

Hemp's Cannabinoid Quandary

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Jolene Hansen | October 2021



Photo by Rick Dahms

Dr. Ethan Russo, M.D., CEO and founder, CReDO Science

When the Agriculture Improvement Act of 2018 (the 2018 Farm Bill) removed hemp from Schedule I of the federal Controlled Substances Act, many cannabinoids now making headlines were virtually unknown to farmers pinning their hopes on hemp. But the hemp market soon spawned a robust cannabinoid industry, with CBD as the star.

Since then, the industry of hemp-derived cannabinoids has assumed a life of its own, expanding to include minor cannabinoids having everything from well-researched benefits to novel, controversial and intoxicating unknowns. Staying abreast of trends and regulatory responses is akin to tracking moving targets. And producers who ventured into regulatory gray areas have become targets themselves.

Yet despite the turbulence, hemp-derived cannabinoids still promise vast potential and profit.

Dr. Ethan Russo, M.D., is a board-certified neurologist who's studied cannabis and cannabinoids for a quarter-century. Now CEO and founder of CReDO Science, Russo served as senior medical adviser to GW Pharmaceuticals, the British company that developed Epidiolex, the first and only CBD drug to win U.S. Food and Drug Administration (FDA) approval.

Russo explains that understanding the potential of cannabinoids rests on understanding the endocannabinoid system, a system of endogenous cannabinoids and receptors within the human body. These same receptors are where cannabis-derived cannabinoids, such as THC, also lodge.

"The endocannabinoid system is the master homeostatic regulator of human physiology. It is the thing that keeps in balance our bodily functions," Russo explains, noting brain function, emotions, nausea, hunger and more. "You name it. Any aspect of how we work is affected by this system."

Therein lies the reason cannabinoids have tremendous potential for so many conditions and uses—and what's at risk when zeal for new cannabinoid profit streams sprints past science into unknowns.

Fact or Fiction?

A quick internet search on virtually any minor cannabinoid yields multiple articles and blog posts implying vast amounts of research behind even obscure compounds and their effects. Russo acknowledges a wealth of knowledge exists about cannabinoids and their work in the human body, but with an important qualifier: "We know a great deal about what are considered the major cannabinoids: THC [tetrahydrocannabinol] and CBD [cannabidiol]."

When it comes to all the cannabinoids *Cannabis sativa* can produce, which Russo puts near 150, he says the surface is barely scratched. Beyond a dozen or so, Russo says the vast majority of known cannabinoids remain uninvestigated to any significant degree.

"But what is really intriguing is, of the cannabinoids that have been researched so far, all of them have obvious medical applications and are quite distinct from one another in how they act. So, there is a tremendous amount yet to be learned here," Russo says.

One might think the farm bill facilitated U.S. cannabinoid research, but Russo disagrees: "There remain considerable roadblocks to research, such that I would say the situation is not that different now than it was in the late '90s. Even with the [farm] bill, there are severe restrictions on what one can do. ... This is one explanation for why I've spent the majority of the last 25 years working for foreign-based companies."

Russo explains that without governmental support and funding, biomedical research on therapeutic applications of cannabis and its derivatives often falls on private companies. But many private studies involve subjective feedback from patients, not rigorous research.

"That's all well and good," he says. "It can provide some evidence of benefit, but in the scheme of drug approvals, like by the Food and Drug Administration [FDA], or the opinion of physicians or scientists, that's very low-level evidence. And it really doesn't push the proverbial ball forward in terms of acceptance on a scientific level."

Conversion and Quality Concerns

Anyone following hemp's cannabinoid boom witnessed the rapid rise of delta-8 THC. This high-inducing cannabinoid naturally occurs only in small amounts that are cost-prohibitive for growers to produce and process at scale. However, delta-8 is synthesized easily from CBD. Both the chemical conversion process and the intoxicating result have put delta-8, along with similar THC's such as delta-6, delta-7 and delta-10, at the center of controversy.

What About THC-O Acetate?

Another cannabinoid of both up-and-coming popularity and concern is THC-O acetate. Unlike delta-9 THC and its other numbered analogues, the semi-synthetic THC-O acetate is made with a toxic chemical called acetic anhydride, says Dr. Ethan Russo. And while it's more potent than delta-9 THC, that may not necessarily mean it's "better," Russo warns. As for producing and selling THC-O acetate, Russo says, "Don't go there." Read the full Q&A with Russo on the cannabinoid.

Russo shares that a 1990s study in Israel found delta-8 beneficial in treating nausea in children undergoing chemotherapy. He also reports delta-8 THC is more shelf-stable than delta-9. But his primary concerns with delta-8 products flooding the hemp market lie with potential contamination issues and lax quality control. Though much of the marketing around delta-8 suggests extensive research, Russo puts it in context: "We have heard, but it's not yet proven, that it's not as potent or not as intoxicating as delta-9. But that really hasn't been tested head-to-head in humans in any kind of formal basis."

Russo shares a recent conversation with a respected Canadian analytical lab that's tested large numbers of delta-8 samples. "When they see delta-8, there are always other compounds present—delta-10, delta-6. We know even less about those," he says. Of greater concern are what Russo calls the "unknown unknowns," potentially toxic byproducts that can be created during chemical synthesis.

Cannabis scientist and educator Dr. Greg Gerdeman, Ph.D., president and CEO of NASHCX (Nashville Commodities Exchange), also has concerns.

"My biggest concern is not that the known cannabinoids that have occurred in cannabis are harmful to human health. Cannabinoids are by and large resoundingly safe and work on the endocannabinoid system in ways that I think are much more likely to be supportive to health than hurt it," Gerdeman says. "... The problem is in contaminants. The problem is that synthesizing these isomer cannabinoids is easy enough to be dangerous, and there's not control over who moves their experimental ... product directly to a marketplace."

Cannabis and hemp consultant Kenneth Morrow, owner of Trichome Technologies, isn't surprised by the surge in intoxicating hemp-derived cannabinoids. "There's so much financial incentive to do so," he explains, noting that hemp processors avoid strict regulations and heavy taxation that the state-legal cannabis industry faces.



Greg Gerdeman
Courtesy of Greg Gerdeman

Morrow, who pioneered the art of terpene isolation in cannabis, says it's important to make a distinction between extraction and conversion involved with cannabinoids like delta-8. He explains that the extraction methods being used are typically the same accepted and approved methods commonly used for other hemp and cannabis products.

"Those are the same methodologies, so there's no increase of contaminants or potential problems with the extraction methods," Morrow explains. "It's when they extract the CBD or whatever chosen compound and then they start doing the conversions. ... If there is a lot of harmful chemicals left in the resulting conversion, obviously, it's a bad thing."



Kenneth Morrow
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Regulatory and Legal Hurdles

Attorney Nolan Jackson, part of the business litigation practice group at Frost Brown Todd, advises clients nationwide regarding hemp laws and regulations at the state and federal levels. He also serves as regulatory counsel to the U.S. Hemp Roundtable, a national nonprofit hemp industry advocacy organization.

Jackson sees two central issues facing hemp-derived cannabinoids at this moment: the FDA status of CBD in food and dietary supplement products and the issue of intoxicating cannabinoids and intoxicating hemp-derived products.

On the first issue, Jackson explains that while the 2018 Farm Bill removed hemp and hemp-derived THC_s from Schedule I controlled-substance status, it didn't remove the FDA's regulatory jurisdiction nor enforcement ability. And, right or wrong, the FDA maintains adding CBD or THC to food or marketing either cannabinoid as a dietary supplement is illegal under the federal Food, Drug and Cosmetic Act.

On the second issue of intoxicating hemp-derived cannabinoids, such as delta-8 THC, Jackson breaks down current arguments regarding legality, pro and con.

The primary argument for legality is simple: The 2018 Farm Bill defines hemp to include derivatives, extracts and cannabinoids, as long as delta-9 THC does not exceed 0.3%. "In other words, if it's hemp, ... it's protected, regardless of the presence of an intoxicating cannabinoid such as delta-8 THC," Jackson says, explaining the argument for its legality.

But counterarguments are several. One argument against legality is that Congress intended for the 2018 Farm Bill to legalize non-psychoactive or non-intoxicating hemp and believed the 0.3% delta-9 THC limit accomplished that.

Jackson explains another argument against legality maintains that, according to the August 2020 U.S. Drug Enforcement Administration (DEA) interim final rule on hemp, all synthetically derived THC_s remain Schedule I controlled substances, regardless of their delta-9 THC content. The catch, he explains, is that federal law does not define "synthetic" or "synthesis," and opinions on delta-8's standing differ.

An additional position, held by Russo, is that delta-8 and similar CBD-derived cannabinoids remain illegal analogues of delta-9 under the Federal Analogue Act, which says that if someone creates a similar molecule to a federally illegal substance, such as delta-9 THC, that analogue is illegal.

Jackson reports the U.S. Hemp Roundtable's position on intoxicating products made from legal hemp is clear: "It does not believe in a wholesale ban against intoxicating products. What it prefers is to see those products regulated in the same way as other intoxicating cannabis products like adult-use marijuana."

As this story went to press, Jackson said he was aware of at least 17 states with delta-8 THC laws, regulations, policy statements, or law enforcement actions, including similar THC_s in some cases. Law enforcement action against delta-8 has also happened in states without formal policy statements, including product seizures from a vape shop South Carolina.

Jackson says recent state action regulating intoxicating cannabinoids falls in three camps: "[Some] states have banned the manufacture or sale of delta-8 outright. Some states are allowing delta-8, but only as part of an adult-use marijuana program or regime—that would be the position of the Roundtable. Then a third group of states is addressing the issue through their definitions of total THC, so their laws would limit legal hemp products to 0.3% total THC." Some of those definitions refer to all THC_s, while others specifically mention THC_s such as delta-8, delta-7 and delta-10, along with delta-9.

Jackson expresses concern that this regulatory patchwork may exacerbate marketplace confusion, disrupt interstate commerce, and lead to greater compliance costs for businesses.

Industry and Consumer Savvy

Gerdeman says the hemp industry's understanding about cannabinoid science has varied significantly from its start. At one end of the spectrum were traditional family farmers, unfamiliar with CBD. At the other end were experienced cannabis growers shifting to CBD-dominant cannabis—considered hemp if it contains a maximum of 0.3% THC—for cannabinoid extraction.

While many hemp farmers are interested in new derivatives liked delta-8, Gerdeman says many are not. "I've talked to farmers who are very upset that in order to even try and sell their product now, it's turning into a drug that gets people high. That's not what they thought they were doing. It's not what they're wanting," he says.

On the consumer front, John Kagia, chief knowledge officer for New Frontier Data, describes a gulf between the hemp industry's interest in commercializing minor cannabinoids—intoxicating or not—and consumer awareness.



Courtesy of Jackson
Nolan Jackson

“While these minor cannabinoids may present considerable wellness or therapeutic potential, we think that it is going to be absolutely critical that there’s a major component of consumer education if these cannabinoids are going to enjoy anything close to the types of successes that CBD and THC have enjoyed in terms of adoption. Because even though consumer interest may be high in learning more, as it currently stands, there remains a very significant knowledge gap,” Kagia says.

Eric Singular, NFD senior hemp analyst, notes this limited consumer awareness dampens hemp industry excitement surrounding minor cannabinoid production. Delta-8 was an exception easily marketed to consumers through comparisons to delta-9 THC, he says. He adds that extremely high costs for many minor cannabinoids, largely due to low supply compared to CBD, also hinders growth. (See sidebar below.)



John Kagia

Photo courtesy of New Frontier Data

“The other thing that has to be considered in any conversation about cannabinoids at this point is FDA’s rejection of the CBD New Dietary Ingredient (NDI) status. I think any producer out there who would be making [a] white label bulk cannabinoid ingredient probably should be looking at that rejection of the new dietary ingredient with some pause and hesitation,” he says. “In other words, if FDA is unwilling to grant CBD dietary ingredient status, what is FDA going to be granting any of these other cannabinoids? That should be a concern in folks’ minds at this point.”

What Does the Future Hold?

Looking forward, Gerdeman is reflective. “For hemp-derived cannabinoids, I hope that there can be a path forward, but it must involve transparency, honesty in labeling and quality control checkpoints in the development,” he says.

“We are at a place in time where we have the knowledge and sophistication to understand more about the cannabis plant and to breed more into the cannabis plant than ever before. And part of what’s so amazing about it is how adaptable the plant is, in its physical properties and phytochemistry,” he says. “To chase a monoculture CBD because we can cook it up in different kitchen labs to have the molecule of a moment—that’s a shame to me if it distracts from using modern genomics and breeding and intelligent farming.”

Morrow, like many in the hemp and cannabis industries, says he’s conflicted about the path industry regulation should take. He worries that unscrupulous practices and exploitation of legal loopholes could trigger blanket bans and hinder the next medical breakthroughs.

“To stifle development on these first emergers, be it delta-10 or delta-8, pretty much stifles research and development for all the rest coming forth. To stifle that development, to me, is a shame,” he says. “But I don’t want [regulators] to tell manufacturers they can unleash any chemical they want on the general public without any oversight. I don’t believe in that either. I’m very conflicted on both sides.”



Eric Singular

Photo courtesy of New Frontier Data

Kagia believes the stamp of federal approval is necessary for major retailers and national consumer packaged goods companies to dive into cannabinoid-infused consumable product development. “To us, that is going to be one of the really consequential outstanding developments ... which will be instrumental in shaping the trajectory of this market,” he says.

Jackson echoes that sentiment. “Until we address the issue of the FDA on CBD and food and dietary supplements, I think there will continue to be negative market consequences. There is undoubtedly an oversupply of CBD waiting to hit retail shelves. But until we answer the question of CBD and food and dietary supplements at the federal level, big box retailers and national food companies will continue to be reluctant to get into that business. And those consequences go all the way down the line to hemp growers,” he says.

Russo says there’s a bright future for cannabis and hemp commerce and research. “On the pharmaceutical side, in particular, I want to see the roadblocks to research being liberalized so that it’s easier to do the kind of work we should be doing in this country but are ceding to other nations of the world,” he says.

“We need the straight jacket off for this to really take off and be part of a burgeoning industry that potentially can help a great number of patients, improve quality life for them and also provide employment for many people.”

Will that require federal legalization of cannabis in the U.S.?

“It would sure help,” Russo says.

The information in this article is not intended to be medical or legal advice, should not be taken as medical or legal advice, and should not be relied upon in place of consulting with qualified medical/legal professionals.

Jolene Hansen is a freelance writer specializing in the hemp, horticulture and specialty ag industries. Reach her at jolene@jolenehansen.com.

4 Minor Cannabinoids in the News

CBN (cannabinol): Naturally produced when delta-9 THC breaks down, CBN is well-researched. Dr. Ethan Russo, M.D., a board-certified neurologist and CEO and founder, CReDO Science, says it’s more shelf-stable than and has about one-fourth the potency of delta-9 THC. Although CBN is frequently touted for sleep, Russo and cannabis scientist and educator Dr. Greg Gerdeman, Ph.D., say research doesn’t support that claim. And, while some CBN producers are using innovative processes to hasten natural breakdown of THC, Gerdeman says many are using synthetic shortcuts instead.

U.S. bulk isolate price per kilo: \$7,000-\$9,000 (September 2021 data, courtesy of New Frontier Data (NFD))

THCV (tetrahydrocannabivarin): This cannabinoid was described by Russo as “a very promising agent” with a very different profile than THC. Unlike THC, Russo says this extensively researched cannabinoid reduces hunger—a quality that’s captured the attention of the weight management industry. He also notes it’s been shown to benefit certain diabetic conditions and nerve-based pain, plus it has anticonvulsant properties that may benefit seizures. Naturally occurring

in some types of cannabis, THCV is limited in supply, making it one of the costliest cannabinoids on the market.

U.S. bulk isolate price per kilo: \$45,000-\$50,000 (September 2021 data, courtesy of NFD)

CBG (cannabigerol): A “real up-and-comer” in Russo’s estimation, CBG in cannabis typically goes on to become THC and CBD. But selective breeding for CBG-dominant varieties has made this cannabinoid more readily available. “We have just had accepted for publication the first big survey of cannabigerol-predominant cannabis usage,” Russo says, noting the paper was published in the journal *Cannabis and Cannabinoid Research* in September.

“So [in the study], we have 127 adults that have used predominantly CBG cannabis products for a wide variety of conditions—including pain, depression, anxiety, some gastrointestinal complaints,” Russo says. “People have found these quite effective by their own estimation and often preferable to conventional drugs used to treat the same kinds of problems. They also reported very few side effects and little to no withdrawal effects if someone was taking it and then stopped.”

Russo shares that prior research with animals indicates CBG may have antidepressant and anti-anxiety effects. It’s also a very powerful antibiotic against certain types of bacteria. “As if that weren’t enough, it seems to be active in treatment of some tumor cell types, particularly prostate cancer and some breast cancer. So, this is a very, very promising agent,” he says.

U.S. bulk isolate price per kilo: \$2,000-\$3,000 (September 2021 data, courtesy of NFD)

THCP (tetrahydrocannabiphorol): The most recent cannabinoid discovery, along with CBDP (cannabidiphorol), THCP was isolated for the first time in 2019, with researchers indicating this analogue of THC may be more than 30 times as potent as delta-9 THC. But Russo says this potency may not be an advantage. “My suspicion is it’s going to be too powerful to harness as a drug,” he says. “But it could explain why every once in a while, there’ll be a type of cannabis where it tests out as only having a relatively lower or moderate amount of THC, but consumers find it extremely powerful.” CBDP’s potency is still being studied.

No confirmed pricing information available.