>> Hello, everyone, or good morning, good afternoon, or good evening, whatever -- depending where are you located. Welcome to the last day of this symposium that NCI has put together on cannabis and cancer research. And today in this session, we are going to approach something that has been mentioned over and over, that is what are some of those research challenges pertaining to cannabis research and probably how to navigate for that. And for that, I have the pleasure -- my name is Alejandro Salicrup, Senior Advisor for Global Health Research at the Center for Global Health and the Division of Cancer Treatment and Diagnosis at the NCI, NIH, and I have the pleasure to have as co-chair for this session, Dr. Ziva Cooper. Dr. Cooper is the Director of the Cannabis Research Initiative at the University of California in Los Angeles, UCLA, and she's also an associate professor of the Department of Psychiatry at UCLA. Dr. Cooper has published extensively and her research involves understanding dose variables that could influence both the therapeutic potential and also the adverse effects on cannabis and cannabinoids use in double-blind placebo controlled studies. Importantly, Dr. Cooper was also part of the National Academy's own Sciences Committee on the Healthy Effects of Cannabis where they recently published a very comprehensive report in this topic. So we will introduce some of the speakers momentarily. But before, next slide please, we thought it would be important to share with all of you since many of you probably didn't join the whole conference or some of you might have joined too late, but from the very onset, both Dr. Sharpless, Director of NCI, and Gillian Schaeffer (ph.), the keynote speaker that we had from day one, they both talked about that there has been significant changes related to the policy landscape surrounding both cannabis legalization, its production and the use. And we had seen change after change. During the past 20 years, we have 35 states plus the District of Columbia that have legalized cannabis for medical conditions or retail sales at the state level, and there is 15 states plus the District of Columbia that has legalized both the medical and the adult use of cannabis. So the landmark in policy have impacted both the patterns and how -- the risk and the perception from both the users and the public. But as we heard in each day of the sessions presented here, there is still significant challenges and hurdles that can affect cannabis research, but also there is a great opportunity. I should say that we are expected -- you should be expecting more and more changes. As recently as a couple of weeks ago, during the elections, general elections, here in the United States there were seven referendums in different states regarding policies pertaining to cannabis and its use. And as recent as yesterday, the Drug Enforcement Agency, the DEA, issued a final rule for licensing more growers in marijuana. And as you know, in the recent months as well, both the House and the Senate have been trying to pass bills to promote marijuana research or cannabis research. So next slide. So for that, we have assembled a great group of speakers. We will have Dr. Steve Gust. He's the Director of the International Office at the National Drug Abuse Institute, NIDA, at the NIH, and he will share with us updates on the federal regulatory landscape, but also he will share with us the NIH research portfolio pertaining to cannabis and cannabinoids and also he will share light about NIDA's drug supply program. So Steve, please go ahead. After Steve, we are going to hear a representative for all the very important entities like FDA and also the researchers' point of view. But let's start with Steve, please. Go ahead. Thank you.

>> Okay. Can you see my slide, and can you hear me okay?

>> Yes.

>> Okay. Luis, thank you very much. You gave a nice summary of my talk, so we can save some time. No, he did a very nice job of summarizing some of the recent developments that I think are affecting research. I want to thank him and Ziva as well for putting together this panel, and I also would like to thank all of the participants today for taking some time off and a break from their holiday shopping to participate in the workshop today. I'm a big fan of the BLUF acronym, bottom line up front, so I'm going to spend my time today telling you a little bit about, maybe perhaps in a little more detail, what's going on with the federal situation in terms of the regulatory landscape. And as we've been hearing over the last couple of days, it remains challenging. But as Luis said, there are signs of optimism and certainly very recently, some signs of change happening, and I'll talk a little bit more about that in detail. And the second kind of take home message I hope I leave everyone with is that there are resources that exist to support research on cannabis and cannabinoids, both fiscal resources and material resources, and they're increasing and improving. And I'm going to spend some time, a little bit of time going through that as well. As we've heard several times over the last couple of days, there's a federal regulatory landscape and then there's a state regulatory landscape. And the state situation, as you've heard, is very diverse, changing rapidly. More states voted on, just in this last election, on some changes. Currently, most states, all but three states have at least some law on the books that allow some use of cannabis for medical purposes, for example. So even the -- I can't remember exactly which three states those are, but it's almost all the states and probably very soon will be. And so it just even drives home more the point and the need and the urgency for getting more research done to help drive and direct these policies and practices. I think interestingly and importantly, out of all the states that have legalized either recreational or medical cannabis, only four states have designated any tax revenue towards support research. I think as members of the research community, I hope you can all take to hear perhaps any role and any interest you might have in encouraging the dedication of some of the tax income that's coming in from the states to be directed back into the research enterprise. So in a nutshell, where are we now federally? Well, as of today, still, cannabis remains a Schedule I controlled substance, which according to the Controlled Substances Act means that it has a high risk for abuse and dependence, and there's currently no accepted medical use. It does allow for research in limited circumstances. Much of the research that you've been hearing over the last couple of days represents some results from some of that research, researchers that have gotten through the process of registering with the DEA and obtaining cannabis for research. One important aspect that I will also touch on in a few minutes when I talk about the recent changes in the DEA's position on registering new growers is that the current situation in the U.S. aligns with international treaties on cannabis and narcotics. There is an important international convention called the Single Convention. That was first passed in 1961. It covers primarily opium, but also coca and cannabis, which puts restrictions on the ability to grow and possess and distribute cannabis and also importantly gives each participating nation the authority to designate a single source of marijuana for research purposes. And up until today, the Drug Enforcement Agencies has designated NIDA as that source that we support through a contract with the University of Mississippi to grow and product marijuana for research. Now, the situation that's changing. Two years ago, the Agricultural Improvement Act was passed, which quite importantly redefined hemp or defined some cannabis plants as hemp, those containing less than 0.3% THC and removes them from the Controlled Substances Act. So products from hemp is no longer a cannabis plant that is controlled under the Controlled Substances Act. It has lots and lots implications for many things. Perhaps most significantly, it reaffirms the regulatory role of the FDA for many, many hemp-derived products, and I'm sure you're going to hear more about that from Doug in his talk next. And there's currently a plethora of marketed projects, products for not only medications, but dietary supplements and food additives, all which contained CBD for the most part. The implications for research with CBD are not really completely clear yet. The DEA seems to be of a mixed opinion and mixed mind about why there are not --synthetic CBD, for example, is still controlled under the Controlled Substances Act, for example. Just yesterday, the DEA publish its final rule for new cannabis growers and producers. This will bring -- in the opinion of the Department of Justice, bring the DEA into compliance with that international treaty, the Single Convention. And in order to do that, the DEA is now going to become the single agency controlling all aspects of cannabis production and distribution for research. Some of the bigger changes that this new regulation is going to bring are the fact that the DEA is going to be required to purchase and take possession of all the cannabis produced shortly after harvest, but there's going to be a new system of fees charged for the growers and users of the cannabis. And any use is going to be subject to a bona fide purchase agreement between a final user and a producer. All these things are the detail -- the devil's always in the details as we know, and there's going to be a significant amount of shakeout in terms of how this is actually all going to work. In principle it makes sense, but there's still a lot of questions, even for the NIDA program, the NIDA drug supply program, which I'll talk a little bit more about. We are going to become one of these licensed producers. We're not really sure of all the -- what all the rules, the changes in rules and meaning of all -- the DEA's new role is going to mean for our program. And despite the fact that they've published the final rule, it's really not clear if or when the DEA will approve any of the current relatively long list of applicants. I think the current number of applicants is somewhere -- I think it's 41. Other very important federal actions that are happening: The House recently passed the MORE Act, the Marijuana Opportunity Reinvestment and Expungement Act, which does several very, very important things. It removes cannabis entirely from the Controlled Substances Act. From a research perspective, one huge change this would bring would be there would be immediate access to dispensary marijuana products for research purposes, which are currently not allowed. It does a number of things. It eliminates criminal penalties for individuals who manufacture, distribute or possess cannabis. It puts a 5% excise tax on cannabis products to support a trust fund, which would help support business and other opportunities for those that have been impacted through previous cannabis persecutions, prosecutions. And the other law that is currently in play, there's a House and a Senate version of that. The Senate version is the Cannabidiol and Marijuana Research Expansion Act, which clarifies the non-controlled status of plant-derived and synthetic CBD. It streamlines some of the DEA registration hurdles that exist. It does continue the NIDA drug supply program. It does require action on those 40-plus applications for new grower applications, and quite importantly, it would apparently allow any entity that was considering developing cannabis medications to grow their own cannabis. So we'll see where these go. This is more action in Congress than we've seen in many, many years. There does seem to be quite a bit of momentum certainly behind the Senate bill, which is the Cannabidiol and Marijuana Research Expansion Act. So I would not be a bit surprised myself as a long-time observer of some of the federal activities that this does become law. So that's kind of the lay of the land in terms of what's currently happening with the legislation. Certainly some of the consequences of these versions and differences between the state and federal policies have had a lot of impact. One of the things that I think is most impactful, again, is that there's no researcher access to the state legal products. And that is something that we at NIDA would very much like to see happen. There's certainly a wide, wide variety of products being used out there that there's not much, if any, research being done on. You know, also I think as -- there's a number of other kind of non-research aspects of how marijuana and cannabis are being used and distributed around the country that are causing other kinds of issues and problems, you know. For example, there's really no national level guidance, oversight, testing of products. No standardization. So lots of -- which I think leads to a lot of uneven quality in terms of what is going on around the country. So not only those kinds of issues, but there's also some challenges that arise because of these differential policies in terms of research. Obviously, as I said, cannabis remains a Schedule I drug. There's a complex and lengthy registration process. For those of you who have gone through that know all about that. There's still, as of today, still a single approved source, single federal source for cannabis for research, and the Schedule I status of some of the constituents of cannabis remains uncertain despite the passage of the Farm Bill. There's also a number of scientific challenges that I think we have not able to adequately address because of the complexity of the planet itself. There's a number of other challenges, I think, to doing good solid research in terms of doing placebo controlled trials, getting access to products that are the same or at least similar to those that are actually being used by individuals out there in the country. And while NIDA's supply has diversified, it's costly and time consuming to grow new products, and it definitely does not represent the wide diversity of products and formulations currently available. So a little bit more about the products currently available from the federal provider, from NIDA. There are requirements to obtain marijuana from NIDA for research. There are really only three. If you're doing research in humans, you need to have the FDA review your proposal and get an investigational new drug application approved by them. You need to get a DEA Schedule I registration, and you need to demonstrate that your protocol has been reviewed and approved by an institutional review board. That's your university or elsewhere. At that time, a researcher can order marijuana from the NIDA drug supply program. There, I think, is some misinformation out there that NIDA has a large and controlling role in who actually gets marijuana for research, but in actuality, NIDA really is just -- takes orders and fulfills them. Anybody who has met these other three requirements is fully and wholly qualified to get marijuana from NIDA. NIDA has a fairly wide variety of types of marijuana available to the research community, both in cigarette form and in bulk form. The marijuana products available you can see on the right here, the kind of variety of both THC and CBD content and mixtures of all of those in terms of low, medium, high and very high concentrations. One point that I'd like to make -- this is data from a long-running program that monitors the THC potency of illicit marijuana as determined through drug seizures around the country. And you can see to no one's surprise how the potency -- this is the THC potency, how it's increased over the years. Until at least fairly recently, NIDA's cannabis has fairly closely tracked the THC potency of the marijuana generally available to the public, which, again, is demonstrated by that chart that shows kind of the increasing -- the most recent data on this slide shows that THC potency around 12%. Another important thing about the NIDA marijuana is that it does provide a research product, which is, I think, important for researchers, because it's consistent, reproducible in terms of content. It's pesticide free and herbicide free, and provides a constant, consistent source for the researchers. We do recognize that there's a large demand for new varieties of marijuana, new products, certainly higher potency marijuana than the potency that's currently available, even though we do have some that's over 10% THC. We're fully aware that there's products available in some of the dispensaries that's much, much higher than that. Certainly other cannabis products, edibles, vape products and so forth certainly are needed. Other cannabis constituents, terpenoids, recognize these are all needed and necessary and are working towards reducing them for research. I see that I am already starting to run out of time, so I'm going to kind of go quickly through this last section, which is basically to make the point that there's a fair amount of research going on at NIH. It has been going on for several years in a wide variety of topic areas. NIDA itself still is the primary supporter of research on cannabis, and we support research in a number of areas in terms of epidemiology and prevention, treatment of cannabis use disorder, and a lot of the research on -- kind of basic research on the endocannabinoid system. However, NIH has been tracking cannabis research now for a couple of years in several major areas, overall, a cannabinoid research category. And within that, some subcategories, basic research on the endocannabinoid system, therapeutic cannabinoid research and cannabidiol research. This is just a snapshot showing you that it's a growth pattern from over the last five years. The most recent year 2019, there's over 400 cannabinoid and cannabis projects being supported by NIH. The budgets are --

>> Steve, I'm just going to jump in. We're almost out of time for you, so if you want to wrap and jump to your conclusion. You'll have a minute or so.

>> Okay. I've got about 30 more seconds. I'll try to wrap it up. This just shows kind of the corollary budget increase, about $189 million in the most fiscal year dedicated towards these categories of cannabinoid research. It's not just NIDA, even though NIDA remains the primary and key supporter. There's some 20 institutes of the 27 in NIH that are supporting some aspect of cannabinoid research in many, many different areas. These are just a list of not just cancer, which we're focusing on obviously the last few days, but many, many other areas of potential health benefit. And just a closing thought or two. The federal barriers remain, but there's certainly some important changes happening. NIDA, as I said, supports a lot of the research, but many of the other institutes are jumping in, in particular I'll mention NCCIH. That is particularly taking a lot of steps in expanding their research portfolio, particularly on minor cannabinoids and terpenes. Hopefully this workshop will also generate a bunch of new work for Luis and others at NCI in terms of research on cancer. So sorry I went over a little bit, but I'll stop there.

>> Thank you so much, Steve, for that comprehensive view about NIDA and some of the things that NIH is doing. Any discussion related to cannabis research? You always would hear about what should be the role of the Food and Drug Administration or FDA. And to address that, we have today, Dr. Douglas Throckmorton. He's the Deputy Director for Regulatory Programs in the Center for Drug Evaluation and Research at FDA. As such, he works in the regulation of several research, relational research related to the manufacture, marketing of both prescriptions and genetics, and he has (unint.) in his portfolio since related to cannabis and cannabis-derived products. So Dr. Throckmorton, please. Thanks.

>> Thank you, Luis, and can everybody see my slides and hear me okay?

>> Yes, we can.

>> All right. Thank you very much, and I'm really glad I'm following Steve, because he was able to talk a lot about the sort of nuts and bolts of cannabis as a supply for the development of products for human use and for animal use. Think the dietary supplements. Think the drugs and things. I'm going to focus on the FDA part, which follows that development of supplies, if you will. And I'm going to do it for a couple of reasons, but one thing in particular is to just emphasize when we think about the regulation of products for human use, human consumption especially, but cosmetics are used, that contain products derived from cannabis, there have always been two players. There's been the DEA player, because there's been controlled substances, and as Steve said, that's recently changed. What has not changed, however, is the role that the FDA plays in regulating products intended for human use and consumption. And so I’m going to talk a little about that piece, because as DEA role has changed, the FDA role has become more prominent, and people have been asking a lot of questions about what we are doing and what we could potentially do to encourage the availability of safe, effective, and high-quality products for the American public. Just my standard disclaimer. What I'm going to talk about is cannabis-derived compounds, which include products like CBD and THC, as well as many other cannabinoids. And you all have learned many things about many of those in the last few days. I won't belabor the point. The major point to make though is that THC remains a controlled substance. It remains a Schedule I compounds. CBD-derived from the hemp plant, as Steve just said, has been decontrolled, and the FDA performed the decontrolled scientific assessment and concluded that while CBD was psychoactive, it was not -- it did not have abuse potential. So the compounds have to be split between those that continue to be controlled by the DEA and those that don't, because those that don't then are in the purview of the FDA only, if you will, but anyway, large group of those. Our role is to regulate both the cannabis-derived compounds as well as synthetic versions of those compounds. And we're aware of over 80 naturally occurring substances, as well as many others that are identified and understudied. Bottom line is there's a lot we don't know about them, but there's an awful lot of interest and promises as others have said. Our responsibility in that setting is on human foods, on drugs, on biologic products, such as, you know, medical devices, electronic products, cosmetics, veterinary products, etc. Some of these things touch the cannabis world, many of them do. Some of them we have less direct oversight in terms of those products. The consequences of our regulation have led to the approval of four products as drugs. Three products derived from THC-like molecules for nausea, neuropathic pain, cancer chemotherapy, and nausea from cancer chemotherapy and one product, epidiolex, made of highly purified cannabidiol from the plants approved for childhood seizures and more recently extended to approve for tuberous sclerosis, a condition that also affects adults. But we know that the world is changing, and Steve has given a little bit of flavor of that. I'm sure that people have showed you variants of slides to illustrate the challenges of the marketplace. From the FDA's perspective, there are a number of things that are making it challenging as we think about how we regulate in a world where the DEA is no longer engaged in day-to-day regulations, the specific compounds. First and foremost, cannabidiol products are almost literally everywhere, and this is just a schematic showing some of the variations of the kinds of products that we see. Our surveillance network tries to keep track of all of the various products, at least the kinds of products, but you can get CBD-infused socks if you feel that those are valuable to you, illustrating the extent of the interest in the use of cannabidiol, the extent of -- by association, the extent of the interest in other products that are found in the hemp plant. That interest is being driven in large part, we think, because of the changes that occurred under the Farm Bill or the Agricultural Improvement Act of 2018. And as Steve said, it did two things. One, it removed hemp from the definition of marijuana, which meant that it was no longer controlled by the DEA. But it did, however, say that, first, marijuana continued to be regulated by the DEA under Schedule I. So things with higher content THC continued to be illegal under the Controlled Substances Act, but it also specifically identified the FDA's authorities under the Food, Drug and Cosmetics Act and said those authorities are unchanged. So those authorities over the health products that are marketed that the FDA regulates are subject to the same authorities/requirements as any other substance, penicillin, ampicillin, you know, whatever. We have roles in regulating them. Dietary supplements, we have roles in regulating them. Hemp-derived products are no different. And so the FDA regulation then became something that people were very interested in. The second challenge for us was the change that's been going on at the state and now the national level. I won't belabor this. This slide obviously was put together before the most recent wave of activity at the House and Senate level. I believe the Senate actually passed out a bill on Tuesday. I can't keep track of which bill it was. Steve would know. So there does seem to be movement in this area. None of the bills that I'm aware of have changed fundamentally the fact that the FDA authorities over the compounds when used in FDA regulated products stay the same. We still have to regulate the way we have historically regulated these products. And that's centrally a scientific challenge, because there is a lot we do not know about cannabidiol. And if you talk about cannabidiol, there's even less we know about the other species of cannabinoids, those other 80-odd things and the terpenes and the other things that are found in the cannabis plan. We know next to nothing about the cumulative and long-term human exposure in the way that I would expect to understand it for a drug, for instance. We know very little about the impact of these products in susceptible populations: Children, pregnant, women, elderly. We don't know what happens when an adverse effect occurs and whether it is reversible when the drug is stopped. There are questions about drug interaction data. There are questions about unique pharmacology, and there are questions about some of the products that are being marketed. We have concerns about excipients or the things that sit around the cannabidiol, if you will, the talc and the things like that, and we don't know what happens when these products are used with those excipients. We do know that there are organs of concern. We do know that based on the data we have available from the drug development program for epidiolex based on the published literature, based on the available other data that there are targets that we believe we need to know more about with regards to safety. There are liver injury signals that have occurred in placebo controlled trials where we're very certain were the consequence of the use of cannabidiol. We don't know exactly how serious those signals are. We don't know exactly what they mean. We think they're important to understand better. In the non-clinical data, we have seen (unint.) of male reproductive injury, including injuries that appear to potentially be non-reversible. Again, a very serious thing that we think we need to understand better. We don't know enough about. We don't know its impact with regards to human health, but we need to understand better. And then obviously there's a -- coming from NIDA, you all would know this. There's always a concern about the impact of substances that would be used in an abuse setting on the developing central nervous system, and Nora obviously has been working very hard for the last decade to develop the ABCD trial. We're all interested in seeing the data that come out of that. So the impact of this means the FDA has a lot of work to do. This is a slide that shows all of the parts of the FDA. The FDA is broken into centers by expertise, if you will. As you can see, all of the green boxes represent groups that meet with me every week to talk about cannabis, talk about cannabidiol. We exchange information. We have regulatory activities that we're taking. An extensive fraction of the agency is at work on cannabis at any given time. Going forward, we have a plan, because we understand that there is broad interest in the public in expanding the availability of safe, effective, and high-quality products made from the cannabis plant. First, we understand we need to get more information about the science. I identified some places we really need to understand better. We have a research agenda that we're working through, some forwarding studies to develop the kinds of database that we believe we need to understand how these products can be used safely in consumer products, dietary supplements, drugs, cosmetics, pet foods. We also think it's important from a policy perspective to think about how we might enable a broader availability of these safe, effective, and high-quality cannabidiol products. Whether that's to continue our activities around enforcement in addition to potentially allowing broader use of these products under appropriate circumstances is something we're in the process of working through. There have been a variety of activities, variety of proposals, rules that people have suggested to us. It's a very complicated area. We understand the need. It's something we're working very carefully on. Obviously, there is intense interest in Congress, and as necessary, we are providing them whatever information they ask of us. And then finally, we continue to engage with outside groups, because we understand how important that is. I was on a call with New York State last week, because they're in the process of finalizing their rule making for state-based marijuana, they call it marijuana, availability. And they wanted to talk to us about standard setting. They wanted to talk to us about the general regulatory frameworks that we were thinking about. And we obviously were eager to be as helpful as we possibly could. We also held a public hearing early in 2019 that we continue to get comments from. We continue to make use of the data that people have provided to us as a result of that public meeting. And in order to facilitate that, we've recently reopened the docket, that's basically standing open, as people are able to send us material if we will make use of it. We do, however, continue to take enforcement actions, and I'm sure you've seen the news about these. Fundamentally, people are not always marketing their products appropriately. And when they are (unint.), they open themselves up to potential actions from us. We have identified claims that are being made that are not substantiated by evidence. You know, right now, we're seeing claims that CBD cures COVID. No data on that. Making that sort of a claim is clearly a drug claim that requires evidence to be submitted to the agency to be reviewed. So when we see those sorts of egregious and potentially harmful claims being made, we need to be able to step in and take action. We're also working to encourage botanical drug development, including botanicals that are cannabis-derived, and I won't go into detail except to say that I have an entire team whose job it is to encourage plant-based drug development. And they are ready to talk to anyone at any time, to make them be as helpful as possible. And then lastly, we have a web page where we list the things we know, the things we don’t know, the questions we can answer, the questions that we don't answer, and offer any assistance that we can to further the development of products derived from cannabis appropriately on safe, effect, high-quality products for the American consumer. And with that, I'm going to end with my summary, which is just to say, again, we have a well-defined role in this space. Our role has not changed based on the recent activities at the legislative level. We continue to support the scientific assessment of cannabis-derived products and cannabis-derived compounds. We think it needs to be robust and scientific. We understand the broad interest in expanding the availability of these products. We're looking at various regulatory pathways to lawfully allow that, that would appropriate for the safety of the American public. And we are committed to protecting the public health with respect to these products wherever possible and to the extent we possibly can. With that, I thank you for your attention. I'm happy to answer any questions I can.

>> Thank you so much, Doc, for putting the context on some of the regulations and issues that FDA is currently working. And when we were planning this symposium, we thought it would be very important to hear and understand at least some of the perspective or point of view of the researchers themselves regarding challenges and hurdles related to the clinical cannabis research. For that, we had invited our co-chair, Dr. Ziva Cooper from UCLA, and also you will hear from the person that you had heard before this week, Dr. Donald Abrams, professor emeritus of medicine at the University of California in San Francisco, very active in the research related to cannabis, and he was -- in fact, he called for a chapter on cannabinoids and cancer in their hopes for university press, (unint.) text. And he also was part of the National Academy's Committee on the Health Effects of Cannabis and Cannabinoids. So we will hear from Ziva, Dr. Cooper first, and immediately then after Dr. Abrams. Thank you. Ziva.

>> Okay. Thank you so much for having me, and I'd like to thank the NCI organizing committee for inviting me to be a co-chair. And it's been wonderful working with Dr. Salicrup, as well as the other panel members to talk about this really important issue as we've heard for the last couple of days, you know, the gaps in knowledge with respect to cannabis and cancer research. Why do we have such significant gaps in knowledge? So I'll be talking about my own experience having worked through some of the regulatory hurdles in two states over the last five years, two states, New York State and California. I was at Columbia University in New York, and now I'm at UCLA. And so I've had some difference experiences, and I'll just talk about some of those hurdles. And then Dr. Abrams will talk about how those hurdles apply to him as he was embarking on cannabis and cancer research. So my studies are funded by the NIH as well as the California State Funded Center for Medicinal Cannabis Research. Independent of these studies, in the past year, I have served on the Scientific Advisory Board of FSD Pharma. So the skeleton for my talk will be the urgent need for clinical data, which you've already heard a lot about, some insights into regulations, so taking off from what Steve and Doug shared with you, explaining how that really applies to a researcher in this field. I'll then talk about additional barriers that we don't usually hear about, and then path forward. So we all know that there's a desperate need for clinical data, and this is complicated given that there have been widespread changes to regulation, and Steve highlighted some of these very graphic changes that are occurring. And at the state level, they're really inconsistent. So even though cannabis is Schedule I, understanding how all the different states regulate cannabis is really important in understanding the shifting market and the shifting trends in use. We know that there have been rapid changes in perceptions of harms, as well as medical benefits of cannabis and cannabinoids. And we also know, as we've heard a lot, that there's been an exploding market in the area of cannabis-based products for therapeutic use as well as adult use. There have been changes in the different types of products that are available. There have been changed with respect to the medical indications that people are using cannabis and cannabis-based products, and we're definitely starting to see a shift in who is using these products, both for potential therapeutic use as well as for adult use. And we've heard a lot about this, especially on day one of this event. So we know that people are using cannabis in different ways these days. So now people are using cannabis and cannabis-based products topically. They're vaporizing plant material. There are vape pens to vaporize extracts. We know that the oral cannabis-based product industry has exploded. We know that there are different products. We're moving away from just the plant at this point where we're shifting to very high potency extracts that are available in many states that are almost 100% THC and are thought to provide an efficient, intoxicating experience. We know that there's been an exploding cannabidiol market. You can get -- as Doug pointed out, CBD is used in clothing, pillow cases, CBD-infused food, CBD-infused capsules and tinctures. We also know now that there has been a lot of interest in the market apart from CBD. So we're starting to see products that are focused on other minor cannabinoids, CBN, CBG, and other minor cannabinoids that are thought to have potential medical benefit. And we're also starting to see an explosion in the terpene market. So frequent questions that I get as a cannabis researcher from family, friends, community members, as well as physicians is, you know, what is this product good for? Which cannabidiol product, or which CBN is best? What is the highest quality? And what do I use if I have this indication, and what doses do I use, and what are the risks? And we've already heard that it is really hard to answer any one of these questions at this point in time. And why is that? So I'll give you some insight into the regulations and barriers to study. These compounds, these drugs, which will explain why at this point we don't know very much and in part, we don't very much because, as scientists and regulators, you know, we can't even keep up with the booming industry. So we have three main barriers to research that I'll be highlight today. The first is drug scheduling, which we've heard a little bit about; few available products, which is really important to think about. A lot of people focus on the drug scheduling as the main barrier, but I think one of the primary issues here is that there are very few products that we can study as researchers. Also funding and institutional support are really important when thinking about the barriers to research. So we'll focus first on drug scheduling, because I think that that is one of the most predominant barriers that we know most about. So cannabis is Schedule I, federally Schedule I, which means that anybody who researches cannabis, we have to obtain a Schedule I license, which requires a great deal of investment of both time and money. And I'll talk in detail about this. So, you know, these are some of the needs that we have to have in order to obtain a Schedule I license. So, for instance, in my lab, I have these 24 hour monitors that are connected to Wi-Fi, and I get alerts every time somebody is in my lab. And it's important to note that I don’t just have one camera, I have two cameras pointing towards my storage facility in case the power goes out for one of them. I have double locks on my storage facility, again, connected to wireless so I can see if anybody is coming and going. I can track who is going in with the keypad, because everybody has their own code to enter. And inside of my facility, I have a 750-pound safe as well as refrigerators and freezers that are braced to the wall and the floor and have their own locks. We need both federal and state approval. So it's not just the DEA. We also need to get approvals from the state, and I'll talk a little bit more about that. We need to comply with institutional requirements for storage. So not every institution has the same type of requirements for storage of Schedule I substances. And all of this presents extreme limitations to study design, which Dr. Abrams will talk about in detail. The drug scheduling is a confusing and evolving situation. For instance, CBD, the schedules have changed over the last two years dramatically. So now if you're getting plant-derived, specifically hemp from the hemp plant, it is not scheduled. CBD is not scheduled. If you're getting synthetic CBD, that is considered Schedule I, but there are some exceptions to this, and this makes things very confusing. If you're using THC and it's plant-derived, that is Schedule I. If it's synthetic, I can be one of three schedules. So if it's marinol where it's an oral capsule, it's Schedule III. If it's the liquid form of Dronabinol, it's Schedule II. If it's an API, so just straight THC, that's Schedule I. So it's very confusing. So in order to obtain a license, you first have to identify what drug, what source are you going to use for your study? Then you have to obtain funding for the study as well as funding to be able to support a drug storage facility, which is not an easy task for many researchers. Then you have to get additional IRB approval. You submit your protocol to the IRB and they say, "Okay. You can go ahead with this, but you need to get your DEA license and you need to apply for an IND to the FDA." Then once you get your conditional IRB approval and you have the IND to the FDA, you can submit your application to the DEA. And then at some point in time, which is not very clear as to when this happens, and this is my own experience. Some people might have had an easier, more transparent time. At some point in time, the DEA receives your application. They contact the FDA to make sure that the IND paperwork has gone through. At some point in time, usually about 30 days, the FDA responds to the DEA and says, yes, they know about this protocol. And then the DEA schedules a site visit. But, again, you're not quite sure when that site visit is going to happen. Then once you have a successful site visit, the DEA sends your license and the 222 forms, which are required to order drug. And then you can request drug from the supplier and hope that they have it in stock and that you can get it and have your study underway. Now one thing I didn't mention here is that there are state specific regulations. So in New York State, you have to apply to the State Narcotics Bureau for a license before you get your DEA license. In California, you have to submit your protocol to the Research Advisory Panel of California and that panel, they look at all studies related to Schedule I and Schedule II substances, and they're not just making sure that you have the proper storage facility. They're actually looking at the protocol, and they will ask you questions about protocol specific details, even about the science. So even if you're an NIH funded researcher and it's gone through the IRB, they will still ask you questions that aren't necessarily related to how you're storing the drug, questions that you would think that the DEA might ask. So some concerns about this or some hiccups is, you know, will your storage facility be approved when the DEA finally comes out? And it's hard to know that, because there aren't clear guidelines. And every institution or every laboratory has some oddities where you can't necessarily comply with everything that the DEA has on their website. For instance, if you have to have your drug frozen, do you put a safe in your freezer and then have a lock on the freezer? If you have it in the refrigerator, the same thing. Do you have that safe in the refrigerator? These are very confusing items to comply with. And also there are facility specific limitations. How much space do you have in your laboratory, or can your product be stored at a research pharmacy, which has more space? Very little communication with the DEA where you can ask for clarification of these parameters. And in general, if you want to make sure that your storage facility is up to par when that DEA comes out for their site visit finally, it requires a great deal of money. For instance, the cameras that you have that are connected to wireless, they might cost about $3,000 plus monthly fees so that you can get that wireless feed. The double locks might be about $5,000. The 750-pound safe is $11,000. So who is going to pay for the storage facility? That's a really important question to ask. Next we have the barrier to research of few available products. As Doug pointed out, we have to have a product that complies with the FDA standards. So you need to identify a source. Where are you going to get your study material? And this study material has to meet FDA criteria and the supplier has to be able to work with you when you're submitting your IND. You have to be able to provide the FDA with the important information about the chemistry, manufacturer and control information. If they have a drug master file on file with the FDA, they have to be able to provide a letter saying that you can access, the FDA can access that DMF. So there's a lot of communication between the researcher and the manufacturer or the provider of the study drug material. If the study drug is scheduled, of course the supplier has to have an appropriate license. So if it's a cannabis supplier, they have to have the schedule on license. The manufacturer also has to have the available drug supply for study. So if you're looking at a study over two or three years, you have to make sure that that drug supplier can be able to provide you with the study material that is consistent for those three years so that you know when you are studying your first participant, they are getting the same product that your 100th participant is getting. What about available placebo? So some companies might have a product that you can study, but they don't necessarily have a placebo. And if you're doing a placebo controlled study, you need a placebo. And that placebo is taken into account when you submit your IND to the FDA. And that's also something that people don't necessarily think about is that when you ask a company if they can provide you drug, do they also have a placebo that they can also give you. And what is the cost for this drug? And all of these factors have to be thought about when you're thinking about how you're going to design your study and how you're going to apply for your DEA license. And really this is a central challenge to research. Next we have funding and institutional support. So like any researcher, you have to apply for funding and, of course, your funding or your grant application has to explicitly state how your research will advance the field. That's, you know, basic. That's -- all researchers have to do this, of course. Now, the next part though is really unique to cannabis and cannabinoid researchers. Is your research feasible? So you will not -- well, I guess this is my perception of the situation. You will not have good luck in submitting a study related to cannabis or cannabinoid administration if you can't demonstrate that it's feasible. And what do I mean by "feasible?" Does the researcher have experience working with cannabis and cannabinoids? Do they have experience with Schedule I drugs? Is there an existing storage facility? I already talked about how you have to prepare a storage facility to get your schedule license. So if a researcher wants to submit a grant, it would behoove them to demonstrate how they have an existing storage facility. Has that researcher identified a drug supply? And, again, I mentioned how this is a central barrier to researcher is knowing where you're going to get your drug and knowing that it will be available for the duration of the study. And is your institution supportive of this research? So I am lucky that I've been in two institutions that are supportive of this research, but there are many institutions that are skittish. They aren't -- that institution hasn't looked at cannabis and cannabinoids before. So there's a lot of hesitation at some institutions about actually supporting this type of research. Once you receive funding, amazing, congratulations. You're one of the very small percentage of researchers that have received funding. You have to get your regulatory approvals, right? You have to have your IRB approved, submit your IND to the FDA. You have to get your DEA license. You have to work with the state specific organizations that allow Schedule I substances to be studied. Then you have to have your annual updates prepared to all these organizations. You have to have annual updates to the IRB, the FDA, the DEA, in the California the Research Advisory Panel. And then you have to think, "Oh, my gosh. I didn't budget for all the personnel, all the man hours, all the extra expenses that goes along with getting drug from a cultivator or from a manufacturer." There are always other costs that come into play that you don't necessarily think about when designing your budget. So to summarize, there are countless pressing public health questions that are being asked right now, and they are growing daily. The industry is booming, and people are using products that we would never have even conceived of three years ago. There are several barriers to research. We have drug scheduling, which is a very important barrier, but another one is drug sources. Where are we going to get that study medication? And funding. How are you going to fund your storage facility in order to even get your license and be able to apply for grant funding? So one important point is that, yes, research is difficult, but it is not impossible. It is not impossible in the United States. But the important thing to know here is that even though research is possible, these obstacles, which are not insignificant, they essentially limit the number of researchers that are able to do this work. And when that happens, you don't have the scientific inquiry that is needed to be able to address so many pressing issues that are happening right now. So, you know, there are a handful, ten universities that I can think of off the top of my head that are doing this research, but there are so many questions to ask right now and so many researchers that are interested in getting involved in this work, but there are an incredible number of obstacles that are just pushing people out, or having people give up when they're, you know, reaching one milestone, the second one is just too difficult. And so people are throwing the towel in, and I think that's a really important thing to think about when we're thinking about the barriers to research. And please feel free to email me if you have any questions, and thank you so much for your time. And I'm looking forward to hearing from Dr. Abrams about how these barriers have impacted his research.

>> Donald, you have to unmute your line. Since you're sharing your screen, if you move your mouse to the top center, you'll find the mute icon.

>> Okay. Hi. Thank you, Ziva, and all of the presentations this morning have sort of led up to my comments, which are going to be very practical in discussing some of the clinical barriers to conducting research with cannabis. Hang on. I'm unable to advance my slide.

>> You might have to click back on it since you clicked away to unmute your line.

>> Okay. So with regards to disclosures, I am a scientific advisor to two companies and have stock options. So the first study that I did actually as in 1992, and it was a study in -- it was a study that I was trying to do in 1992, looking at cannabis in patients with the AIDS wasting syndrome. After five years, it became apparent that it was difficult to fund a clinical trial looking at the potential therapeutic benefits of cannabis. So by 1997, I was actually funded to do a study looking to see if it was safe for patients with HIV on protease inhibitors to add cannabis to their regimen, because at the time NIDA was not particularly fond of supporting studies looking at the potential therapeutic benefit of a Schedule I substance. At the end of the last century, the State of California had a budget surplus and Senator John Vasconcellos, one of our state senators, appropriated $3 million a year for three years to establish a Center for Medicinal Cannabis Research at the University of California. And the purpose of this center, which still exists to this day, now funded by revenue from recreational cannabis sales, was to conduct and support clinical trials on the efficacy of cannabis, now expanded to cannabis and cannabinoids, to determine optimal dosing, timing, and modes of administration, comparing the efficacy and safety of various methods, assess the safety and toxicity, and to conduct limited preclinical studies. So we were funded by the Center for Medicinal Cannabis Research in their first round of funding in 2001 to conduct two studies that I began simultaneously. One was the study effect of inhaled cannabis on neuropathic pain in patients with HIV-related peripheral neuropathy. This was going to be a 16-person pilot study. And at the same time, I was funded to do a study of cannabis in combination with opioids for cancer pain. This study was originally designed for patients with breast and prostate cancer who had painful bone metastases. And again, both of these were 16-patient pilots to assess the activity and calculate the sample size needed for a follow-on randomized controlled trial. Both of them were designed at nine-day inpatient studies in the San Francisco General Hospital Inpatient Clinical Research Center. This we learned from our first study funded in 1997 that if we were going to -- that study was a 21-day inpatient study, and their concern was that if we gave patients cannabis to use at home, how do we know that they're not diverting it. So that's why all of our studies at San Francisco General have been done in the Inpatient Clinical Research Center setting. And both of these two pain studies that we started in 2001 were done in conjunction with my colleagues from the Pain Clinical Research Center at the University of California, San Francisco. And they felt that since we were studying such a controversial substance that we should anchor the patient's subjective experience of pain with the so-called heat/capsaicin experimental pain model. I'll explain that in a second. So our participants, as I mentioned, spent their days and nights in our clinical research center. They were not allowed visitors, and they could not depart the ward without accompaniment, because they were in a study of a Schedule I substance. We had to ventilate the rooms that the patients stayed into vent to the outside with fans. And to standardize an inhaled dosing procedure, we used a so-called Foltin puff procedure, which had been previously reported in the literature. Our nurses needed to observe the inhalation episodes from the extra of the room. The heat/capsaicin experimental pain model involved heating an area of the forearm to 40 degrees Celsius with a thermode and then applying capsaicin cream, the active ingredient in chili peppers, to that same rectangle, which produces an area of allodynia and hyperesthesia, or weird feeling and hypersensitivity that can then be mapped with a brush and a piece of foam with the person looking off in the other direction, and the areas could be measured before and after exposure to the study drug. So what happened with the two studies, we rapidly enrolled 16 participants into the HIV neuropathy study, and 17 of 50 were enrolled in the follow-on randomized controlled trial at a time when we had only enrolled three participants in the cancer pain study. So we decided that this was not going well, and we altered the design of the cancer pain trial to include any cancer and any pain as opposed to just breast and prostate with bone metastases. We completed the HIV neuropathy trial successfully, but we were unable to advance accrual in the cancer pain study. And the Center for Medicinal Cannabis Research ultimately withdrew the funding. We discussed what was going on with one of our cancer symptom nurse PhDs who really felt that some of the barriers were that cancer patients are not particularly interested in spending unnecessary inpatient time, hence, as we're doing all the studies in the Inpatient Clinical Research Center that would be a detriment. And our institutional review board was concerned about inflicting experimental pain model on the cancer patients, although that wasn't a concern of them for the HIV patients, interestingly. And finally, patients with cancer in San Francisco have long had access to cannabis without having to consent to a clinical trial and risk possibly getting placebo. So we then got funded by the Center for Medicinal Cannabis Research to do an outpatient study. This study funded in 2003 was to look at treating chemotherapy-induced delayed nausea with cannabinoids. And patients who had experienced delayed nausea after a first cycle of chemotherapy were then randomized to receive truth cannabis cigarettes and a placebo Dronabinol capsule, placebo cannabis cigarettes and active Dronabinol capsules or double placebos. And the sample side for this, like one of the studies we heard about yesterday in chemotherapy-induced nausea and vomiting, was calculated to be AD1. And we enrolled eight patients in this outpatient study and then aprepitant was approved for treatment of delayed chemotherapy-induced nausea and vomiting, which definitely decreased the interest in San Francisco oncologists in referring patients to our trial, and we ultimately lost funding only enrolling 10% of those patients despite it being now an outpatient study without an experimental pain model. So one of the questions that we asked were, are these cigarettes from NIDA a 21st Century drug delivery system? Our HIV neuropathy study was a positive study showing that inhaling cannabis was better than inhaling placebo, but we were concerned that colleagues were not going to feel that smoking a cigarette was a good drug delivery system. So we then used the volcano vaporizer in a study funded by the Center for Medicinal Cannabis Research. Actually, the easiest study I've ever enrolled was 25 to 40-year-old chronic cannabis users admitted for the six days to the Clinical Research Center. On each of those days, they either smoked or vaporized half of the NIDA cigarette, three different strengths THC, 1.7, 3.4, and 6.8. And the left panel shows that the THC concentrations were superimposable and the right panel shows that the patients' experience of high was also equivalent. The middle panel shows expired carbon monoxide, which is a marker of exposure to noxious gases. The flat bottom line is in the vaporized patients, and the top line is in the patients who were smoking half a cigarette. So we concluded that vaporization was a safe and effective delivery system. And subsequently, all of our studies have used the volcano vaporizer. So I really felt that the cannabinoid opioid question was a significant question that I wanted to answer. So in 2006, I proposed to NIDA to do a pharmacokinetic interactions study in patients with cancer on sustained release morphine or sustained release oxycodone to see if it was safe to add vaporized cannabis to their regimen. And as long as I was looking for safety and potential harm, this study was easily funded by NIDA. Again, it was cancer patients on BID or twice a day morphine or sustained release oxycodone. We enrolled one participant after screening 218 cancer patients who expressed interest. Either they were not taking the correct opioid analgesic, or more commonly, they were taking the twice a day morphine and oxycodone sustained release preparations three or four times a day. And that wouldn't allow us to draw the 12-hour kinetics curves that we wanted, or they were receiving concurrent chemo, radiation or bisphosphonates, which were exclusion criteria. So after a number of months, we modified this protocol to eliminate cancer-related pain as an entry criteria and included any participant with any pain as long as they were taking the morphine or sustained release oxycodone twice a day. So that study was really the backbone of the study that we expanded on when Kalpna Gupta, a mouse scientist then at the University of Minnesota, now at UC Irvine, came to me and told me that she has a mouse model, transgenic mice that are expressing the human sickle hemoglobin gene, and they experience pain. And morphine is useful for this pain, but in her laboratory cannabinoids, laboratory cannabinoids also ameliorate the chronic and hypoxia/reoxygenation-evoked acute pain in the these mice. So she asked me if I would be interested in doing a human proof of principle study to accompany a large grant she was submitted to the National Heart, Lung, and Blood Institute. And I felt that since we had already done the cannabinoid/opioid interaction study and most of these patients with sickle-cell were going to be on opiates, that it would be easy to put together a protocol. She asked me what I wanted to study, and I said -- this was at a time when CBD had suddenly jumped onto the most favorite cannabinoid list. And I said, "I'd like to do THC, CBD, both and placebo." And she said, "That's fine, but you need to do only two arms and one has to be placebo." So since we'd already studies the interaction of the 3.5% THC/0 CBD with the opiates, I said, "Okay, let's do a one-to-one ratio." And I asked Mahmoud and NIDA, Mahmoud ElSohly who grows at the University of Mississippi and NIDA, to give me a one-to-one preparation, and then they did provide one. So in this study, we were going to enroll 35 patients with sickle-cell disease on opiates into a randomized double-blind placebo controlled cross over study. Our patients would spend two five-day inpatient admissions following a five-day outpatient diary with one month between these two admissions. And on one of the five-day admissions, they would vaporize three times a day the 4.4 THC/4.9% CBD and on the other, they would vaporize NIDA's placebo cannabis. And we were going to assess pain using a visual analogue scale, the Brief Pain Inventory/Drug Effects Questionnaire and side effects monitored by the nursing staff every four hours. So, again, as Ziva pointed out, first we had to have NHLBI approve the grant. And then our clinical research center at San Francisco General Medical Advisory Committee and the Dean's Office of the University of California, San Francisco at San Francisco General needs to approve it as well. Then, of course, the University of California, San Francisco Committee on Human Research needs to approve it, because I am a professor at UCSF. The Research Advisory Panel, as Ziva mentioned, also needs to improve all studies of Schedule I substances conducted in California. And I might parenthetically add that I feel responsible for having them change their name from the California Research Advisory Panel because in the old days, I used to refer to them by their initials, CRAP, so they changed it. The DEA, as we've heard, needs to provide a Schedule I license, both the federal and, as Ziva mentioned, the local DEA needs to inspect our facility. We have been very fortunate at San Francisco General. We only need to have a locked freezer without a safe, but it has to be locked and alarmed to the police department as if people are going to come for 4% THC when in San Francisco, 27% is pretty much the norm. And then, of course, for reasons that remain a little bit confusing to me, because we're not developing cannabis, which is an illegal substance, for sale, but we still need to obtain a Food and Drug Administration IND. And finally, we approached NIDA for the cannabis. So just because I saw in the chat box people are asking how long this all takes, this trial was approved by the UCSF IRB in July of 2013, and that's when we submitted the IND to the FDA. Interestingly, I need to say that the FDA put a hold on the IND when I submitted it, because they said that CBD was an NME, a novel molecular entity. It had not yet been studied in humans, and they wanted two animal pulmonary histopathology studies, or for me to demonstrate in rats and monkeys that CBD doesn't harm the lung. And I told them that's not what I do. I'm a simple oncology. So I got letters of support from two colleagues, one in London and one in Sydney, who were studying vaporized CBD for schizophrenia, telling me it was safe. And I sent pictures of rolled cigarettes that were 10% CBD and a menu from a dispensary where many products had high CBD, and I said, "This is not an NME." And so the FDA replied that I could proceed with the study if I sent them two animal pulmonary histopathology studies, or only enrolled patients in the study who had previously experienced inhalation of CBD so I wasn't putting them at any greater risk than they had already put themselves. So then we ordered the study drug, and the study drug was received in relatively good time. Remember I already had a long-standing DEA Schedule I license, so that was not an issue. Our first patient was scheduled about one year after our IRB was approved and enrolled one month later. Unfortunately, as I mentioned in my monitoring of Professor Twelves' discussion yesterday, they enrolled 27 patients over two and a half years at ten sites. It took us quite a long time as well to enroll only 23 of the 35 patients with sickle-cell disease that we were seeking. In doing this trial, I appreciated that patients with sickle-cell disease have more barriers to inpatient participation in clinical research even than patients with cancer. So as mentioned, here we are today. These are dispensaries and what they have available. Are we going to study buds? Are we going to study gummies? Are we going to study elixirs? Are we going to study that? Are we going to study -- Ziva left out that the most frequent question that I'm asked by patients is, "What is the right ratio of CBD to THC to study?" And, you know, really don't know, and is it even CBD anymore, or should it be CBG, or maybe CBN? So are we at a stage where all we can really do are observational studies? Michelle Sexton, who spoke the other day, and I just submitted a manuscript on the results of 400 patients in San Francisco, San Diego and Chicago using CBD-enriched products where we asked them to fill out a one-time survey telling us what they were using, how they were using it, what they were using it for, and if it worked. Certainly, these are not the same as doing randomized placebo controlled clinical trials, but I wonder if we can really do those anymore in the current environment. I mean, it was really much easier when all we had was NIDA 3.5% THC cigarettes. So again, to reiterate what everybody said today, Schedule I status definitely creates excessive regulatory hurdles. Potential participants have increased opportunity to utilize medical cannabis and obtain it without participating in a clinical trial. The scope of currently available products complicates the decision regarding what interventions to be studied. And I didn't really go into this into detail, but once complicated, cannabis clinical trial results can be challenging to publish. My experience is that the people that are assigned to review my studies often contain prohibitionist who wonders why we would even consider studying such a toxic substance. And then when you try to do a placebo controlled randomized trial, the reviewers say, "This cannot be placebo controlled because patients know if they're inhaling cannabis versus placebo." So these studies, once they're completed, have been challenging to publish. And with that, I'll stop and thank you for your attention.

>> Thank you so much, Donald and thanks to both you and Ziva. I (unint.) comments and observations from the audience thanking for such details. Now for this, we are going to a panel, and I would like to invite my co-chair and all the (unint.) speakers to join with your camera so we can address the questions. And for this part, Dr. Cooper will be helping me to address some of the questions received from the audience, but she will be also participating as a speaker. So let's start -- I should say also that I noticed that some of the speakers already answered some of the questions by the chat, using the chat. Thank you so much. And in fact, others do during the presentation, like Dr. Abrams just did, also addressed several questions we had seen. But having said that, Ziva, let me start with you, because there is a lot of questions related to the study of one. I have ten questions. So what is your perspective, and Donald, feel free to add if you want to. Would clinical research change if cannabis was going to be removed from a Schedule I classification?

>> So I think that if cannabis were to be removed from the Schedule I, I think the main change that would occur is that it would open up the possibility for more researches to get involved in this work, because it would hopefully, in theory, remove some of the barriers that are required to obtain your Schedule I license. That being said, although it would remove some of those barriers, you still have the issue of identifying your drug source and being able to use that drug source in the clinical study. So you're still left with that issue. But I do think that removing some of the barriers, introducing more flexibility with respect to how the drug is stored would definitely help pave the way for more people getting into the field.

>> Thank you, Ziva. Donald, do you want to add something to this?

>> I think I would agree, although I wonder how many people are out there eagerly awaiting to get into the field of cannabis research since it's so fraught with so many other challenges and barriers. It's not supported by a pharmaceutical industry. It's difficult to publish the results. I just wonder if it's going to open up the flood gates to having more people become involved. I'm not sure.

>> Thank you. We have also a question that reads like, "Is it legal to have a randomized trial of medical cannabis versus just under care therapy for a cancer-related symptom in a state where medical cannabis is legal?" It's a compound question. It also asks, "Can the cannabis be provided at a reduced rate as part of the study if medical cannabis dispensary agrees to do that?" So any one of you can take it.

>> So I think the question is, "Can we use state regulated cannabis for our studies?" And so the answer is that, no, at least in California, UCLA or at Columbia or at many, if not all, of the universities. We are not allowed to use state regulated cannabis. And that's because it's still considered, you know, federally -- it's still a Schedule I. So I cannot bring cannabis from a dispensary onto campus, even if I was just testing it to see what was in the cannabis. I can't bring it onto campus. I cannot obtain it. And Donald, you probably have some experience with this as well.

>> Well, no. I was going to ask Steve, because I've called NIDA, I think, a few times, because -- for example, I have a friend on the East Coast who has a company willing to donate cannabis and money for research. And my understanding is if it passed good manufacturing procedures that it might be possible, but I don't know. Steve, do you want to comment?

>> Yeah. I'll start with that, and I think Doug might have a few things to add as well. There are certainly -- the part that I think Doug can comment on is whether or not the FDA's review of the manufacturing process is independent of its legal status, and I think there are examples, you know, where a private company could pass FDA muster, but still not be federally legal because of the Schedule I status. Now, separately from that, I think we're all of the same mind that we really need to get access to dispensary products for research purposes. Once that happens, I think Ziva's point is a good one, that there will still have to be -- in order to do something -- to get an IND approved, you're still going to have to provide a lot of data and a lot of information. But that's not an insurmountable barrier at all. And so there are dispensary providers who have already and who are certainly willing and able to produce and provide that kind of information so that the source problem could go away I think very quickly. There would be some very reliable, you know, sources. But that -- of course, we have to get past the barrier of getting access. This is one of the key issues that's being addressed by this current legislation efforts and could be -- you know, keep our fingers crossed, there could be some significant changes made. And while I have the floor, I just want to mention a couple of clever models out there that some NIDA supported researchers are using to actually study dispensary products in somewhat of an arms' length way, but it's being done. You know, one of those, Kent Hutchison Laboratory at the University of Colorado where they've gotten around some of the issues around the concerns that universities have about bringing dispensary or other federally illegal products onto campus property. And he's done that by having a van basically that drives around to individual study participants' homes where they consume the cannabis that they've procured and then come out to the van to participate in the study. So Kent and his colleagues there avoid any transgression of federal law by not touching or possessing the products. There's a second example of that, Rajit Singhi (ph.), Yale, who has also -- the Yale attorneys have not expressed, apparently, quite the level of concern that many other universities around the country where they have allowed her to bring dispensary products into a laboratory setting, into her laboratory at Yale. Again, she doesn't take possession. She doesn't distribute, but my understanding is that the subjects and the patients in the study basically use the dispensary products, you know, on the university property, but without -- Dr. Singhi has possession and then they take part in the protocol. So these are workarounds. There could be more of these done, at least in this interim period where, you know, things are changing so quickly. But, you know, it's not insurmountable to study some of these dispensary products.

>> Yes, I guess I'll just add a couple of comments. First, my comments relate to studies done under national controls for drug development federally. I mean, I know there are tons of studies that are ongoing that may have a different standard. Basically, I think Ziva had it right. When I'm asked about sourcing materials for drug development, you know, at the FDA, I say two things. First, I say, get me a legal source, a legal source for that product. That means "legal," that the DEA has said you're an approved source, in this case, for cannabis or cannabis extract or whatever. If you do that, the FDA will treat you like we treat every other drug developer. You're going to be treated the same way, the same rules, except to the extent we're going to go above and beyond. We've got a botanicals team that you'll have access to, things like that, so that getting a legal source is really the first hurdle, and there is a single recognized legal source. Steve and I have worked for years to try to encourage a broadening of that number of approved growers, because we just think it's essential. Several of the bills that Steve mentioned hopefully are going to help with that. The rule that the DEA just issued was intended to do that. I'm not exactly sure what its impact is going to be. But bottom line is we need more growers. We need more products to be available for study. The other thing about that though is the Farm Bill gave investigators a new avenue in this area, I believe. Products that are extracted from hemp are not subject to the DEA. And so if you're studying extracts from hemp, you're subject to FDA's authorities, the things we talked about before, but our preliminary understanding is that they are not subject to DEA's authorities. And we believe that makes an important difference. Those products, those non-smoked, non-vaped products that could be ingested, I think are in an important place for people to be looking to for investigation. And Donald, just to address your comment that you can't imagine people doing that, they are. The number of INDs that we have for investigation products of -- generally in that description has gone up since the Farm Bill came out, and our guidance recognizes that, we're hoping makes it easier to have that area blossom, no pun intended. Because I think as we sort out this grower issue, we need to look for other opportunities, and I think the Farm Bill gives us an opportunity to make it easier to do research on components of hemp.

>> While you have the floor, can I just ask why do we really need to get an IND to study NIDA cannabis? We're not developing it as a drug, are we? They're never going to sell NIDA cannabis. What is the purpose of the IND step?

>> Well, the NIDA marijuana is -- and I'm using "marijuana" with care there. Largely, it's being used as a drug source. So behind the marijuana -- you know, yes, it is cannabis. I'll go back to that, with a particular set of characteristics. But the intent is to deliver a drug. The intent is to delivery CBD or CBN or THC or whatever. And so because we don't know the safety and effectiveness of those, this is in fact human subjects investigation, and it falls under investigation new drug requirements, human subjects protections requirements, all the things that we're talking about. And then some companies are trying to do (unint.) drugs. So they would, of course, trigger those requirements for that purpose.

>> Thank you. And thank you to both Doug and Donald, because there was in fact three questions related to the IND. So you already addressed it in a very short time. But there is a question -- there is a few questions related to CBD products. "How does FDA determine the status of CBD products on the market?"

>> Sorry. Did you say how do we determine the status?

>> Yes. Yes, of CBD products on the market. Yes.

>> Well, so we determine the status of all of those various kinds of products that I mentioned. If you remember, I had that chart that had all the different boxes on them. First and foremost, by claims. So first and foremost, what is the product being intended to do? So if the product says, "I'm going to cure cancer," has on its label or by other means that we can determine is being marketed with an intent towards treating, diagnosing, mitigating, preventing human disease, it is a human drug. And then it's regulated by the Center for Drugs if it makes those claims about the Center for -- for animals, it goes to the Center for Veterinary Medicine. Under some circumstances, there are claims that can be made, so-called structure function claims. And these are different kinds of things. They're not intended to treat, diagnose, etc., etc. Those are under some circumstances potentially available for dietary supplements and foods. And so short answer, begins with the nature of what you're trying to market your product for. Obviously, if it's a cosmetic, that's a little -- you know, you go to intended use there, you know, smear it on and things like that, or used on the lips or something like that. After that, each of those blocks on that chart that I had have their own sets of legal authorities. And so how a food and a dietary supplement are regulated differs from how a drug is regulated differs from how a cosmetic is regulated in important ways. So it sort of matters. Those details matters, and it's probably not worth trying to walk through here today. There is one really important thing for people to understand. There is a statutory provision that basically says approved drugs shouldn't be in foods. I mean, it's more complicated than that, and there's a lot of other language, and I don't want to -- but fundamentally, Congress has said in the act that if a product -- a component of an approved drug shouldn't be in a food, you know, and that's a barrier. It's a barrier for things like people that are interested in marketing foods that contain cannabidiol, because cannabidiol is found in an approved drug product. And so when people come to us, they're interested in marketing a dietary supplement, we have to recognize that that's a legislative challenge. It's one of the things we're trying to work through is find a way that we might be able to enable the marketing of those products as foods or dietary supplements, because at present, there are legal hurdles to doing that. That's why my job is to make sure that drug development is as easier and efficient as possible so that while we work through those things, you know, Ziva and others make progress in terms of drug development, because we think that's ultimately terribly important to continue.

>> Thank you, Doug. Very related because then I'm going to go a question for Ziva. But there is a question about CBD products and all that are available in the market. "Could you tell us very briefly which one has been reviewed and approved by FDA?" We don't have to go into much detail.

>> The one that has been approved by the FDA, been reviewed and approved by the FDA is epidiolex. Full stop. No other product has been reviewed and approved, cleared, whatever it is by the FDA.

>> Thank you. Ziva, so we have a question for you very specific and then you can take over with some questions that you might want to address from the public. But there is a question, Ziva, about the cameras and the wireless locks that you mentioned. "Are they required by DEA in order to get this Schedule I licensing?"

>> So they are not required. It's hard to know what will pass DEA's investor when they come. So as Dr. Abrams pointed out is that his safe was hooked up to an alarm where the police department would be notified if that alarm went off. Okay. So they had that provision. Not everybody can have that provision put in place. And so researchers try and construct a foolproof plan that will pass DEA's inspection. And you can imagine that because you don't know when they're going to come out and if you -- if the inspection doesn't go well, you don't know when they'll come out again, you're going to want to do everything you possibly can to make sure that you are confident that your drug supply is very well protected. And as a scientist, you know, we have a tendency to maybe over prepare or just make sure that all situations are covered. So, right, even if one of the cameras goes out, we know that there's another camera, you know, just to make sure that we can pass that DEA inspection. So some of these aren't required. The 750-pound safe, you know, is required. You're supposed to have your drug product in a safe that meets those standards. But, again, sometimes when you have a freezer and you can't fit a safe inside of it, what are you going to do to work around those regulations? And so you put together a plan, which can sometimes be expensive, and you hope that it will pass your local inspection. So they're not necessarily required per se, but we just want to make sure that it passes DEA's inspection. So, you know, it's been interesting to hear the responses. And Steve pointed out very elegantly how different universities have different policies. So we have some studies happening at Yale where people can actually bring dispensary product on campus. That would not happen at UCLA. We hear from Kent Hutchison in Colorado where they have the mobile van, and people are allowed to use their product inside their house and come out and have these tests be done where their blood can be drawn. So you can see that there's all these different types of models and creative ways to work around these regulations to get work done. So there are a couple of interesting questions. You know, Doug, one thing that caught me was that the FDA is working towards a research agenda to be able to shed light on specifically a lot of the CBD products that are emerging. And I imagine with time, that research agenda will be broadened to look at other cannabinoids. So there's a question here, "Has there been any effort in creating a national cannabis patient registry, similar to what, I think, Canada has and other European countries?" This person says, "I've been working with companies to try and create one specifically for patients with cancer, which is applicable to this event, to this NCI event." So, Doug, can you comment on that, or maybe even Steve. Do you know if there's a national cannabis patient registry?

>> Steve, I can take that and you can chime in. Great question. Actually, absolutely foundational question. We don't have the safety vigilance net that we need to be collecting, you know, information about populations and demographics and safety of people that are using all of these cannabis products. It's been one of the real central weaknesses we've had for some time. Colorado had done some work when they had their explosion in use a few years ago. All of the states are struggling with this same issue. I've talked to Health Canada a bunch of times about their vigilance network and the things that they're doing there. They have a very different regulatory posture when it comes to cannabis than we do, and so their collection is a little bit different. But fundamentally, we need to do better than we are. We held a three-day meeting with Duke earlier in the year to try to figure out how to set this up. Whether it's a registry or whether there are other ways to go about collecting sort of real world experience and then the follow-on question I expect you would be asking is, "What can we do with that real world experience? You know, can we use it to expand, I don't know what, safety information and, you know, an understanding of the therapeutic uses of the product or whatever?" Absolutely spectacular questions. We've been talking to a lot of companies that are interested in doing that, and I would love to say, yes, we know the next steps there. But it's not that easy, unfortunately, because people's experiences are very different. At the FDA, we're very interested in dose and explicit identity of what cannabinoid is being consumed. That's information that's unlikely to be obtained from, you know, at least a lot of registries in typical real world experience data collection. So it's really hard for us to see how much we'd be able to use those data, but, yeah, we need to do better than we are. No question.

>> And do you think that it's because cannabis is Schedule I? I mean, that seems to be a primary hindrance in being able to create a national registry where there is the unregulated state market, the regulated state market. And so it seems like it would be hard to even envision how it would be possible to set something up like Health Canada has set up.

>> Well, in drugs what we know is that until we mandated reporting of adverse events, drug adverse event reporting was limited for exactly those reasons. Patients didn't want to take the time. Doctors didn't want to take the time, pharmacy organizations, whatever. It wasn't until pharmacy organizations were required, manufacturers were required to report, doctors were required to report under IND, etc. that we started collecting better information. At present, of course, as you know, there's no such requirement. And it's hard to imagine that working in this setting. So I think we've got to look for other ways to try to improve the data collection here. Some of it is probably going to be a matter of us doing, you know, targeted collection and testing, NIDA has a lot of interest in testing the products, for instance. We've gone out and done purchases and at least measured the cannabinoid content in products to try to figure out whether they're dangerous. But the experience, the safety experience, the therapeutic, potentially therapeutic experience, pieces we don't yet have a really good tool to collect.

>> And Dr. Gust, is NIDA or is NIH helping to support a research initiative to collect data on a state-wide basis? I'm sorry, on a country-wide basis.

>> On the patient registry question you mean, that kind of concept?

>> Yeah.

>> I'm not aware of anything other than a few grants, but I had two thoughts when I was listening to the discussion. And one is this is a workshop sponsored by the National Cancer Institute. And if there's any institute at NIH other than NIDA that would, could, should be interested in establishing a nationwide patient registry on cancer, it might be NCI. So I think this is a nice idea and might be proposed to the leadership at NCI about whether or not something like that, you know, could and should happen and be supported. The other thing is there's a number of states, as we know, that have approved medical uses of marijuana. So one place to start would be statewide. A number of states could establish, and I think are doing some work in terms of establishing statewide registries that I think could be used to answer a lot of questions.

>> Thank you, Steve. I have a couple of questions here that maybe will help us to transition to the next panel, but it is for -- the first one is for Donald and it's, "What do you foresee as being some of the most promising areas for research related to cannabis (unint.) at therapeutics?"

>> Yeah. As I mentioned yesterday, I think that the investigation into whether or not cannabis or cannabinoids in humans have any impacts on tumors is something that needs to be studied in some way, because as an oncologist, I see patients all the time who are foregoing conventional cancer care and treating potentially curable cancers with highly concentrated oils of THC or CBD or some combination. And by the time they get to see me, they have metastatic disease and, you know, I don't think that there's enough of a research base out there to support that cannabis in humans has any anti-cancer activity. And I know it's a daunting question as to how to study that, but I think that for me it's the one that really needs to be studied. For symptom management, you know, I've been an oncologist in San Francisco for 38 years. It works. You know, I don't know -- I say I need another randomized placebo controlled trial to tell me that cannabis is an effective anti-emetics like I need a randomized placebo controlled trial to tell me penicillin is an antibiotic. It works, and it works for pain, for nausea, for sleep, you know, symptom management I wouldn't pursue further again, especially not with placebo controlled trials. So I'd like to see some evidence that there's an anti-cancer effect.

>> Dr. Abrams, there is one substantive location on glioblastoma and CBD. I don't know -- that hasn't -- isn't published. I'm not familiar whether it's been replicated and things like that. I agree with you. Further careful study of anti-tumor activities would be really valuable.

>> Thank you to both of you. So two questions, and the other questions you can always write directly to all of the speakers. They made themselves available, but there is one important question here that there is a lot of information by both the media and industry promoting emerging cannabis-derived products for medical indications. So the question per se is if there hasn't been clinical studies, where did all this information for these product come from? I don't know, Ziva, do you want to take that one? Yeah. You're on mute.

>> Yeah. So there are about 700 hypothesized indications for which cannabis and cannabinoids might be helpful for, and we can see that the industry is capitalizing on these hypothesized potential therapeutic effects. And people assume that what they're hearing from the media and industry is backed by data. Unfortunately, it's not. And I think what happened is that there's a lot of promising signals from in vitro and preclinical studies that are really giving people hope. And sometimes the media and industry does not necessary translate the fact that what we know about a particular cannabinoid for a particular potential indication is really rooted in those in vitro or preclinical studies. And we know as scientists and community members that, you know, a study in a cell or a study in a rat is a far cry from knowing if cannabis or cannabinoids is going to be effective in humans.

>> Thank you. I would like to finalize this session and, Steve, you might not have the complete answer to this, but I think it would be a good transition for the session that will follow after the break, which is related to next steps. Are you aware of any NIH planning or coordinated effort across the different institutes and centers to generate more needed research related to cannabis and cannabinoids?

>> Once the panelist answers this question, we'll need to jump to a break.

>> Yes.

>> Yeah. Sure. I can give a quick answer to that. No. There's not a coordinated effort across the NIH Institutes to expand planned direct research on the cannabinoids. There's some grassroots emergence of interest, NCCIH being one. I think this workshop is another indication of that. But what is sorely missing, in my view, is essentially coordinated focus on cannabinoids and their application.

>> Okay. Thank you so much. I want to thank all the speakers, Dr. Abrams, Dr. Throckmorton, Dr. Gust, and of course my co-chair, Dr. Cooper for this excellent panel and also to all the audience for all the good questions that you came.

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