreover, applicants have to show "prior compliance with the CSA and DEA regulations." It is possible that companies that have grown cannabis for state-authorized programs would be excluded from consideration because such activities are illegal under the CSA.

Besides meeting the criteria under the CSA, applicants also have to be in compliance with US obligations under an international treaty, the Single Convention on Narcotic Drugs. To meet that requirement, the DEA would take physical possession of the cannabis within 4 months of harvest and be responsible for selling the product to researchers. Growers would have to notify the DEA at least 15 days before harvest. The DEA would also have the "exclusive right of importing, exporting, wholesale trading, and maintaining stocks of cannabis and cannabis resin," excluding cannabis-derived drugs and cannabis preparations that are regulated by the FDA, according to the proposed rule. Presumably the DEA would honor the supply contracts between growers and researchers.

Cannabis community concerns

In general, the cannabis industry claims that the rule would further hinder cannabis research in the US and make it harder for organizations other than the University of Mississippi to provide cannabis to legitimate researchers.

"The DEA is not a public health or a scientific organization and has much different priorities and expertise than those organizations," the NCIA's Fox says. The DEA doesn't have expertise related to facilitating research and is not in a good position to judge what research is necessary and appropriate, he notes. "So overall, we feel that they are not the appropriate agency to be charged with being the gatekeeper for research production," he says.

The NCIA suggests that the National Institutes of Health or some other agency within the Department of Health and Human Services would be better suited to oversee cannabis produced for research.

In addition, to improve the diversity of cannabis products available to researchers,

a great place to start "would be approving applications for production, particularly ones that have been sitting in the application process for up to 4 years," Fox says. Regulators should also find "some way to allow researchers to be able to legally do research on products that are available in legal regulated cannabis markets."

Some lawmakers agree. In comments submitted to the DEA, Sen. Brian Schatz (D-HI) urges the US Attorney General to waive the requirement that cannabis growers register with the DEA. Such a waiver would allow researchers with appropriate DEA licenses to obtain cannabis products from state dispensaries for research purposes.

Researchers point to the recent outbreak of severe lung disease linked to vaping cannabis-based products to emphasize why it is important to study products that people are actually consuming. The outbreak "is extremely frightening, yet the issue cannot be effectively studied because researchers cannot work directly with cannabis products that are in actual use," says Theresa A. Maldonado, vice president for research and innovation for the University of California system, in comments submitted to the DEA. She asks the DEA to allow university researchers to study cannabis products that are legally purchased from state dispensaries "without being subject to prosecution, withdrawal of federal funds, or other sanctions."

The University of Mississippi's ElSohly isn't worried about increasing the pool of growers who supply cannabis for research. "I have no problem with that," he says. The University of Mississippi has been the sole provider of cannabis for research for more than 50 years. "It doesn't really take away from what we are doing. It is not a competition per se, it just adds to the variety of products that are out there to be tested." But he questions how realistic it is to test cannabis purchased from various dispensaries across the US. "Every product is going to be different," he says.

Researchers turn elsewhere

As the DEA drags its feet in approving new cannabis sources for research, some university researchers have resorted to studying cannabis-based drugs imported from countries such as Canada. For example, a research group at the University of California San Diego is studying a cannabis-derived drug imported from the Canadian company Tilray to treat a movement disorder called essential tremor.

Tilray has also provided researchers at Columbia University with a cannabis-based product to test for efficacy in treating breast cancer patients suffering from taxane-induced nerve damage, a side effect of treatment with the chemotherapy drugs paclitaxel and docetaxel.

"Sourcing materials from other countries is currently pursued by NIDA in an attempt to provide more products," says Heike Newman, a senior regulatory manager at the University of Colorado Denver who provides regulatory guidance to clinical researchers at the university who are interested in studying cannabis. "We know it is an option," she says. "But working with these companies directly to get their products is costly and our researchers with approved funding don't have the financial means to continue with that approach."

In addition to wanting a more varied cannabis supply, "what researchers really need are more and different formulations," such as oral solutions or dermal products rather than rolled cigarettes, Newman says. "Not everyone who is willing to participate in a clinical trial wants to smoke cannabis," she says. The University of Mississippi does supply two cannabis extracts, one that is high in THC and low in CBD and another that is high in CBD and low in THC, ElSohly says. Because of the growing interest in CBD oil, "we had an option to prepare 50 kg of extract," he notes.

Even so, the chorus of lawmakers calling for change is growing. Several members of Congress grilled regulators in January about the barriers to cannabis research during the first-ever cannabis hearing of the health subcommittee of the Committee on Energy and Commerce in the US House of Representatives.

The bulk of the hearing centered on how to resolve a dilemma that has plagued cannabis policy for decades. The DEA classifies cannabis as a Schedule I drug—a category for substances that have no medical value and high potential for abuse. Other Schedule I drugs include heroin, LSD, and ecstasy. The Schedule I classification means that researchers must jump through all sorts of hoops, including seeking approval from three federal agencies, to study cannabis. The DEA can change how cannabis is categorized or take it off controlled substance schedules entirely if it has sufficient scientific evidence to justify the change, but researchers are impeded from doing the work that might provide such evidence because of the drug's Schedule I status.

House lawmakers are considering several bills that would reschedule or deschedule cannabis. There does not appear to be broad support in Congress or within the federal government, however, to legalize cannabis at the federal level.

One possible solution to expedite medical research on cannabis is to create a subcategory of Schedule I, NIDA director Nora Volkow testified at the January hearing. NIDA has been working with the FDA and the DEA to create such a pathway, not just for marijuana but for Schedule I substances in general, "so that researchers don't have to go through all of the obstacles and the delayed process," she said.

Another obstacle that researchers face is extremely competitive funding for cannabis research. In fiscal 2018, the NIH funded about $148 million on cannabinoid research, of which about $38 million was devoted to cannabis therapeutics. The NIH prioritizes funding for cannabis therapeutic studies focused on treating pain, addiction, and inflammatory disorders, as well as for studies examining the adverse health effects of cannabis on prenatal and adolescent development.

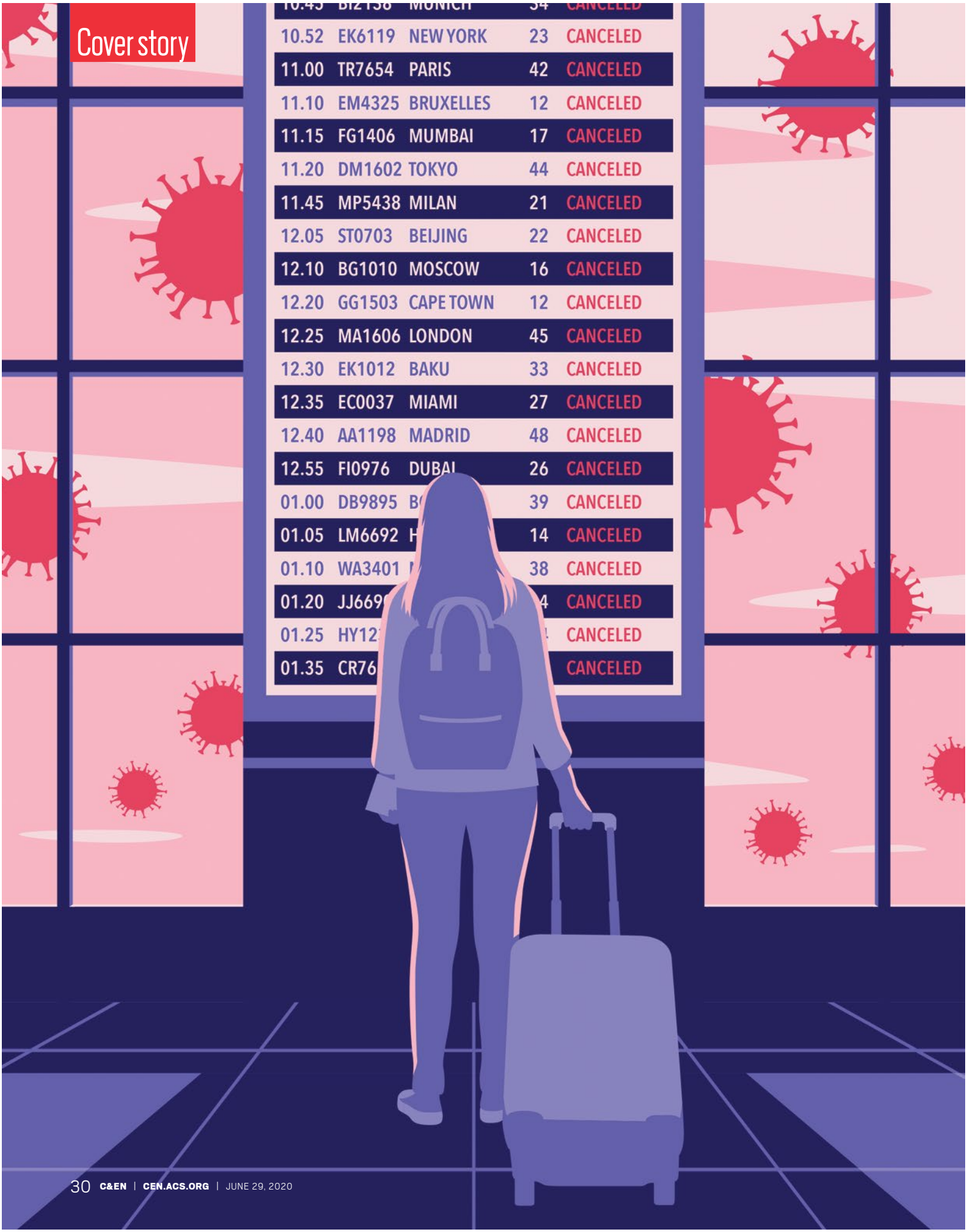
As the number of states legalizing cannabis for medical and adult use grows, nearly everyone agrees that more research is needed to better understand the benefits and risks.

"Thirty-three states now allow the medicinal use of cannabis and 11 states and the District of Columbia have legalized cannabis for adult use," subcommittee chair Anna G. Eshoo (D-CA) noted during the hearing. "As more states allow cannabis, the federal government still strictly controls and prohibits it, even restricting legitimate medical research." ■

Changing criteria for growing cannabis

Growers must meet the following requirements under the Drug Enforcement Administration's March 23 proposed rule:

- have a supply agreement with a DEA Schedule I licensed researcher or have their own license to conduct cannabis research and an authorized research protocol
- be able to consistently produce and supply high-quality cannabis
- show prior compliance with the Controlled Substances Act and DEA regulations
- notify the DEA at least 15 days before harvest and allow the DEA to take physical possession of the cannabis within 4 months of harvest
- give the DEA exclusive rights to distribute the cannabis, including importing and exporting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STRANDED BY THE PANDEMIC

Hundreds of international graduate students and postdocs are stuck in their home countries because of canceled flights or closed embassies. The delays will affect the trainees, their labs, and chemistry departments worldwide

ANDREA WIDENER, C&EN STAFF

When he left Canada for India in February, Varoon Singh thought he was just heading home for a brief visit before starting a postdoctoral position at Ghent University in Belgium.

Singh had just finished a postdoc at the University of Waterloo. He'd struggled in Canada to get a medical checkup required by Belgium, so he thought he would visit family in India and get his visa straightened out at the same time before moving to Belgium in March.

Then the COVID-19 pandemic halted travel worldwide. Now Singh and his wife have been stuck in Mumbai, where they're staying with family, for almost 4 months. He has had his visa since early March, but he can't get a flight.

Singh is among hundreds of graduate students and postdoctoral scholars across the globe who are stranded by the COVID-19 pandemic. Closed borders and canceled flights have kept them away from their labs. Shuttered embassies and consulates prevent them from picking up visas or participating in interviews. And no one knows when the situation will improve.

"Research is a second job these days. My first job is to find out whether I can make it to Belgium or not," Singh says.

The situation could have a devastating effect on the young scientists, who will have lost half a year or more of research and studies to the pandemic. The Donald J. Trump administration's recent travel ban could make things worse for those still waiting for H-1B visas (see page 12). And the fate of hundreds more new international graduate students who are not able to start in the fall is still unclear to many university researchers and chemistry departments.

In some ways, Singh is lucky—his Ghent advisor, Lynn Vanhaecke, arranged for him to start working remotely. They are writing grant proposals, and he's participating in lab meetings. He's writing up

In brief

The COVID-19 pandemic has left many international students and postdocs uncertain about their future. Caught on vacation or between jobs, they are unable to travel to their labs because of closed borders, canceled flights, and shuttered consular offices. And as restrictions continue, the fate of these trainees, their labs, and their departments are up in the air. The pandemic adds to concerns by US scientists that the country is no longer seen as a welcoming place for international researchers (see page 34).

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