



BY MALORYE ALLISON BRANCA

CANNABIS ANALYSIS TAKES OFF

WITH MEDICAL MARIJUANA (CANNABIS) LEGALIZED IN MORE THAN 20 U.S. STATES, SEVERAL MAKING RECREATIONAL USE LEGAL, AND MORE THAN 30 DISPENSARIES APPROVED IN CANADA, THE DEMAND FOR CANNABIS CHEMICAL ANALYSIS HAS SOARED. THE CURRENT MARKET FOR LEGAL CANNABIS IS ABOUT \$6 BILLION AND IS ESTIMATED TO GROW TO \$11 BILLION BY 2018.

The tools needed to verify composition and safety are already available because of the long-standing foods and natural products testing markets. But cannabis is being used in a wide range of products, including edibles, which can complicate studies. Most analysis is currently performed in established analytical labs, but there is rising interest among cannabis growers, processors, dispensary owners and others in being able to do such analyses themselves, not only to monitor the quality of their products, but increasingly to be able to make claims about them as well.

“Right now, this is not one of the largest markets in the analytical chemistry field, but it is growing at a fast rate,” says Scott Kuzdzal, general manager of marketing at Shimadzu Scientific Instruments.

Besides the growing market for the drug, it’s also expected that there will be a marked increase in research on the health effects of cannabis, although there are still hurdles. The US Drug Enforcement Administration (DEA) recently ruled that cannabis will remain a Schedule I drug, alongside heroin.

That ruling came in response to a petition by two former state governors who had urged reclassification of the drug based on the growing medical use. The DEA ruled that the drug “does not meet the criteria for currently accepted medical use ... and there is a lack of accepted safety for its use under medical supervision.” It’s a position that proponents of medical marijuana object to.

However, the agency also announced that it would allow more research into cannabis’ possible medical attributes. Until now, DEA has only allowed federally sanctioned research with cannabis from a single supplier—the University of Mississippi, which operates under a contract with the National Institute on Drug Abuse. But in its August 2016 announcement, DEA said it would take steps to expand the number of DEA-registered manufacturers. Researchers say this is vital because there can be substantial variation between plants grown at one location or another, and there are many different cultivars (or strains). People are keen to study those variations and how they impact the drug’s performance.



VAPE PENS LIKE THE ONE SHOWN ARE POPULAR WAYS TO CONSUME CANNABIS.

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WHO ARE AUTHORIZED TO CONDUCT RESEARCH ON MARIJUANA AND ITS COMPONENTS. THAT NUMBER IS LIKELY TO SWELL AS NEW SOURCES OF CANNABIS FOR RESEARCH BECOME AVAILABLE AND AS THE INTEREST IN THE DRUG'S MEDICAL EFFECTS GROWS.

Because the federal government still considers cannabis an illegal substance and states have varying regulations about the drug, it is important for laboratory operators to be aware of local regulations and thoughtful about the transportation of the drug.

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marijuana and its components. That number is likely to swell as new sources of cannabis for research become available and as the interest in the drug's medical effects grows. It's also important to consider that given the current legal status of cannabis, some studies can be done on analog materials that provide close alternatives.

KEY TYPES OF ANALYSES

Except for heavy metal testing, the most commonly used separation techniques are gas chromatography (GC) and liquid chromatography (LC), with a conventional detector or coupled to mass spectrometry (MS). It's important to note that products that are smoked have different physiological effects than those that are eaten. Tests may need to be adjusted based on the multiple delivery methods used—edibles, topicals, tinctures, etc.

“This complicates testing especially on matrix effects and sample preparation,” says André Luis dos Santos, Americas market development manager at Agilent. For example, “if you are testing an edible, the tetrahydrocannabinol levels may not be uniform across the product, so representative sampling is important,” says Robert Packer, senior manager of foods and pharma strategy at PerkinElmer.

There are dozens of cannabinoids, but eight are of the most interest in potency testing, and the primary objective is usually the

quantification of the tetrahydrocannabinol/cannabidiol (THC/CBD) ratio. THC is psychoactive, but CBD is not, so a higher ratio of the latter is often preferred for medicinal marijuana. Hemp is a strain of cannabis that is bred to reduce the amount of THC to 0.4% or below. It is commonly used for clothing and other nonmedicinal purposes.

THC is formed by decarboxylation, through smoking, cooking or other forms of heating, of the major cannabinoid in the natural plant—THC acid (THCA). That creates an important consideration when testing for potency. “GC has a hotter ionization,” Kuzdzal says, “It will convert more of the THCA to THC.” Typical instruments used for such testing include LC-UV or UHPLC-UV (or -PDA equivalents).

Since state-sponsored marijuana production is still in its infancy, there are few regulations governing the use of pesticides with this plant. Some of the classes of pesticides that are relevant to screening include organophosphates, carbonates, pyrethroids, and avermectins.

“You can use LC-MS or GC-MS for pesticide screening, but more labs are now adopting the triple quadrupole mass spectrometers due to their ultrafast speeds and quantitation capabilities,” Kuzdzal says. Such instruments include Shimadzu's LCMS-8050 and 8060, Agilent's 7000D and 7010B GC Triple Quad Systems, the Agilent 6400 Series LC Triple Quad Systems, PerkinElmer's Qsight Triple

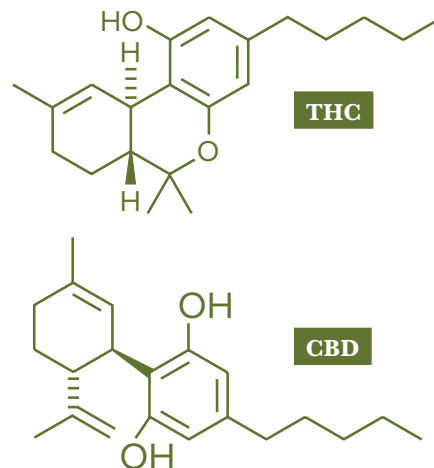
Quad MSMS, and Shimadzu's GCMS-TQ8050. "We have the world's fastest triple quadrupole with high sensitivity," Kuzdzal says. "Normally, a lot of labs will run a test for positive pesticides then they have to switch the polarity to do negative analytes. With Shimadzu ultrafast mass spectrometry (UFMS), you can analyze more pesticides in a single run."

A lot of pesticide screening is targeted, but "for a broad-based, unknown screening of pesticides, high-resolution, accurate-mass (HRAM) systems such as the Agilent 7200B GC-QTOF and the 6500 Series LC-QTOF Systems can be used," says Dos Santos. Agilent also supplies QuEChERS kits for sample preparation, including the EMR-L (Enhanced Matrix Removal—Lipid) dispersive kits. Santos adds that "since currently, there are no guidelines or authorized pesticides for use with cannabis, screening techniques such as GC- and LC-QTOF will continue to be important as laboratories may need to check for everything that might be present in a sample."

Terpenes are another class of compounds of interest. For one thing, they give cannabis its taste and aroma. But they can also have other effects. "Pinene is a terpene that acts as a bronchodilator, and there are other terpenes, such as linalool, that act as sedatives," Kuzdzal says. Instruments that can be used to test for terpenes include gas chromatography-flame ionization detector (GC-FID), GC-MS, and GC-MS/MS.

Other tests include those for residual solvents, often done using headspace coupled to GC-FID or GC-MS; heavy metals using ICP-OES, ICP-MS, and ICP-MS/MS; and mycotoxins using LC-MS and LC-MS/MS. With residual solvents, "you are looking at the volatiles released by the sample," Packer explains. And with heavy metal screening "ICP-MS lets you look a wider range of metals," he says.

Growers, Packer says, are also particularly interested in moisture content, which can influence the growth of molds. As a plant gets over 10% moisture, there is a higher likeli-



hood it will become contaminated. Moisture content and other quality measures such as THC and CBD levels can be carried out using infrared spectrometers—FT-NIR and FT-MIR. "Infrared is simple to use and requires less skilled staff," Packer explains. "With no sample prep you can analyze within 30 seconds," he says. For those just starting their labs, certified preowned instruments available from manufacturers including Agilent may be



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an economical choice. But whatever testing they do on their own, growers will still be required to send their products to third-party labs for testing to meet state regulations. Kuzdzal believes that going forward, “fine-tuning compounds such as terpenoids, flavonoids, and the cannabinoids will be important.” Understanding “the way things work together, or their ‘entourage effect,’ is one of the key goals, he adds.

“AS WE MOVE FORWARD, THERE ARE GOING TO BE INCREASING REQUIREMENTS FOR HIGH PURITY AND REPRODUCIBILITY.”

— MICHAEL BISHOP, HEIDOLPH NORTH AMERICA

REFINING CONCENTRATES

Cannabis oils have also become a growing business. These oils are used in vaporizer cartridges for e-pens (also called vape pens) as well as in several types of infused products (IPs) such as edibles, transdermals, sublingual, drinks, and suppositories.

“The first wave of cannabis extracts were called ‘shatter’ and were essentially produced by vacuum drying, creating an extract with a brittle consistency,” explains Michael Bishop, director of applied markets at Heidolph North America. That meant they could only be used with smoking devices. But some people can’t smoke, so the development of e-pens, which produce a vapor rather than smoke, and IPs has further expanded the market for cannabis. Extracts don’t usually have to be tested for pesticides, mold, or other contaminants if the plants they were extracted from have already been tested. However, they do need to be tested for potency.

Extracts can be refined using rotary evaporators, such as those in the Heidolph Hei-VAP series. These instruments are used for standard, complex, and automatic distillation.

CANNABIS-INFUSED BROWNIES AND OTHER EDIBLES CAN BE DIFFICULT TO ACCURATELY ANALYZE FOR THC/CBD CONTENT.

They feature overheat protection, a detachable panel for easy use from outside closed fume hoods, and a vacuum seal and vapor tube system. A typical setup includes a rotary evaporator, vacuum pump and chiller. The goal is to end up with just the cannabinoids you are aiming for. As noted earlier, the balance between THC and the nonpsychoactive cannabinoids is a priority. As a result, getting a pure extract is important.

Although precision is obviously a priority, “safety is our primary concern,” Bishop says. The companies’s main clients are research institutions and traditional labs, but “with the

CANNABIS SCIENCE CONFERENCE HELPS PIONEERS FORGE VIBRANT NEW MARKET

When Josh Crossney, President of jCanna, admits he may have been a little ahead of the curve when he started planning his first Cannabis Science Conference. “I had been going to a lot of general analytical chemistry conferences,” he says, “and I began seeing more and more about cannabis.” While there were plenty of meetings on how to grow the plant or turn it into products, there wasn’t a lot of dependable scientific information on how to analyze it. “I saw this as a clear unmet need.” So, in 2015, he decided to jump in and found a conference that would focus just on that.

At first, the interest was tepid, but with the surge in states approving medical marijuana, jCanna’s Cannabis Science Conference has grown exponentially. “This year, we had to change the date to accommodate all the sponsors who wanted

to participate,” Crossney says. “Now, when I’m at analytical chemistry meetings, there are lots more people who say they are very interested in reaching this market.”

This year the Cannabis Science Conference features over 30 distinguished speakers, including Tracy Ryan of CannaKids; Dr. Kevin Rosenblatt, CannabiLabs/Integrated Biosource; Dr. Uma Dhanabalan of Uplifting Health & Wellness; and Dr. Dedi Meiri of The Technion Institute of Israel, just to name a few.

You can view the full technical agenda for the conference, which is in Portland Oregon Oct 5–6, at www.CannabisScienceConference.com. For 2016, Crossney is also introducing a preconference workshop called Canna Boot Camp—a hands on, full-day session on cultivation, extraction

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and testing of cannabis. There will be participants from at least ten regions in the world.

The growing interest in Cannabis is not surprising, given that analysts have estimated the market for legal sales could grow from \$5.4 billion in 2015 to up to \$11 billion by 2018. Big challenges still lie ahead. For example, there is currently a lot of state-by-state variation in regulatory requirements, and the drug is still technically illegal according to Federal statute. But sales are headed up and many believe demand for analytical services will continue to surge.

“It’s definitely an area of growth for analytical chemistry companies,” Crossney says. “At some of the companies I’ve spoken to, this is actually their biggest growth area.” Most of the analysis is currently being done in established labs, but the market will grow further as growers and dispensaries seek to distinguish themselves from their competitors by citing the potency, composition and safety of their products.

Crossney finds this field exciting, in part because it’s a developing science. “There are no well-established methods and standards,” he says. “People will make something, such

as a tincture, and take it for testing at different places and get different results.” As a result, it’s up to the field’s pioneers to help determine what those standards will be.

Something Crossney and all of the pioneering instrument companies are passionate about is patient safety. “Doctors are recommending medical marijuana for many conditions now, including in children with cancer, autism, epilepsy and Crohn’s Disease,” he says. A pesticide or mold could seriously harm such patients who may already be immunocompromised from traditional treatments, like chemo and radiology. Plus, since there are many strains of cannabis and different ways to formulate them, it’s critical to determine which types are best for which conditions. “There’s a lot of work ahead,” says Crossney, “But we’ve definitely made big progress already.”



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spread of legalization, a lot of labs that were already producing extracts are moving from clandestine basement and garage operations, using rudimentary equipment, into regulated lab environments that have the same safety requirements as a traditional chemistry lab.” Consequently, many of the people in these new labs have little classical analytical chemistry training or experience. As a result of the cruder, underground approaches, there were sometimes accidents as well as big variations in quality.

For that reason, Heidelph has been focused on making its instruments as automated and easy to use as possible. The company also provides a high degree of training.

“This market has seen pretty fast growth,” Bishop says. Starting around 2014, after both Colorado and Washington legalized recreational cannabis sales, there was a huge growth in demand by nontraditional labs for equipment and training. “As we move forward, there are going to be increasing requirements for high purity and reproducibility,” he adds. There are hundreds of compounds in cannabis and thousands of cultivars. “With new research, we’ll be able to identify which constituents of the cannabis plant are efficacious and for what,” Bishop says.

OUTLOOK

In the future, dos Santos expects the bigger multinational testing companies are going to want to participate in this market, which he thinks will lead to productivity gains “By shifting some tests from conventional GC and LC detectors to more sensitive and selective tools, such as GC- and LC-MS/MS.”

Packer, meanwhile, expects that some of the most successful growers will highlight that they are doing traditional lab quality testing on their products themselves. Growers, processors and dispensary owners will need to continue to seek third-party analysis of their products, but they could distinguish their products through higher quality analysis. Another key trend is the expansion from the dry product, or flower, to more alternatives such as tinctures and edibles.

Instruments are also getting easier to operate. “We are even offering push-button analyz-

ers,” Kuzdzal says. “Everyone is simplifying these tools so they are easier to use, but can also deliver the highest accuracy and reliability for routine cannabis QC testing.” He continues, “In this regard, analytical instrument manufacturers are applying decades of experience in other, more mature markets such as environmental, food safety,

clinical, and pharmaceuticals to help improve the quality of cannabis testing to help ensure safer products for cannabis consumers.”

Experts also agree that it is crucial to start seeing the establishment of better standards and to see those enforced nationwide. “Because it is not legal at the federal level,

every state has different regulations,” Packer explains. With better standardization, labs will have a much clearer understanding of the requirements for testing. •

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