National Center for Complementary and Integrative Health

2024 NCCIH Cannabinoids and Pain Research Annual PIs Meeting

Meeting Summary

nervous system (PNS) and the central nervous system (CNS) and in neuroinflammatory markers following paclitaxel administration; 3) beta-caryophyllene (β-CP) was the most effective treatment strategy to prevent the development of inflammation and sensitivity in rodents with orofacial pain from pulp exposure; and, 4) robust, anti-inflammatory effects of β-CP for chemotherapy-induced neuropathic pain, with robust neuroinflammatory effects of β-CP compared to cannabidiol (CBD). Future research should list, rank, and prioritize pain models based on features such as inflammation and systematically test cannabis constituents in a standardized way across laboratories.

Identifying the Mechanisms of Action for CBD on Chronic Arthritis Pain

Yu-Shin Ding, Ph.D., New York University School of Medicine

Dr. Ding's laboratory sought to determine the mechanisms of action of CBD on pain treatment for chronic osteoarthritis (OA) in rodents. They demonstrated CBD binding to the serotonin 1A (5-HT1A) receptor through positron emission tomography (PET) and computed tomography (CT) scans, and they observed higher uptake when administering CBD after OA onset to the rodent's right leg compared to the left leg. In a behavioral assessment study, they observed a reduction in sensitivity from CBD through Von Frey testing; a recovery through daily CBD after high anxiety in the OA state via light/dark box testing; and recovery through daily CBD after an increase in mobility and decrease in locomotor activity through Porsolt forced-swim tests. They noted significant effects only in female rodents across all aspects. They did not observe differences in their combined agonist and antagonist drug treatment study. Future research will help fine-tune mechanistic studies in humans, such as by imaging 5-HT1A modulation and anti-inflammatory effects in humans before and after CBD treatment.

Synthetic Biology for the Chemogenetic Manipulation of Pain Pathways

Andrew Ellington, Ph.D., University of Texas at Austin

Dr. Ellington and his colleagues sought to dissect human neural responses by functionally expressing individual receptors, such as cannabinoid receptor 1 (CB1R), cannabinoid receptor 2 (CB2R), and transient receptor potential vanilloid type 1 (TRPV1), into yeast. They found that dose responses in CB1R and CB2R yeast mimicked mammalian cell expression. Using machine learning, they compiled PubMed and patent literature databases to create compound signatures and English-language correlations, enabling them to confirm and predict the relationships between cannabinoids and receptors. Next steps include 1) using yeast strains to characterize previously unknown structure-activity relationships for cannabinoid compounds for CB1R and CB2R; 2) developing CB2R-specific ligands, enhancing therapeutic effects, and decreasing psychoactive effects; and 3) using yeast sensor strains to explore whether machine learning can predict novel cannabinoids.

Mechanistic Studies on Analgesic Effects of Terpene Enriched Extracts from Hops

Cassandra Quave, Ph.D., Emory University, and Isaac Chiu, Ph.D., Harvard Medical School

Dr. Quave and Dr. Chiu's laboratories sought to investigate mechanisms by which *Humulus lupulus*, or hops, and its extracted terpenes may affect sensory neurons and pain signaling in rodents. They prepared six formulations of hops and, following subjection to mass spectrometry, chose three distinct hops compounds (myrcene, alpha (α)-humulene, and e-caryophyllene) and topically applied the formulations to mice under hot plate conditions. They found that the hops extract formulations had a similar efficacy to CBD in blocking heat pain, and female rodents exhibited greater sensitivity. They also observed effects from a mixture formulation. They did not find effects with cold plate conditions or Von Frey thresholds. These findings may suggest future use of hops, which is unscheduled, as a source of analgesic terpenes for pain management. Future research should explore the mechanisms of receptor sensitization and the potential synergistic effects of extract mixtures.

Systematic Investigation of Rare Cannabinoids With Pain Receptors

Aditi Das, Ph.D., Georgia Institute of Technology, and David Sarlah, Ph.D., University of Illinois Urbana-Champaign

Dr. Das's and Dr. Sarlah's laboratories sought to assess classes of cannabinoids that are not commercially available and characterize their pharmacologic properties related to metabolism and inflammation in rodents. They elucidated the metabolism of the minor cannabinoids CBG and cannabichromene (CBC) by cytochrome P450s (CYP) (i.e., Phase 1 drug metabolizing enzymes) and showed that the metabolites are bioactive. They found that CBG formed epoxides at the 2',3' position and cyclized to cyclo-CBG in rodents, culminating in an anti-inflammatory effect in microglial cells. CBC metabolized at CYP sites in the brain, nasal, and cardiovascular pathways of rodents, producing 6',7'-epoxy-CBC, 8'-hydroxy-CBC, and 6'7'-dihydroxy-CBC; and cyclo-CBG was formed in rodent blood within 30 minutes of CBG administration. Future studies should 1) define the metabolism of CBG, CBC, and cannabinol (CBN) by human CYPs, 2) determine the molecular interactions of cannabinoids with CYPs using biophysical methods and molecular dynamics, and 3) elucidate the interaction of the cannabinoids and their oxidized metabolites with selected receptors and transient receptor potential (TRP) channels.

Minor Cannabinoids and Terpenes: Preclinical Evaluation as Analgesics

Steven Kinsey, Ph.D., University of Connecticut, and Thomas Gamage, Ph.D., The State University of New York Upstate Medical University

Dr. Kinsey, Dr. Gamage, and their colleagues sought to screen and evaluate minor phytocannabinoids and terpenes from cannabis in rodents to determine suitability for developing novel analgesic agents. Using semiquantitative and qualitative measures, they found that delta-8-THC (Δ8-THC) reduced arthritis severity and hind paw edema. Δ8-THC decreased proinflammatory cytokines, such as interleukin (IL)-1β and IL-6, and recovered vascular endothelial growth factor A (VEGF-A). In behavioral assays, the Δ8-THC intervention slightly recovered grip strength and climbing and reduced temperature preference to control levels. They did not observe changes to immobility compared to controls. Δ8-THC was an agonist at CB1R and CB2R. Future research should 1) determine the pharmacology of minor cannabinoids, terpenes, and terpenoids at molecular targets implicated in pain; 2) evaluate drug psychoactivity using Pavlovian discrimination; and 3) compare the anti-arthritic effects of additional minor cannabinoids in both male and female rodents.

Mechanism and Optimization of CBD-Mediated Analgesic Effects

Zhigang He, Ph.D., Boston Children's Hospital, and Kuan Hong Wang, Ph.D., University of Rochester

Dr. He's and Dr. Wang's laboratories sought to identify the actions of CBD and the underlying neural circuit mechanisms for analgesia in rodents. They found robust analgesic and selective inhibitory actions of CBD on neuropathic pain behaviors and hyperactive somatosensory circuits. CBD suppressed tactile allodynia and hyperalgesia in rodents with spared nerve injury, but it did not disturb tactile or nociceptive responses in intact rodents. Additionally, CBD suppressed the hyperactivity of somatosensory corticospinal pain but did not affect its activity in controls. Future research should continue investigating the efficacy and specificity of cannabinoids across mechanistic levels to optimize therapeutic translation, noting the potential for CBD effects across the central neural pathway.

Modulation of Pain Hypersensitivity by Terpenes via Endocannabinoid Release in Descending Circuits

Myra Alayoubi-Rice, Ph.D. Candidate, University of California, Los Angeles

Dr. Alayoubi-Rice and her colleagues sought to elucidate the mechanisms of myrcene's antinociceptive effect on neuropathic pain. In rodents with chronic constriction injury, she observed a dose-response curve for myrcene with greater force-withstanding potential in female mice. She also observed that a CB1 antagonist pretreatment

of myrcene blocked antiallodynic affects. She found differences between myrcene and a CB1 agonist, and myrcene did not modulate the activity of eCBs, 2-arachidonylyglycerol, or anandamide on supine 1 receptors. Future research should 1) investigate myrcene's ability to enhance eCBs using in vivo fiber photometry imaging in the ventrolateral periaqueductal grey, 2) investigate the lateral hypothalamus to ventrolateral periaqueductal gray circuit, and 3) explore sex differences in eCB release.

Session 1: Q&A

Dr. Belfer thanked presenters from the first session and introduced the question-and-answer session. A speaker asked Dr. Ding to clarify whether she displayed PET imaging for rodent knees in addition to brain imaging. Dr. Ding confirmed her laboratory's use of a whole-body scanner for rodent knee and brain imaging.

Session 2: Advances in Nonclinical Studies on Cannabinoids and Pain

Dr. Belfer introduced the second session on advances in nonclinical studies. She introduced the researchers, who provided 5-minute "data blitz" presentations.

Kratom and Cannabinoid Constituents: Mechanisms and Interactive Effects in Neuropathic Pain

Sara Jane Ward, Ph.D., and Scott Rawls, Ph.D., Temple University Lewis Katz School of Medicine

Dr. Ward and Dr. Rawls sought to demonstrate whether the co-use of cannabis and kratom constituents increases positive or potential adverse effects. They tested CBD, CBG, and Δ8-THC individually and in combination with the kratom compound mitragynine in male and female mice. In a chemotherapy-induced peripheral neuropathy (CIPN) pretreatment model, CBG and mitragynine both prevented the development of mechanical sensitivity in female mice, demonstrating protective effects from mitragynine. In a formalin model, CBG and mitragynine both attenuated Phase II licking behaviors in male mice, indicating a possible sedative effect from CBG. In a tetrad model, Δ8-THC and mitragynine both produced catalepsy-like behavior and a significant interactive effect. Finally, in a hot plate model, mitragynine did not have antinociceptive effects but did reduce the latency of Δ8-THC and CBG. Additional clinical and translational research on kratom is needed, as mitragynine effects may not reflect kratom use in humans.

Terpenes from *Cannabis sativa* Relieve Chronic Pain and Block Opioid Reward

John Streicher, Ph.D., University of Arizona

Dr. Streicher's laboratory sought to investigate the therapeutic and mechanistic efficacies of *Cannabis sativa* terpenes in chronic pain models. In a CIPN model, terpenes were highly efficacious in relieving neuropathic pain by activating the adenosine 2A receptor (A2aR) in the spinal cord. In addition to efficacy, the terpenes showed no abuse liability, moderate analgesic tolerance, and an ability to enhance opioid pain relief through a combined approach on neuropathic pain. Additionally, β-CP and α-humulene blocked dopamine release in the A2aR striatum, indicating that a combination therapy with β-CP and morphine may improve pain relief while blocking opioid reward aspects. Future research should 1) continue exploring and clarifying the mechanisms of terpenes on receptors, and 2) explore the therapeutic aspects of terpenes, including drug potential, effects on opioid self-administration and potential for relapse, side effects, and dosing. Dr. Streicher also noted the importance of informing the public with evidence-based findings on cannabis, given widespread claims and misinformation from commercial actors.

treatment response. Given the wide range of research interests and goals, he asked how NCCIH considers the funding applications it receives.

Dr. Belfer clarified the steps through which applications are evaluated before NCCIH reviews them. First, applications are reviewed by field colleagues for the study's novelty, mechanisms, plan, and feasibility. She encouraged prospective applicants to check the NIH RePORTER portal for previously funded study areas. Next, NCCIH reviews applications for their alignment with NIH and NCCIH organizational priorities. She noted how this meeting helps to highlight potential research gaps and opportunities for collaboration.

Another speaker discussed harnessing machine learning for compound development and discovery, target discovery, and behavior. As a trained behaviorist, he said there is a preclinical bottleneck effect and discussed his considerations for testing known and new cannabinoid compounds with efficacy in mouse models. He highlighted a colleague's method of using zebrafish and associated benefits. He emphasized that, as the field considers high-throughput measurement in assays, it is important to remember behavioral considerations as well.

Another speaker referred to the previous discussion on vaporized versus oral administration of cannabinoids, asking how much we know about the metabolism of inhaled and oral cannabinoids. She wondered about the potential metabolic differences that may exist. Dr. Chideya-Chihota agreed that this topic area is worth exploring in depth, given known use preferences in the United States.

Another speaker mentioned a study that found that phytol was toxic, which relates to cannabinoid inhalation, and that vitamin E acetate has been reported to have associations with acute lung infections. He expressed support for his colleague's inhalation study methodology and offered caution about adulterated formulations, whether they are used orally or through inhalation. He asked whether there is organizational interest in funding studies on the toxicology and safety of cannabinoids in the context of translational (nonclinical to clinical) use and/or chronic dosing.

Dr. Belfer said this was a great question. She clarified that NCCIH allows a component for adverse effects and toxicity in the context of studying therapeutic potential for cannabinoids. She noted that NIDA is particularly interested in clarifying potential toxicity and adverse effects. If a study is about therapeutic and analgesic potential, it would align better with NCCIH; if the study's main focus is on toxicity, it may potentially align better with NIDA.

Another speaker discussed some limitations and merits of computational predictions in cannabinoid research. He likened computational predictions to hypotheses, noting that these are essentially useless without real-life testing. He said computational predictions can be an incredible resource for prioritizing compounds and combinations to test, and it would be helpful to have a database that combines both computational and experimental data. He discussed how recently developed tools have enabled the screening of billions of compounds each day through machine learning.

Another speaker referred to the new DMSP that Dr. Belfer had mentioned. He discussed the challenge of reaching agreement on where data should be saved. He said that there are existing, general repositories that the researchers could use if an agreement on a general repository is reached. He said that NIH created the DMSP with the hope that this would help congregate data.

Dr. Belfer noted that later there would be a special presentation from her colleague, Patrick Still, Ph.D., program director in the Basic and Mechanistic Research Branch at NCCIH, about the NCCIH Resource Center initiative.

Another speaker said he also feels a push and pull about standardizing methods, noting the difficulty of trying to agree on methodology while technology, such as machine learning, is simultaneously changing. He said that researchers should keep this in mind, especially when reviewing one another's work. He felt unsure of how behavioral assays would change over time.

Dr. Chideya-Chihota noted that she had not heard anyone discuss a topical mode of administration which, from a clinical standpoint and given study considerations for OA, neuropathic pain, and diabetic neuropathy, made her feel curious as to why. She asked if anyone had thoughts about studying topically administered cannabis products.

A speaker said his laboratory has given topical administration a lot of thought and noted that two of his colleagues listening on Zoom have studied topical administration for OA and fracture healing in rodents. He agreed that this is a remarkably rich area to explore. He shared his experience with a human study in which it was unknown how much of the topical intervention would get into the participants' circulation and whether participants might fail a drug test if they use it on their knees. He said he received support from his institutional review board (IRB), while the FDA requested an investigational new drug (IND) application. The speaker said that descheduling or rescheduling should help researchers immensely with this area of research, and he expressed belief that the lipophilicity of cannabinoid molecules will make them marvelous for use in the topical form.

The same speaker raised the topic of pharmacogenomics in cannabinoids research. He discussed how, in the last decade or two, the concentration of THC in the cannabis plant has reached its upper limit of 30 to 35 percent by weight. He discussed some of the side effects his laboratory has been observing, such as psychosis and cannabinoid-induced hyperemesis syndrome. He pointed out that these drugs are metabolized by CYP2C9, CYP2C19, and CYP3A4; for the latter, there are 26 star alleles that compromise the activity. He said some people are ultra-metabolizers, extensive metabolizers, intermediary metabolizers, and non-metabolizers, but researchers cannot predict these yet. He asked others to consider: 1) What are the genotypes of our participants? 2) How does genotype influence how participants will respond to cannabis? 3) Will participants have side effects? and 4) Does it work for the participant? The speaker noted that ultra-metabolizers may experience fewer benefits, while non-metabolizers may experience more side effects.

Dr. Belfer noted that this is another point that goes with the list of challenges and potential complexities for clinical trials. She agreed that thinking about therapeutic biomarkers and how we can predict who will respond faster and better to interventions through individualized approaches would be essential steps in clinical trials.

Another speaker expressed curiosity about the translational question. She said that many of the presenters' nonclinical studies seemed to use synthetic cannabinoids, but this is not what her laboratory's participants buy from their dispensaries. She asked whether we have good evidence that synthetics work in the exact same way, biologically, as natural products do in terms of pharmacodynamics. How do we know what doses to use in human participants? Do nonclinical studies elucidate clinical doses?

paper, which had been cited 1,996 times at the time of his presentation, while the Rogeberg paper had only been cited 132 times, despite the similarity of study topics and publication dates.

Dr. Piomelli discussed strategies for addressing bias in cannabis research through: 1) self-awareness through acknowledging bias, reflecting on your experiences, and seeking feedback; 2) learning about different types of bias, such as "white hat" bias and anchor bias; 3) mindful decision making through pausing, reflecting, and considering alternatives; 4) interacting with other groups, with better communication among advocates, physicians, and scientists; and 5) cultivating an open mindset by not ignoring published studies that challenge your ideas.

Dr. Piomelli further noted that the Meier et al. paper title implies causality, while the Rogeberg paper's title starts with the word "correlations." He emphasized that correlation is not causation. From Galileo Galilei's (1612) *Discourse on Floating Bodies,* Dr. Piomelli quoted, "Cause is that which is placed, the effect follows; and removed, the effect is removed." In philosophy, this is called an "interventionist approach," which is more difficult to apply in disciplines that rely primarily on observation. He emphasized the importance of observation in cannabis research.

Dr. Piomelli discussed strategies for addressing causality in cannabis research, including: 1) discordant sibling/twin study design, by which researchers can compare outcomes when homozygotic twins are discordant in their cannabis use; 2) Mendelian randomization, by which researchers can exploit genetic variants associated with cannabis use as a variable to test the causal effect of cannabis on an outcome; 3) quasi interventions, by which researchers can study how an external event or intervention affects cannabis use in one population but not another; and 4) experimental studies, including controlled studies with subjects randomized to the administration of a defined quantity and type of cannabis or cannabinoid.

Dr. Piomelli discussed how cannabis product diversity, with differences in mode of use, excipients, and potency, is a confounder. He compared cannabis product diversity with potato chip product diversity, and he emphasized how the existence of THC has led to today's meeting. He discussed a Watts et al. (2021) paper from the Netherlands titled, "Cannabis Labelling Is Associated With Genetic Variation in Terpene Synthase Genes," the results of which indicated that cannabis plant strains, sold as *C. indica* or *sativa*, are genetically and chemically the same. This study would not have been possible in the United States due to restrictions.

Dr. Piomelli discussed strategies for addressing cannabis diversity in research. He said: Ignore marketing ploys; the terms *indica, sativa,* and "entourage effect" have been hijacked by the industry for marketing and sales purposes. Don't ignore the "feel"; organoleptic properties (aroma) have functional consequences (e.g., placebo effect, study blinding issues). Pay attention to potency, given that THC drives the pharmacology of cannabis, and its concentrations matter; route of administration, since mode of use can affect THC concentration, bioavailability, and actions; and excipients, which can affect bioavailability, interact functionally with THC, or have effects of their own.

Dr. Piomelli addressed the question of whether cannabis can cause psychosis. He refined the question into two related questions: 1) Can cannabis cause acute psychotic symptoms? 2) Can persistent cannabis use cause schizophrenia and/or other psychotic disorders? Dr. Piomelli acknowledged that while cannabis can produce perceptual disturbances (e.g., visual illusions), "cannabis-induced psychosis" relies on distinguishing that

hallucinations occur in the absence of intact reality testing, according to the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5).

Dr. Piomelli discussed a study by Andréasson et al. (1987) titled, "Cannabis and Schizophrenia: A Longitudinal Study of Swedish Conscripts," which famously indicated that using cannabis during adolescence was associated with a sixfold increase in the risk of developing psychosis in adulthood. Dr. Piomelli contextualized how, at the time, society was hearing that the use of cannabis makes people go crazy. As an example, he referred to a news headline, "Evil Mexican Plants That Drive You Insane," which stated, "Not long ago, a Mexican of the lower class […] who had smoked a marijuana cigarette, became insane and killed a policeman and badly wounded three others." Dr. Piomelli emphasized that these problematic ideas pervade in media today.

Dr. Piomelli reviewed conclusions from "The Health Effects of Cannabis and Cannabinoids" by the National Academies of Sciences, Engineering, and Medicine (NASEM, 2017), which stated, "There is substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with the highest risk among the most frequent users." He emphasized the text's careful use of "substantial" rather than "conclusive," noting that the text also concludes, "There is moderate evidence that, among individuals with psychotic disorders, there is a statistical association between a history of cannabis use and better cognitive performance." Dr. Piomelli said this suggests inverse causality.

Dr. Piomelli also discussed a longitudinal study by Schaefer et al. (2021) titled, "Associations Between Adolescent Cannabis Use and Young-Adult Functioning in Three Longitudinal Twin Studies," which suggested that cannabis use is causative for negative socioeconomic outcomes (i.e., educational attainment, occupational status, and income), but not for IQ or schizophrenia. He said this paper had only been cited 38 times at the time of his presentation.

To address the causal nature of the link between cannabis and schizophrenia, Dr. Piomelli suggested Mendelian randomization and quasi-intervention studies on large human cohorts. Human or animal experimental studies are unlikely to be useful due to the complexity of schizophrenia.

Dr. Piomelli then addressed the question of whether cannabis is a safe and effective analgesic. He discussed a paper by Abrams et al. (2007) titled, "Cannabis in Painful HIV-Associated Sensory Neuropathy: A Randomized Placebo-Controlled Trial," which indicated that a small number of patients with HIV who smoked low levels of cannabis experienced less pain during the treatment period. Abrams et al. (2007) based their study on the "Commentary on the Pharmacopoeias of Great Britain and the United States, 1848" by Robert Christison, which stated that a cannabis intervention had a "cessation of pain" effect, as well as side effects such as "a pleasant numbness in the limbs, giddiness, a rapid succession of unassociated ideas and impossibility to follow a train of thoughts, frequent intervals of sleep, and slight increase in the force of the pulse." Dr. Piomelli quoted NASEM (2017), which concluded, "There is substantial evidence that cannabis is an effective treatment for chronic pain in adults." Nonclinical scientists convened and arrived at the same conclusion in Finn et al. (2021), "Cannabinoids, the Endocannabinoid System, and Pain: A Review of Preclinical Studies."

Dr. Piomelli mentioned a paper by Cooper and Haney (2016), "Sex-Dependent Effects of Cannabis-Induced Analgesia," which sought to address causation. The paper concluded that in both men and women, THC produced

Dr. Weber asked whether researchers could cite references that might use cannabis as a whole but specify the amount of an individual constituent and then propose an intervention within that dose range for the FDA to review. Dr. Reissig noted the challenge of isolating compounds from whole plants while eliminating effects, such as a protective, entourage effect. He mentioned running a study on kratom and having similar challenges. Dr. Weber added that when studying a single component, the compound will be taken in much higher doses than in other studies. Dr. Reissig discussed the FDA's preference for a standard, ascending dose study, noting the ability to see adverse effects in a dose-dependent manner for safety.

Another speaker noted legislative distinctions between naturally derived cannabinoids (e.g., THC or CBD extracted from a plant) versus synthetic cannabinoids (e.g., THC or CBD made in a laboratory). He asked: Is there anything we can do to convince members of Congress that these are the same molecules? Dr. Hobin agreed that clarity and education are needed to support policy making. She noted that there are opportunities for researchers and scientific societies to engage with Congress and weigh in on policy making.

Another speaker commented that, in the past year, she has successfully navigated the FDA IND process for a hemp-derived CBD product. She asked for insight and advice for researchers navigating the FDA for an experimental study using a THC product from the NIDA drug supply, in which the focus is not on a therapeutic indication, but on risk or abuse potential. Dr. Reissig reinforced that this study falls under FDA's purview because THC is a drug. There was a follow-up question: is there any option where an experimental study in the laboratory without focus on a therapeutic indication could get an FDA exemption, or would it be run through the whole IND process? Dr. Reissig said that the researcher's outcome measures probably would be a structure-function claim as it investigates people's liking of the drug, which means it is a clinical investigation and drug trial that requires an IND. There was another follow-up question: have there been THC-based studies that have met the criteria for exemption? Dr. Reissig said that an FDA-approved THC product would not require an IND in an indicated population.

Dr. Weber noted that the same process and questions apply to NCCIH-funded research on botanicals. NCCIH considers whether the product is being used to treat, mitigate, prevent, cure, or diagnose a disease. If a researcher is using the product for any of these reasons, whether for marketing or a new drug application (NDA), the published study can be used by someone else to make an indication. Many of these considerations apply to all botanicals and are not necessarily unique to cannabis, other than elements related to hemp-derived products.

Another speaker asked Dr. Reissig to describe how controlled substances staff, botanical staff, and review division staff coordinate during an IND review. Dr. Reissig said that once the FDA receives an IND, it is assigned a project manager and a primary review division, such as the divisions of psychiatry, anesthesia, analgesia and addiction products, or neurology. The division assembles a large internal team, including physicians, chemists, toxicologists, statisticians, and controlled substances staff. There is a meeting with 15 to 20 multidisciplinary reviewers who follow protocol to consider the IND and determine hold issues, which are generally related to safety. If the IND is placed on hold, the FDA drafts and sends a hold letter within 30 days. When the FDA receives a response to the hold, reviewers may reconvene. From a controlled substances perspective, marijuana, cannabis, and THC have well-characterized abuse liability. Controlled substances staff may refer applicants to the DEA for scheduling concerns. NDAs have a longer review process.