Advancing Psychedelic Clinical Study Design
Virtual Public Meeting
Day 2: February 1, 2024 | 10am-1pm *(eastern)*

Transcript

Welcome
Susan C. Winckler, RPh, Esq., CEO, Reagan-Udall Foundation for the FDA

Susan Winckler (00:00:29):

Hello and welcome to day two of our two-day virtual public meeting where we are exploring various dynamics of clinical research with psychedelics, or welcome if this is the first day that you're joining us for these discussions. I am Susan Winckler and I have the honor of serving as the Chief Executive Officer for the Reagan-Udall Foundation for the Food and Drug Administration. And we are pleased to be working with the US FDA to host this virtual event today. We had great discussions yesterday. We started with an overview of FDA's psychedelics clinical investigations guidance document, and then explored various dynamics of clinical research, including study design and blinding, dosing, including consideration of the product and accompanying therapy, and concluded yesterday with a discussion of efforts to assess the durability of treatment response, which leads us into today's discussion, which I'm looking forward to, as we continue to explore scientific issues that arise while working with psychedelics in clinical trials and drug development.

(00:01:40):

Before we begin, I have just have a few housekeeping parameters. Because of the size of the meeting, attendee cameras and microphones will remain off throughout the event. We have a great lineup of speakers and panelists, and we used questions that you submitted during registration to inform the discussion as well as preparation of the presentation. We may have a few moments in each session to address audience questions, so submit your questions and comments through the Q&A function. Note, however, that this is not the venue for addressing application specific questions. We are recording this meeting and we'll post the recording along with the slide deck and transcript on the Foundation website next week. You may also find the slides and the agenda and speaker bios on our website. The link has been posted in the chat.

(00:02:33):

So, let's talk about our plan for today. We will begin with session five to discuss set and setting. In session six, we'll have an overview of FDA regulatory authority, thinking about the parameters of where it begins and where it ends. And then, to close out our two-day meeting, we will have a panel discussion on considerations for potential psychedelic use outside of clinical trials, in the real world, should any of the products that have been discussed navigate the regulatory requirements to demonstrate that their benefits outweigh known and potential risks.

Session 5: Set and Setting

Ido Hartogsohn, PhD, Assistant Professor at Graduate Program for Science, Technology and Society Studies, Bar-Ilan University
David Yaden, PhD, Assistant Professor, Johns Hopkins University
Brian Anderson, MD, Assistant Professor, Psychiatry, University of California, San Francisco
Javier Muniz, MD, Associate Director, Division of Psychiatry, Office of Neuroscience, Office of New Drug, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Susan Winckler (00:03:13):

So, with that, it is time for me to step out of the way and to bring our experts to the virtual stage, so that you can hear directly from them. Let's get started and we will discuss set and setting. And for today's discussion, when we say set, we are referring to the mindset of the participant prior to and after the psychedelic session and the role of psychotherapy. And are thinking of setting as the physical environment, such as the room design and the activities that participants will engage in during their psychedelic session.

(00:03:49):

Our session today has two presentations and is then followed by discussion with a reactor panel. We'll begin the session with a presentation from Dr. Ido Hartogsohn, an Assistant Professor in the program for Science, Technology and Society at Bar-Ilan University in Israel. Dr. Hartogsohn, please proceed and thank you so much for joining us today and sharing your insights.

Dr. Ido Hartogsohn (00:04:17):

Thank you, Susan. So, good morning everybody. I'm Ido Hartogsohn, and I'll be speaking today about set and setting, what it is, why it matters, and what we might want to keep mind when approaching clinical research and applications of psychedelics. Also, keeping in mind cultural context. So, set and setting. I'm trying to move the slide here. Let me see-

Susan Winckler (00:04:47):

If you click on the screen, yep, click once and then there are arrows or use your down arrow. There you go. Got it?

Dr. Ido Hartogsohn (00:04:54):

Okay. Now. So, let's start with the basics. What is set and setting? So, set and setting is the crucial insight that psychedelic effects are fundamentally defined by context. In other words, in contrast to how we often think about drug effects, the effects of psychedelics are not predetermined, not universal, rather, there are always highly responsive to the basic elements of context. Things like personality, intention, expectancy, social, sensory, and cultural environment. The idea of set and setting is folded in the very concept of psychedelic. The etymology of the world psychedelic, what it means literally is mind manifesting or mind revealing, psyche, mind, and delic. So, that's revealing or manifesting and it gestures towards the basic mechanism of action these agents have. So, psychedelics reflect, they manifest the mental context for psychedelic experience, things like personality, expectancy, and intention.

(00:06:09):

And it's interesting to note that another name that's been given to these agents is ecodelics, so manifesting the environment. Psychedelics manifest both the inner psyche and also the external

environment. So, what exactly is included in context? We can conceive of this in several ways, but in the most simple terms, we can divide these to internal and external context. Set refers to internal context. It includes things like personality, expectancy, intention, so different kinds of intention and expectation lead to different types of experience. And setting relates to external context. Psychedelic experience in nature will have a different character than an experience in the city. And having the experience alone can be very different from having it with other people.

(00:07:09):

And we can add other elements to the set and setting model. For example, skillset. It's possible to develop a skillset which can be helpful in psychedelic states. For example, the ability to cultivate steady presence, the ability to diffuse the mind from unhelpful thoughts or let them go. And another recent addition to this model is integration. The meaning of psychedelic experience depends much on the post-experience context. The way we process the psychedelic experience and the narratives we build around it can shift the way we make sense of it. A difficult experience can leave painful memories or it may lead to growth. So, integration techniques and strategies can help improve the outcomes of a psychedelic experience.

(00:08:02):

And contemporary research and psychedelic demonstrates the crucialness of this context and it demonstrates, for instance, these are from different studies, that clear intention is conducive to mystical type experiences that positive set decreases the likelihood of challenging experiences, that social connection correlates with long-term psychological wellbeing. Preparation before the session increases the mental health benefits. The space arrangements mediates the frequency of difficult experiences, and musical selection mediates therapeutic efficacy. So, there's still a lot of work to be done in this area, but what we already have clearly shows that context is crucial.

(00:08:52):

So, psychedelic effects are not universal in nature. They differ in different environments. And one excellent example is the story of mid-20th century hallucinogenic drug research. During the late 1950s and early 1960s, the scientists studying hallucinogens were reducing highly contradictory reports on the effects of these drugs. I'm calling these hallucinogens in these contexts because these were different ways of approaching these drugs, which are psychedelic. So, some scientists argue that hallucinogens create psychotic symptoms, like delusion and paranoia, but others argued that psychedelics produce a new sanity, that they heal the mind. And some scientists argued that hallucinogens disrupt cognition, that they retard the mind, that they impair cognitive abilities. But then, others argued the opposite. They said hallucinogens enhance cognition that they are useful for innovation and creative work. And finally, some scientists reported that their clients were so terrified of the psychedelic state that none of them wanted to return to it, but others reported that their patients wanted to repeat this experience again and again.

(00:10:14):

And these kinds of disagreements led scientists to accuse each other of bias, unprofessionalism. And when really, these contradictions were easily explainable by set and setting. So, for instance, scientists who are interested in the notion of psychedelics as psychotomimetics, agents that induce psychotic-like symptoms, inadvertently created the conditions for such symptoms to emerge. The participants in such experiments were told that they will be given a drug that will make them insane for several hours. So, this radically shifted the expectancy. And often, these participants were psychiatric patients who had little choice but to participate in these experiments, and they did not have any productive intention for this session. The setting was not pleasant. The relationship between investigators and subjects was

usually impersonal and participants were not allowed to rest. They had to undergo countless physical and cognitive tests.

(00:11:21):

Now, compare this to the conditions in trials that were focused on psychedelic therapy, and the contrast is striking. The experience there was often part of a therapeutic alliance between a patient and a therapist. Patients approach the experience with intention and an expectation to get well. They could rest. They could speak with the therapist. They could look at art books, and they had greater freedom to choose how they spend the duration of the experience. Now, I'm talking about ideal types. So, I'm obviously simplifying a bit. But when you see the differences in context, it becomes clear that having a psychedelic experience in one context was very different from the other. And this is not only limited to psychotomimetics versus psychotherapeutic orientations. In fact, when we look at 1960 psychedelic research, we can find no less than seven distinct ways of approaching and co-producing the effects of psychedelics.

(00:12:23):

So, we can think of seven modalities, distinct approaches that produced specific results – psychotomimetic research, therapeutic research, spiritual applications using psychedelics to achieve mystical states, using psychedelics to enhance cultural creativity, the use of psychedelics to enhance technological innovation, military and special operations, thinking about psychedelics as incapacitating agents and truth serums, and also, political use for peace building and for political consciousness raising. So, the idea is that like a musical instrument that allows playing in diverse scales and modes, psychedelics can be approached through different experiential modes. And these produce different types of melodies and harmonizations, so to say.

(00:13:20):

So, the main lesson to draw here is that psychedelic effects are dependent on context. But is this exceptional? So, after all, context always shapes experience. The experience of going to a social event is very dependent on your mood, on who will be there, on the architecture, on the musical selections of the DJ. So, context is always crucial. But I want to argue that context is even more important in the case of psychedelics because of one crucial and specific feature of psychedelics. And this is the [inaudible 00:14:03] experience. Psychedelics have been called magnifiers and amplifiers of experience. They've been likened to telescopes and to microscopes. And what these recurring metaphors gesture towards is their tendency to increase the intensity and meaning of any experience. And this explains why around two thirds of people who take psychedelics in a supportive setting consider them one of the five most meaningful spiritual experiences of their lives. And why, on the other hand, when the context is not right, they can induce intense suffering.

(00:14:42):

British author Aldous Huxley argued psychedelics put the individual somewhere between heaven and hell. And in this stage of extreme plasticity and suggestibility, it's incumbent upon us to carefully consider the set and the setting. So, contemporary psychedelic research puts great emphasis on considerations of set and setting. For example, on the pleasant room arrangement, on soft lighting, possibility of rest, privacy, musical selections, therapeutic alliance, therapeutic framework, the preparatory sessions, and integration sessions. And while much of the talk about set and setting is focused on the individual, as we see from the case of mid-20th century hallucinogenic drug research, the individual set and setting never exists in a vacuum. Rather, it's nestled in a collective set and setting. So, the social-cultural environment frames all the elements of individual set and setting. It frames the

individual's personality, it frames their expectations going into a psychedelic experience and their intentions going into it.

(00:16:09):

And we have a striking demonstration of this in a classic paper by Canadian anthropologist, Anthony Wallace, who compared the effects of mescalin on American Caucasians participating in clinical trials and on Native Americans participating in the peyote rituals of the Native American church. So, we have two groups taking the same psychoactive molecule, mescalin, in two different environments, and the effects are strikingly different. On the one hand, we have participants in clinical experiments who show extreme mood swings, they exhibit sexual and aggressive behavior and paranoia and report feelings of meaninglessness. On the other hand, you have ritual peyotes who show no mood swings. They exhibit calm presence and they report awe, satisfaction, a higher sense of meaning, and integration into their community. And the way to make sense of that, again, is by considering the collective frameworks that shape people's experiences, the cultural mechanisms and the [inaudible 00:17:20], ways of making sense of the world, the way interpersonal relationships are set up within a culture, the values and norms of a culture. All these shaped the experience.

(00:17:33):

So, one thing to avoid when approaching psychedelics is from psychological essentialism, viewing a substance in isolation as having rigid essential effects, irrespective of the context. And one way of curing ourselves from these essentialist forms of thinking about psychedelics is to engage in cross-cultural and comparative historical analysis. There is a rich anthropological literature which looks at the incredible varieties of ways in which psychedelics are used. And in my book, American Trip, I reconsider three fundamental characteristics of 1960 psychedelic culture, and I show how many of the 1960s assumptions about psychedelics and what their effects are were actually culturally grounded.

(00:18:26):

So, for instance, in the 1960s, psychedelics were associated with individualistic rebellion, with defying authority, with widening the generation gap. But in traditional societies, psychedelics are not used to escalate, but to bridge gaps between generations, to instill cultural values, and to create greater group cohesion. And what shaped these cultural perception of psychedelics in the '60s was the particular social and political conditions of the time, including the counterculture and the particular phenomenon of the massive baby boom generation. Similarly, in the 1960s, psychedelics were perceived as drugs that foment anti-war, left wing, humanist, pacifist conviction in those who take them. But again, if we perform cross-cultural examinations, we can see that psychedelics have also been used in the context of war for belligerent purposes, and that much of shamanism is actually attack shamanism. And again, 1960s perceptions of psychedelics were actually derived from the cultural climate of the time, including the anti-war movement and social justice movements.

(00:19:52):

So, these kinds of insights are crucial for today's psychedelic resurgence and the potential approval of psychedelics for medical use. So, as we are approaching this event horizon, it's important that we consider both the immediate set and setting of clinical trials as well as the social and cultural context into which psychedelics later get inserted. So, on the first level, working with psychedelics challenges assumptions regarding scientific construct of objectivity. And I'll give one example of that. In the 1960s, researchers from the Canadian Addiction Research Fund wanted to replicate results of psychedelic research of Humphry Osmond using objective conditions, meaning objective, “set and setting.” And their attempts to replicate Osmond's findings failed miserably.

(00:20:51):

So, as historian Erika Dick shows, their failure was intimately related to the very attempt at objectivity. Once researchers tried to separate the psychedelic agents from the contextual elements by creating an objective environment, they basically undermined the treatment's potential because there's nothing particularly constructive about a “objective environment” that is not too pleasing. And there is nothing particularly instructive in an insistence on maintaining objective social relationships that are not too intimate, not too empathetic, or not too nurturing. And as Tooley, Pratt put it, "The quixotic attempt to eliminate the effect of participant observation in the name of a misplaced pseudo-objectivity is fruitless, not so much because it is impossible, but because it is unproductive. The question becomes not how to eliminate bias of participant observation, but how optimally to account for and exploit the effect of the participant observation transaction in terms of the purposes of research."

(00:22:08):

And this of course has many implications for the double-blind studies of psychedelics and the ways they are a special case in our thinking about RCTs, random controlled trials. And on the collective level, the resurgence of psychedelics beckons us to consider how these social and cultural landscape of today's society shapes the set and setting in clinical trials and applications. And this includes considerations of race and gender relations, and how these inform the experiences of therapists and clients. And this also includes examinations of the manner in which medicalization of psychedelics may obstruct other fruitful and constructive ways of approaching these substances. For example, in community-based use. And such collective explorations can also include examinations of the ways in which commercialization and commodification of psychedelics may impoverish and drain the symbolic backwater on which psychedelic healing draws.

(00:23:20):

So, there are more and more of these discussions taking place today. We are living through a renaissance in thinking about context and how it shapes experience. There's more research being published on the subject of set and setting in one year today than in the entire 1960s. And the new wave of psychedelic research and restoration is exceedingly more literate about these issues of set and setting than it was in the '60s, and this meeting clearly shows that. So, it's essential to maintain and to cultivate and to refine this awareness of set and setting as we go forward because this awareness is crucial for the final outcome of this new collective experiment with integrating psychedelics into mental health care. Thank you.

Susan Winckler (00:24:10):

Dr. Hartogsohn, thank you so much. I have just some words that are coming through in the contextual piece and just your explanation was really helpful. So, thank you. We will invite you back for the panel discussion after we have one more presentation, so we will see you again in a bit. So, let us turn now to Dr. David Yaden, who is an Assistant Professor in the Department of Psychiatry and Behavioral Sciences, and is part of the Center for Psychedelic and Consciousness Research at Johns Hopkins University. Dr. Yaden, if you are ready, we are ready to hear from you.

Dr. David Yaden (00:24:50):

Yes. Hello, I'm David Yaden at Johns Hopkins. I'll be speaking about a much more specific aspect of set and setting, mostly as it pertains to the psychedelic research setting, although with some thoughts about potential clinical applications as well.

Susan Winckler (00:25:19):

You click on the screen and then... There, got it.

Dr. David Yaden (00:25:22):

There's just a lag there, I guess. A couple disclosures. I'm supported by an NIH grant and philanthropic support at the Center for Psychedelic & Consciousness Research. I'm a co-founder of the Hub at Oxford for Psychedelic Ethics, which I'll speak about a bit as well. I want to invite everyone to a kitchen table debate, namely my kitchen table in Baltimore, involving myself. I'm a researcher who runs psychedelic drug studies and my wife, who is a psychiatrist who teaches psychotherapy and also helps facilitate psychedelic research. The issue at stake here is whether preparation and integration should be best considered psychological support or supportive psychotherapy.

(00:26:19):

We'll revisit this debate, but I think it's an important question that relates to both set and setting, especially in psychedelic research settings. Now, both of us work at the same psychedelic center at Johns Hopkins, and I can tell you that a number of us in the center often debate this question, and I think it's an interesting one. I won't provide any definitive answers, but I do think I'll think along with it with you all, and I think it's an important question for us to be considering. So, just a note, when I say psychedelic, I really mean classic psychedelics, unless I specify otherwise. And most specifically, I'll be referring to psilocybin.

(00:27:11):

So, I want to talk a little bit about the current model of psychological support that's used in most psilocybin research currently. I'll discuss some of the concepts that can come into this psychological support model and some of my views on what we might consider best practice going forward. And then, I'll revisit this kitchen table debate about psychological support versus supportive psychotherapy. So, first, the current model, this should be familiar to most who are viewing this, but in the current psilocybin research model, there's generally screening and preparation that occurs before a session, and then integration sessions that occur after and measures throughout this process. So, I will draw from a paper that I wrote, which maybe I would've decided to title differently if I could do it over again, because it's led to some misconceptions. By default, I don't mean banning all other approaches. I just mean unless specified otherwise or given a good reason, otherwise, I think cognitive behavioral approaches are a useful approach, and I'll explain what I mean. So, currently, in the psychological support model that's used in most psilocybin research, this model involves listening and validating, and providing psychoeducation in a participant-led manner. However, I think that this model, given the hours involved, does leave some latitude for facilitators to draw from an eclectic array of concepts that they may be informed by in their own understanding of this process, which just described a number of these. But I think going forward, more and more standardization is ideal, mostly for scientific reasons and communication reasons. So, that we're accurately explaining and providing informed consent and communicating about the psychedelic research more generally as well as to reduce noise.

(00:29:38):

But what set of concepts might one provide in the psychological support model? The idea of providing a set of concepts, I think would be to cut down on the variability of what facilitators are drawing on. So, let me talk about some of these concepts from different paradigms that facilitators might be drawing on in these contexts. So, some in the field have called for more use of indigenous concepts from indigenous traditions. Of course, there are indigenous groups that have used psilocybin and others with other psychedelics for hundreds of years, for which there's evidence, and perhaps longer. And the thinking goes that all of this history and all of this experience may lead to wisdom that could be taken and applied in the medical and scientific research setting. I think the big problem with this view is the danger of cultural appropriation, of taking concepts without permission that may have religious or sacred connotations and applying them into another setting, a quite different cultural setting. Additionally,

many of these concepts have not been studied, and so their safety profile is not known. So I think that is a problematic set of concepts to draw from in, specifically, the psychedelic research setting. Others have suggested another group with substantial experience in some cases of administering psychedelic substances, underground therapists, many of which I think could be accurately described as holding a view somewhat similar to 'new age spirituality,' as it's called, a kind of belief in a vague and non-doctrinal yet supernatural kind of concept.

(00:31:55):

But there are a number of other non-mainstream therapies employed in these settings. And here again, I think the main issue is the lack of safety testing related to these concepts. There's just very minimal careful research that's been done on these concepts. And so I think this is a problematic set as well. Now, I just want to reiterate what I said when I introduced this paper, which is what I'm arguing for is a default, not a ban. And so it may be very interesting and very valuable to specifically study these kinds of concepts, but I think it should be done intentionally and not the case where certain of these concepts are coming into the psychological support model in a non-standardized and non-specified way.

(00:32:54):

So many have argued that psychodynamic and psychoanalytic approaches have more resonance and more richness to draw from in terms of the concepts that they offer that might be more relevant to the psychedelic experience. And here again, I think the issue is the relative lack of safety testing of these concepts as well as in the research setting, the difficulty with measuring many of them as well as articulating them in a way that's expedient for both facilitators and participants to understand in a brief amount of time. So that leaves us with cognitive behavioral approaches. I think here we have a set of approaches that have been most tested, in terms of their safety profile, and they involve a measurable set of constructs, which does allow for advantages in the research context. And these concepts, I think, are more easy to articulate and to explain to both facilitators and participants.

(00:34:13):

Now, some have argued that cognitive behavioral concepts have less resonance or less relevance to the psychedelic experience. And let me just reiterate, here I'm not talking about manualized cognitive behavioral approaches, although those can be used if they're specified and explored deliberately. I'm talking about drawing from a common set of concepts. But I think that there are a number of concepts from cognitive behavioral approaches that are relevant and resonant with the psychedelic experience. Here are just a few. I offer these in a table form having to do with cognitive beliefs and cognitive distortions, teaching mindfulness skills, emotion and regulation skills. Now again, I'm not talking about manualizing these and teaching these in a deliberate way, but the idea of thinking in terms of cognitive beliefs, mindfulness, emotion regulation, provides facilitators with a common constellation of concepts to draw from.

(00:35:24):

Here are a few more that I think are relevant. I'll just isolate two that I think are routine from my observation of psychedelic, specifically psilocybin, research settings. Diffusion and acceptance are very, very frequently employed in conversations having to do with the psychedelic experience, allowing thoughts and feelings to come and go and to move through awareness, for example. I'll just add lastly that the cognitive behavioral approaches have been used in non-clinical contexts as well. They've been usefully employed in psychoeducation contexts, preventative programs, resilience programs, et cetera. And so these concepts are by no means necessarily related to clinical or psychotherapy context. So back to this kitchen table debate. I think here the question is when you have a preparation and integration process and you have a participant and you have facilitators, one of whom often is required to have a

clinical license, the question is what's the best label to apply to those interactions? Personally, I think that it is common to assist people through medical interventions, however, in non-psychotherapeutic contexts, from all of medicine as well as in psychiatry. My wife, though, thinks that if a psychotherapist is involved and they're providing listening and validation and encouragement, then that is by definition psychotherapy.

(00:37:41):

And my rejoinder is that nurses provide this kind of support constantly on an hour-by-hour basis, basically. And there are a number of other examples within medicine, beyond medicine, and even in psychiatry where support psychoeducation is provided in ways that we don't think of as being psychotherapy. But let's go beyond Baltimore and get some other perspectives. So Dr. Goodwin and Dr. Wolf in England and Germany have a public debate that I've been following on this very question, and they've articulated with more specificity the kind of issues that I've raised, and I think we can usefully attend to this debate. Now, some have raised questions about the various COIs, or conflicts of interest, involved here. Dr. Goodwin is at Compass Pathways, which is a company, so might be interested in lowering the cost of psychedelic treatments. And Dr. Wolf is a trainer of psychotherapists interested in getting involved in clinical applications of psychedelics and so maybe invested in the importance of psychotherapy.

(00:39:10):

And I'll be pulling some quotes from a writeup about this debate. So here's a quote from Dr. Goodwin where he says, "There are reasons to think of the clinical effects of psychedelics being more related to the drug than psychotherapy." And he specifically refers here to a clear dose-response relationship. The higher the dose, the more the effect. So let me present some data from a couple of studies that helped to illustrate this. One is a now famous study comparing 25 milligrams of psilocybin to 10 to one milligram in three arms, and many here will have seen this figure. And in short, what you see here is that dose matters most. Maybe I should have called my talk dose matters most, I like that line. But you see here clear separation, I think, and a fairly clear dose-effect curve. And each of these groups will have received the same amount of psychological support.

(00:40:26):

I also want to show, briefly, some results from a study by Roland Griffiths, et al. also comparing three conditions, and this is a nonclinical sample looking mostly at wellbeing-related outcomes. Here we have a low dose condition receiving the standard amount of psychological support. They received one milligrams, actually two sessions of one milligrams. Then we see another condition here that's high dose 20 milligrams and then 30 milligrams. They are also receiving the standard amount of support. And then a high dose, high support condition receiving, again, 20 milligrams and then 30 milligrams, but also involving more psychological support as well as being instructed in journaling interventions and meditation interventions they're encouraged to practice.

(00:41:27):

So here again, I think we see this story of dose matters most. We see the low, very low dose. This is basically a placebo-like microdose with little, if any, psychoactive effects. We see some benefit indeed with the standard psychological support. But we see higher scores, these are acute subjective effect scores in the higher dose conditions. And then, when we turn to persisting effects, we see bigger differences from the dose than from the differences in support. So here I think again, we see that dose matters most. So Dr. Goodwin makes the point that psychedelic-assisted psychotherapy may be too pervasive an expression. However, Dr. Wolf, in response, argues that when you look at statements from psychedelic psilocybin protocols, we see statements like, "Being encouraged to describe and connect

with the range of emotional, cognitive, physical experiences of the psilocybin session and relate them to their personal narrative," and that sounds a lot like psychotherapy. As my wife said this morning, if it looks like a duck and quacks like a duck, which I think is an infuriating response. But I'll reiterate again that I think there are a number of instances in which support is provided, including psychoeducation, listening, validation, that we don't consider psychotherapy. So I think there are a number of medical [inaudible 00:43:35] including throughout psychiatry that don't require pairing psychotherapy, but I believe psychotherapy almost always helps.

(00:43:44):

So lastly, in the last minute or so here, I'll just note that The Hub at Oxford for Psychedelic Ethics, some junior scholars doing important work, Katherine Cheung, Kyle Patch, Brian Earp, and myself have argued that we're seeing a lot of psychedelic, scientific, and ethical exceptionalism. And what we argue is that psychedelics should not be treated as exceptional, in the sense of being completely unique, yet they do have distinct qualities. And rather than treating psychedelics as something new under the sun, I think we can apply existing concepts, guidelines, and standards in psychedelic research and perhaps in clinical applications. And with that, thank you for your attention and look forward to the discussion.

Susan Winckler (00:44:40):

Thanks Dr. Yaden, and particularly for inviting us to your kitchen table and giving us some things to think about in the discussion here. I'm struck as I'll ask Dr. Hartogsohn to return to the stage and invite our panelists that we... We have a lot to explore in the panel discussion here. So let's turn, in addition to our main presenters, we have two additional panelists joining us to react to what they heard and to engage in conversation. First is Dr. Brian Anderson, a psychiatrist in the psychiatric emergency services at Zuckerberg San Francisco General Hospital, and an Assistant Clinical Professor in the UCSF Department of Psychiatry and Behavioral Sciences. He is affiliated with the UC Berkeley Center for the Science of Psychedelics and UCSF Neuroscape. And then our second panelist is Dr. Javier Muniz, who is Associate Director of the Division of Psychiatry in CDER at FDA. And so as we turn to our discussion, I first want to offer Drs. Anderson and Muniz, rather the opportunity... Is there anything that you want to react to, reflect, ask a question, reflecting on the presentations that we just heard? Go ahead, Dr. Anderson.

Dr. Brian Anderson. (00:46:06):

Yeah, thank you and good morning. It's a pleasure to be here and to be part of responding to these really rich talks that I think get at some of the real kind of granular essence of what happens in these trials and what could happen in these clinical treatments if they're approved as medical therapies. I just want to go back to a few things, starting with what Dr. Hartogsohn said about how psychedelics can be meaning enhancers. And I think this is a really fundamental concept for us to really kind of struggle with in a positive way because of how this is so different from our conventional medical therapies. We're very used to working with meaning-making and psychotherapy, but to actually use drugs intentionally to adjust or help patients modify meaning in their life just brings up a lot of questions for how we actually implement this in clinical care and study it. The idea of going back to historical studies and, as Ido had brought up, sort of essentializing sort of seven modes of what he observed of set and setting is a really helpful place to start. It is something I don't see people doing very much in the literature today, is doing a deep reading of the history. There's been a few great reviews of research in the 1950s and 60s and some in the 70s, but really sort of an understanding of those lessons that we don't have to repeat and don't have to make some of the same mistakes is something I think, just as scholars of the field, we could do a better job of and I appreciate Ido's attention to that. That leads me next into this one point from an early slide that Ido brought up was about skillset.

(00:47:47):

And I would love to hear more about that, in particular because I think it sort of mixes well with some things that Dr. Yaden was just bringing up about how preparation, how it's actually done in most of these studies is not just giving psychoeducation about what could happen, but it is giving participants skills to use in the moment when they're feeling overwhelmed, when they're feeling curious, when they're feeling open to new parts of themselves, or just new questions about existence. Even in sort of a PTSD substance use conventional psychiatric study, we are having people grappling sometimes with existential issues. How do we give them skills to deal with that and make good use of that in the moment, is I think a key question for further development in using these as treatments.

(00:48:36):

And then this brings me to sort of one final comment, which is this issue of context I think is really important from the perspective of the collective context as was described. We are looking at data of participants responding to psychedelic medicines for how they understand it in the context mostly of trials. Once there are more people who have taken psychedelics as patients, and once they know more, friends and family members who've now gone and had access to psychedelics in state regulated settings, decriminalized settings, or other settings in other countries, where it's more openly available and often more cherished or celebrated or appreciated in non-medical ways, that change in context is something that will, I think, dramatically impact how psychedelic therapies are experienced. And it's something I just think we cannot predict based off of data from trials now.

(00:49:37):

And that brings me to this point regarding cultural concordance. When we are trying to look for universal skills and ways of bringing in, be it third wave behavioral psychotherapies that are drawing on really important tools of emotion regulation, diffusion and acceptance, when we have a wider set of people with different cultural backgrounds, religious and spiritual backgrounds, how do we anticipate what we may think, as a therapist or a scientist, is a universal or largely applicable concept may or may not actually be concordant with our participants. So the strength of the third wave psychotherapies that Dr. Yaden was highlighting really draws on a lot of work of taking really what our tools and teachings from often Buddhism and other sort of spiritual context, trying to secularize those and make them very accessible and applicable. But acceptance versus inquiry or curiosity may be tensions that start to come out in particular for patients of particular cultural backgrounds. And that's something I want us to start to anticipate and work with. And I'm wondering how our speakers would suggest we handle issues like that.

Susan Winckler (00:50:55):

Dr. Anderson, great underscoring and highlighting of some of the core concepts. I'll turn Drs. Hartogsohn and Yaden, either of you want to respond there? You got the point, Dr. Hartogsohn. You got the point from Dr. Yaden.

Dr. David Yaden (00:51:13):

You have a lot more content from Dr. Anderson to address. So why don't you go first

Susan Winckler (00:51:19):

And you're still muted, Dr. Hartogsohn. There you go.

Dr. Ido Hartogsohn (00:51:25):

I'll first just thank Dr. Anderson for the generous remarks. And I think the cultural specificity of different ways of approaching psychedelics within therapy is one of the really intriguing questions that we're currently approaching, and thinking about things like curiosity and inquiry versus acceptance. I wonder to what extent these are... Do you think about cognitive behavioral therapies as culture specific? So this raises broader questions and ones that have to do with the question of how to approach clinical trials with psychedelics. How do you approach the gap that you mentioned between the clinical trials and what happens next once the treatment moves over to broader populations, which are from other demographics and other groups of therapists that are maybe not from the first circle of those more committed to these treatments.

(00:52:43):

And so there's been this concept of 'cultural controls,' the idea that we need to control in the case of psychedelics, not just for placebo versus active drug, but also for different cultural contexts. And this, I think, poses a crucial challenge that we're still looking for how to tackle, but that I think... That suggests some new opportunities as well as conundrums that research will... That I suggest we won't... I imagine we won't solve in one moment, but will be a path going forward as the treatment develop.

Susan Winckler (00:53:44):

Thank you. Dr. Yaden.

Dr. David Yaden (00:53:46):

Yes. I'll just respond to one comment from Dr. Anderson having to do with the provenance of some of the concepts in cognitive behavioral approaches. He mentioned some Buddhist concepts that may be a part of some of these third wave psychotherapies, which I think is historically probably accurate that there's some of this carryover from mindfulness-type traditions, but I think by no means are all or most or even a large minority of these concepts from mindfulness specifically. And I think those that have come from mindfulness aren't advancing any kind of specific metaphysical religious belief structure. So I think in that way, these concepts would be quite different from drawing from explicitly religious or spiritual concepts.

(00:54:57):

Again, I think these concepts aren't perfect. I'm not advocating that they definitely be used. I'm trying to approach more standardization in the field and trying to find concepts to use in the psychological support model in most cases. Again, not banning research on any of these other approaches, just making sure that the constellation of concepts that are used in the psychological support model are at least specified and clear.

Susan Winckler (00:55:32):

So perhaps more about illuminating and documenting versus a go, no-go kind of approach thing describing what it is that was done and with structure. Want to turn... Dr. Muniz, was there anything that you wanted to highlight or explore before we get into some additional questions?

Dr. Javier Muniz (00:55:55):

Yeah. First of all, I want to say that I'm going to try to... I appreciate all the discussions that's going on here, but I'm going to try to bring it back a little bit to us as regulators at the end and in the context of drug development, what is set and setting and how is that an important thing? And I think, to me at least, this issue of set and setting is very closely intertwined with the same issues that we see with the

psychotherapeutic component. In contrast to most drugs, we usually don't pay any attention in a clinical trial in terms of where and how is the patient taking the drug. And this is the context that Ido was talking about and we've presented and have many discussions before. And the way this context is experienced is highly influenced by cultural and personal influences. So the problem for us as regulators is, well, it's highly variable and also there's a lack of a rigorous definition of what exactly is this set and setting.

(00:57:14):

I think in a previous presentation from Ido, I learned that optimal set and setting may also have a positive treatment effect even in the absence of any pharmacological interventions, right? Oh, yeah and I [inaudible 00:57:31] concept similar to psychotherapy is that the FDA does not regulate the set and setting, that's part of the practice of medicine exception. So why am I talking about it here? And I think this is important because set and setting is not confounding factors in this treatment model, like psychotherapy, there appears to be integral to the treatment to maximize the treatment effect. But just like with psychotherapy, and this is extremely important, and Ido indirectly alluded to this earlier, set and setting may be considered part of the safety features of our experience here.

(00:58:10):

So the problem again, as regulators, that we don't know which features of these set and settings are critical for the efficacy and what are the minimum components necessary to ensure safety. And this is ultimately extremely important because we need to write a label to ensure safe and effective use. And I've talked about this before in the context of the psychotherapeutic component, but for us to fully tease out the safety and efficacy contributions of set and setting in psychedelic trials, we actually need well done factorial studies, which would be extremely informative for labeling. So that's where I want to stop now, just open up back to the discussion.

Susan Winckler (00:58:58):

Yeah, that's really helpful, particularly the challenge that you and your colleagues face in reviewing the information submitted to work through that. Go ahead, Dr. Hartogsohn. And then Dr. Anderson, I have a specific question coming to you about the orientation and integration sessions in research. So Dr. Hartogsohn.

Dr. Ido Hartogsohn (00:59:20):

Thank you. I just want to respond to some of Dr. Muniz comments. First of all, that yes, set and setting is important for any experience in psychotherapy. And it's been shown that people can have psychedelic experiences even when taking placebo by having the entire ritual set up around them in placebo ayahuasca rituals or in placebo trial experiments. And then set and setting is about safety and it's also about optimization, and that has a lot to do with the placebo effect. And to my mind, and I've written about that, the whole issue of set and setting presents an opportunity to rethink also placebo and how we treat it as part of medical care. Because usually in medical care, placebo is kind of seen as this thing that we want to take out of the picture in order to focus on the drug effect. And this is very different than the concept of set and setting where the idea is more about optimizing.

(01:00:27):

And really we know that placebo is always crucial. I would argue more so in the case of psychedelics. But psychedelics actually provide some lessons about how to harness placebo also in other medical treatments. And finally, there was a comment about the systemizing or how to conceptualize set and setting. And I want to mention a study that's about to get published based on a Delphi survey with some 70 something researches in the field of psychedelics, a Delphi study about set and setting. And the

researchers there managed to... So I participated in it, researchers from Maastricht University and Imperial College, and they managed to distill it to 30 variables out of a list of 70 or so variables that were there in the initial list provided by these researchers in four stage process. And I found that really fascinating. And at the same time, I want to say that set and setting, in a sense, and this hearkens back to the whole cultural question, it's always the same factor that may be crucial in one instance may be completely inconsequential on another. So it's so situated, and it will always remain an art and a science. I mean, it must be a science, but at the end, it also crucially remains an art or something that has to be viewed and negotiated in the moment in therapy and in a process.

Susan Winckler (01:02:23):

And I think the challenge on the regulatory side is it's all about the science with recognizing the reality of the art.

Dr. David Yaden (01:02:32):

Yeah, I really appreciate the emphasis on safety. I think that's probably the common ground here on this call. We're all very, very interested in safety. From a regulatory perspective, I can't speak much to that except for my last comments about exceptionalism, which Ido mentioned as well. I think it's important not to treat psychedelics as somehow completely unique and exceptional and something new under the sun. There's actually a lot of similarities across various psychoactive substances and other kinds of psychiatric treatments.

(01:03:12):

So it doesn't seem like there needs to be a new wheel reinvented in terms of the regulatory requirements. Just something to consider. And then lastly, I love your comments about funding factorial designs. That's exactly what we need, we need to fund these kinds of research studies. We can't fund them from philanthropic sources generally, because this is not the big interest and so government funding for factorial designs is what the researchers need, and we all need to know the results of that research.

Susan Winckler (01:03:52):

To share and continue to learn. Dr. Anderson, I want to turn to you to think about a subject in a psychedelic trial, so let's narrow our discussion. And what would you want to explain about the function of orientation sessions and integration sessions in supporting a subject in a trial?

Dr. Brian Anderson. (01:04:16):

Happy to weigh in on that. I want to try to use that question to address something I think is coming up. We've been hearing a lot about the importance of setting and how this involves other people, be that a therapist to support person and frankly, often just the friends and family who need also education to support the participant when they're outside of the context of the study visits.

(01:04:38):

It brings up a question for me going back to how do we regulate this and how do regulators study this? Which is this question that's been dealt with in a few trials recently is when is it appropriate for the psychedelic drug to be given to the patient and someone else who's their support person or caregiver? What is of the justifications of providing the drug to someone with a diagnosed condition and someone who's part of their support system in sort of a diet treatment fashion?

(01:05:08):

And I'm going back to this question of we often talk about psychotherapy as something, of course, we could offer that to a patient and like their spouse or someone else, but is it appropriate given that we define psychiatric disorders based off of a list of symptoms that a person has, which then impact and sometimes social functioning?

(01:05:28):

So is the system of treatment the individual? Do you get them to put the drug in their body? Or is it them plus other people? And when does the FDA approve drugs to be given to someone and a caregiver like has been studied? I just think this issue of context and how, as it was brought up by Edo before, are psychedelics used to address an individual or are they actually addressed… are they used to address community cohesion? Are they used to sort of bring groups of people together? And is that the target, that, in my mind, actually may be a target of psychedelic use, medicalized psychedelic use when it's approved, post-approval? But I don't know how the FDA would deal with that.

(01:06:08):

And I'm sitting with that right now in part in response to your question because when it comes to preparation and integration, I think this is really key. How do we really set people up for success? And when I think of a psilocybin trial that we ran at UCSF, the amount of time we had to spend preparing the support person who is going to come pick someone up and take them home, in order to be with them and provide non-professional support for them for the many hours after they were leaving our care, that was a really important part of work that our team did, and we could orient and prepare the participant so much, but if we were not also engaging their support team outside of the trial, we were not supporting the participant sufficiently.

(01:06:54):

And I'll just come back to this. One thing I wanted to bring into this discussion is that yesterday there was conversations about how we should not treat psychedelics as wonder drugs. They're not panaceas that fix everything. But I do actually think it is important we engage with them as 'wonder drugs,' when we are consenting people, we let them know that these drugs may grant you access to profound experiences of wonder and awe and these sort of mystical-type experiences, and because of that, when we are preparing them, we're also going to be orienting them afterwards.

(01:07:31):

We're helping them orient to themselves and the world and the people around them in a drastically new way sometimes. So integration is also part of orientation, but it's often orienting to being in a new way after you've had this experience. And it takes a community, it takes support people to do that well. So we are targeting a system of not just an individual, but other people in their family and their friends and I just wonder how we regulate that.

Susan Winckler (01:08:03):

I welcome anyone who wants to chime in on that question that Dr. Anderson just phrased, and would observe yesterday, there was some conversation too about the context and the preparation of other individuals, and there was a comparison a bit to anesthesia and post-anesthesia, and what is it that you tell the caregivers and the individual who's experienced that in what are the activities in which they should engage? So I would just put out there, what do you think of that comparison, recognizing it's not precise, but is that one of the ways to think about the broader piece? And then any response to Dr. Anderson. Dr. Hartogsohn, you're unmuted, but that may be leftover.

Dr. Ido Hartogsohn (01:08:51):

Excuse me.

Susan Winckler (01:08:53):

Yeah, and I can turn to you or anyone who wants to jump in there.

Dr. Ido Hartogsohn (01:09:00):

I give the first person a right. Anybody else?

Susan Winckler (01:09:08):

Okay. Let's turn then. Dr. Muniz, you grounded us back to how should the regulator be thinking about some of these components so that you can elucidate the effect of the product under research and then all of the things around it. Are there research priorities that you would flag for better understanding the role of the drug effect in conjunction with psychotherapy? How might you think about that?

Dr. Javier Muniz (01:09:38):

Can you rephrase the question for me again?

Susan Winckler (01:09:44):

Sure. So I was asking about if you were thinking about research priorities to better understand or to better understand the role of the drug effect in conjunction with psychotherapy.

Dr. Javier Muniz (01:09:58):

So that's an excellent question. And again, I go back to the factorial designs. And we've had other presentations where I specifically have talked about the troubles with defining exactly what is the psychotherapy intervention. There's a whole range of… there's a lot of variability in what we're doing as psychotherapeutic interventions here.

(01:10:29):

So we need to be thoughtful in terms of defining what are those minimal components and the reason why that's important is because we don't want to have an unduly burdensome approach to what we're prescribing here. And we also need to write a label. And in the past, we do have, even though we don't regulate the use of psychotherapy, there are provisions in the CFR in which we may be able to include something related to psychotherapy on label and they're already out there, for example, Zyban for smoking cessation, naltrexone, and so on and so on.

(01:11:14):

But in those descriptions in the label, if you go and look through them, the verbiage that we have is actually very minimal. There's no real definition about what the psychotherapeutic interventions are. But in this case, in the case of psychedelic drugs, there's a whole more involvement in the use of psychotherapy here. So how exactly we define that? What are those minimal components to ensure safety? And in terms of efficacy, and most traditional drugs for any indication in psychiatry, we could allow psychotherapy if you're already taking psychotherapy. Anything that you're doing before, and as long as it's stable, it's allowed.

(01:12:06):

So you can have people who've not been in psychotherapy, well, they're not allowed to be now in psychotherapy while you're taking the drug. And in the cases of people who are already in a well-

established psychotherapy, they're allowed to continue to take that psychotherapy throughout the study. So we usually do not make a big deal about that. It is just not something that's variable. Here, it's a completely different approach where we have these preparatory sessions. We have in-treatment sessions, and then we have the post-integrative sessions. So this is an integral part of the psychotherapeutic experience with psychedelics. And how to tease that apart? And if you ask me again, what is our priority? I think those well-done factorial studies are absolutely critical to understanding what those contributions are.

Susan Winckler (01:12:58):

And then that helps with then any structure that might be in a label as it relates to safety, should a product have the...

Dr. Javier Muniz (01:13:07):

Which ultimately, right, we have to write the label to ensure safe and effective use, and how do we do that in the context that we exist, which is framed by our regulatory status?

Susan Winckler (01:13:24):

Yep, go ahead Dr. Ian.

Dr. David Yaden (01:13:26):

Yeah, I just wanted to reiterate my support of the need to fund factorial design studies. That's exactly… my view is simply that we need these data to make these kinds of decisions. I'll just also reiterate the importance of focus on safety and raise a concern that there are likely several or a number of non-mainstream sort of fringe, maybe barely supported forms of therapy that could be much less safe when paired with psychedelic experiences. And so there's likely a spectrum of safety involved. And I think this is an important issue to consider if these medicines are used at scale, I'd be concerned about some of these fringe forms of therapies being paired.

Susan Winckler (01:14:29):

So the more work done to describe and help understand the parameters where there's safe and effective use is helpful.

Dr. David Yaden (01:14:39):

That's right.

Susan Winckler (01:14:41):

Yep. Go ahead. Go ahead, Ido.

Dr. Ido Hartogsohn (01:14:43):

Yeah, I wondering if I can still respond to Dr. Anderson's comment from before?

Susan Winckler (01:14:49):

Of course.

Dr. Ido Hartogsohn (01:14:50):

Yeah. Well, I want to say because I thought that was a really important comment. And so relating to the environment and persons from the individual's life who is going through the treatment, and Betty Eisner who was a pioneering psychotherapist working with psychedelics in the 1950s and '60s. She wrote about this concept of matrix, which is the environment that the individual returns to after the experience and how it shapes the integration factor.

(01:15:22):

And we can also see this in one of the more famous experiments from the '60s, which is the conquered prison experiment where there was really quite extraordinary transformations in prisoners taking psilocybin within a prison setting, but then once they got back to their home environment, then they didn't have that support and things didn't turn out that well. So I think also in relation to that beautiful designation of psychedelics as a wonder drug in the sense of eliciting wonder.

(01:15:55):

So there's this gap that might emerge between these very special, unique experience that these drugs bestow, and at the same time what people may return to. So I've never felt about the possibility of allowing others to participate in the experiment, meaningful others, which was also something that used to happen in the '60s to some extent. But really that raises the possibility or that points towards how these experiences is also something that's broader than just the individual and about how it connects them to their meaningful others and about how this connects to a broader context. That's also a post-session context about creating healing context in life and healing relationships within family and community and about how these can be brought on board in a sense. So that really kind of broadens our conceptions of therapy.

Susan Winckler (01:17:12):

And the relative safety and success of it.

Dr. Ido Hartogsohn (01:17:16):

That too, yeah.

Dr. David Yaden (01:17:18):

I wanted to pick up this idea of awe and wonder as being an important way of characterizing and understanding and even measuring the acute subjective effects of psychedelics. The mystical experience designation has a long history and scholarship going back to William James, and has some utility in that regard. But maybe it's time to move beyond that framing and that term, and awe has been suggested by Dr. Peter Hendricks and others as a useful term to capture the acute subjective effects of psychedelics, and most importantly, communicate them to people in a way that makes sense and jives with experiences that many people have had, and so I like this idea of thinking about more effective ways that we can label and understand and communicate about what a psychedelic experience actually feels like and ways in which more people can understand. And I think awe could play a role in that conversation.

Susan Winckler (01:18:35):

Dr. Anderson, do you want to respond?

Dr. Brian Anderson. (01:18:38):

Just building off of this, what do we communicate to the participants and the patients I think is so essential. So many of my patients are not able to follow up with care, do not follow up with care because of just the complexities of engaging in allopathic medical care sometimes. And so really setting them up for success, and how we communicate and prepare people I think a lot of it we can draw on metaphor. I think we've talked about music as like, do you play different types of music in the room? But actually going back to a comment from Dr. Arkanson on how the psychedelic experience using it can be playing an instrument. Or using that metaphor in the preparation sessions to say you may sort of need to learn how to engage with the tunes and the different overtones of the experience I think has been clinically useful.

(01:19:26):

And it actually goes back to a countryman of Dr. Harkinson, but Dr. Benny Shenone who had written about his sort of study of ayahuasca, he kind of concluded, it's like it's playing an instrument. You're engaging with it in these different ways that's not so cognitive, and if there's ways to bring in these sort of metaphors that we can help participants learn skill sets to make use of the experience and prepare the therapist to treat it, not so much like a drug we give people, but a device, like FDA regulates devices like these are clinicians helping use a device to alter someone's experience and clinical trajectory. I hope that maybe gives us some clarity on how we can regulate this and teach people to use it in safe and effective ways.

Susan Winckler (01:20:13):

And it ties to a rich discussion we had yesterday about that communication to trial participants in helping them understand what it is that they might experience, but also not creating any confounding issues with that communication. So the importance of the communication. And I'm struck as we get to the end of our time, perhaps Dr. Anderson, as you described it, it's not a miracle drug, but it is a drug of wonder, and thinking about it in that component and the experience.

(01:20:51):

With that, I have to say we're at the end of our time in the discussion, although I sense that this could continue as we explore different components of set and setting. But I'll say thank you to each of you for joining us for the discussion. These conversations will continue, but appreciate you investing your time to have a candid dialogue and continue the discussions here.

Session 6: Overview of FDA Regulatory Authority

Tiffany Farchione, MD, Director, Division of Psychiatry, Office of Neuroscience, Office of New Drug, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Susan Winckler (01:21:16):

So thank you. And we will now move to our next session, which is going to talk a little bit, we previewed this a bit in that there are many regulators who are involved in health care and medication use in particular. And so we wanted to turn to a session where we could just think about what are the parameters of that FDA regulatory authority. And for that, there's no one better than turning to Dr. Tiffany Farchione, who is going to return to the screen to share a presentation on that topic. If you recall, she is Director of the Division of Psychiatry in the Center for Drug Evaluation and Research at FDA. So Dr. Farchione, we'll turn it to you.

Dr. Tiffany Farchione (01:22:03):

Great, thank you. Okay. So as Susan said, once again, I'm Tiffany Farchione, Director of Division of Psychiatry, and today I'm planning to talk about something that isn't addressed all that often in meetings like this. But I think when it comes to psychedelics, we really need to. So I'm going to talk a little bit about the limits of our regulatory authority. So this slide provides an overview of all the things that we do regulate. And I realize that the graphic on the left is probably a little small to read on your screens, but the main point is just to show that as an agency, we have oversight over a lot of stuff. So with food and drugs, devices, tobacco, cosmetics and more. We… FDA-regulated products account for twenty-one cents out of every dollar spent by U.S consumers, which is a lot. But obviously we don't regulate everything.

(01:23:06):

And among the things that we don't regulate, and that are particularly relevant to psychedelics, we don't regulate psychotherapy and we don't regulate the practice of medicine. So starting with psychotherapy, I want to talk a little bit about why that's so important. So a common feature of psychedelic development programs is the combined use of drug and therapy in the intervention.

(01:23:32):

Ultimately, this complicates our assessment of the drug's effectiveness and presents a challenge for future labeling. So one of the main problems with the use of psychotherapy in this context, I mean, I don't want to call it a problem, but just in terms of from a regulatory perspective, is the lack of a rigorous definition of what these psychotherapeutic interventions are. And I will say Dr. Muniz kind of stole my thunder a little bit on this one because he already previewed this point.

(01:24:06):

But I'm going to go through in a couple of examples in detail. And so here are some examples as described by Johnson, et al in a 2008 publication. So for instance, the therapy component in many of these programs will involve a preparatory session, and that can be a series of meetings, for example, four two-hour sessions in the month prior to treatment, discussing meaningful life experiences, beliefs, and goals.

(01:24:38):

The goal of the preparatory session is to prepare the patient for drug treatment, build trust and rapport, establish intentions and goals, basically to get to that mindset or the set part of set and setting. Then you have the actual drug treatment session itself where the monitor or the therapist will offer guidance and support, reassurance as needed. People are encouraged to trust and let go to the experience. There's probably music or eye shades, and the goals here are to reduce the adverse psychological reactions and to facilitate the therapeutic session.

(01:25:20):

And then finally, a lot of programs will involve an integrative psychotherapy session, which happens after the experience. So a series of meetings where you talk about novel thoughts and feelings that arose during the drug treatment session. And then the intent here is to ensure psychological stability to process and integrate the experience. But overall, as you can see, the therapy is not just a confounding factor in the overall treatment model.

(01:25:50):

It appears to be integral to the treatment as a safety feature and in order to maximize the treatment effect. But we don't know what the minimum components of the psychotherapeutic intervention are necessary to ensure safety, and ultimately, that's important because we need to write a label that ensures safe use. And we also don't know which features are critical to efficacy. So again, what if

ultimately all that's needed is building rapport and a little bit of psychoeducation before the session and providing calming guidance?

(01:26:25):

That's a hypothetical, obviously. But for us to be able to fully tease out the safety and efficacy contributions of psychotherapy in psychedelic trials, we would need well-done factorial studies. But these are big and expensive, and there's an argument that if you don't have the therapy that that's unethical or problematic in some way. We don't actually know. I think that a factorial study would be highly informative and allow us to write a better label, but we just haven't seen that done. So for now, what we have is an assumption that the psychotherapy is necessary, but that assumption hasn't been rigorously evaluated.

(01:27:10):

All right. So as I mentioned, the psychotherapy component of the psychedelic treatment paradigm is going to present a challenge for any future labeling. We regulate product labeling to ensure that it contains the essential scientific information needed for safe and effective use. And I cite the Code of Federal Regulations here to emphasize that this is the framework for our regulatory authority. And our regulations do allow us to specify if a drug should be used only in conjunction with another mode of therapy.

(01:27:44):

But you can see the language here that the indication can be only in conjunction with a primary mode of therapy if it's indicated only as an adjunct to that therapy. So there are, as Dr. Muniz again mentioned, there are several FDA approved drugs that include a psychotherapy-type content in their labeling. So for naltrexone, it talks about a comprehensive management program that includes psychosocial support, for buproprion for smoking cessation...

(01:28:20):

We've got counseling and support throughout treatment. Buprenorphine has in conjunction with psychosocial counseling as part of a comprehensive addiction treatment program. But what I want you to notice here is that the descriptions of the therapy-type intervention that are in labeling are very abbreviated and very general. We don't go into detail about what those interventions entail.

(01:28:48):

One of the reasons why I think this is going to be a challenge when it comes to reviewing any future application is rooted in the idea that somehow psychotherapy is a key component to achieving a therapeutic response here. But what aspects are going to be considered the essential scientific information, like what's in our code of federal regulations as part of our authority that belongs in the label? And if we're going to go so far as to say that a drug should be used only in conjunction with a primary mode of therapy, we probably ought to know if that mode of therapy is necessary.

(01:29:23):

So even though we just had an entire session on set and setting, I'm going to mention it briefly here as a sort of transition between psychotherapy, where I think aspects of set are covered, and then the practice of medicine where I think a lot of the setting issues come into play. And of course, I have to also note that most aspects of set and setting are outside of our purview.

(01:29:46):

So again, wondering what the minimum requirements are and how we are going to ultimately communicate this in labeling. So as an example, going back to those monitoring requirements that I mentioned yesterday. We're able to mandate certain credentials in clinical studies, but we don't

necessarily have the authority to say that similar credentials are going to be needed for similar roles in a post-market setting. So this is something that likely is ultimately going to fall under the jurisdiction of state medical boards or other state level authorities. It's not something that is necessarily under our purview.

(01:30:28):

Some folks have suggested that we could simply deal with the psychotherapy or the monitoring piece of these programs by approving the product with a REMS. So a REMS is a risk evaluation and mitigation strategy, and that is something that is a drug safety program that we're able to require for certain medications if there's a serious safety concern and we believe that the drug can't be approved without a strategy for managing that concern. That the only way that the benefits will outweigh the risks is if you take these certain safety precautions.

(01:31:04):

The… A REMS will focus on preventing monitoring or managing a specific risk, they're always program-specific, by informing, educating, reinforcing actions to reduce the frequency or severity of the event. But they aren't intended to assure effectiveness. So, there are some components of the psychedelic session that do address safety concerns and so those might be things that we could incorporate into a REMS, maybe. But if psychotherapy or a specific treatment setting is required to ensure the product is effective, then a REMS isn't going to help with that.

(01:31:45):

So I know I mentioned yesterday that these discussions are about looking forward towards the future and helping us to be better equipped to evaluate these programs and advise sponsors who are seeking to develop psychedelics for psychiatric disorders. But looking towards the future also means trying to imagine a world in which there's an approved psychedelic on the market, and what would that look like? And who, if anyone, might have the authority to regulate provider credentials or the treatment facilities? How are providers and healthcare systems preparing for this possible future? So on that note, I just want to say that I'm very much looking forward to our next panel that is going to take that ball for me so that I don't have to talk about it, and they're going to explore these issues in more detail. And I'm very much looking forward to that discussion. So, thank you.

Susan Winckler (01:32:41):

So we can take that ball, Dr. Farchione, and go to the next session. If I could ask you one question before you step away?

Dr. Tiffany Farchione (01:32:49):

Sure.

Susan Winckler (01:32:49):

Sorry, as we keep you on camera. There was a question I thought that I thought would be helpful to address, and that's in FDA's structure of the product labeling, that's with the product sponsor, correct? And so, it was basically, is there any assessment of compliance with what's in the labeling? And that's distinctly outside FDA's purview. Is that fair?

Dr. Tiffany Farchione (01:33:17):

I'm not sure exactly what you're... So when a company submits their new drug application, they submit their proposed labeling to us, but ultimately we go through and we change it, modify it, make sure that

it's not overly promotional and that the information is accurate and all of that. But in terms of what happens in the post-marketing setting, that is largely practice of medicine.

Susan Winckler (01:33:47):

That's what I was aspiring to articulate, just didn't do it very well. So there is-

Dr. Tiffany Farchione (01:33:52):

But I still understood you.

Susan Winckler (01:33:55):

So there's the construction of the labeling and then that is for the medical community to use, but the actual use of it is outside FDA's responsibility.

Dr. Tiffany Farchione (01:34:12):

Right, right. We see this all the time. We approve drugs for a particular indication or a particular condition, and physicians are free to choose, "Well, this thing is pretty closely related. I'm going to try this medication for this." So it's 'off-label' use. It happens all of the time, and that's part of practice of medicine and we don't get to regulate that. Now what we would comment on is if companies went out there and started promoting based on those things that aren't in the label, but that's where the authority ends.

Susan Winckler (01:34:54):

Right. It's the relationship between FDA and the industry it regulates, which is the product developers and manufacturers. Yep. Great.

Dr. Tiffany Farchione (01:35:04):

Right.

Susan Winckler (01:35:04):

Thank you. Now, I'll let you go.

Dr. Tiffany Farchione (01:35:05):

Thank you.

Session 7: Considerations for Potential Psychedelic Use in the Real World

Richard C. Dart, MD, PhD, Director of the Rocky Mountain Poison & Drug Safety, Denver Health and Hospital Authority
Mason Marks, MD, JD, Visiting Professor of Law, Harvard Law School
Mark H. Rapaport, MD, Chief Executive Officer, University of Utah School of Medicine
Lisa Robin, MLA, Chief Advisory Officer, Federation of State Medical Boards
Marta Sokolowska, PhD, Deputy Center Director of Substance Use and Behavioral Health, Center for Drug Evaluation Research, U.S. Food and Drug Administration
Ilse Wiechers, MD, MPP, MHS, Deputy Executive Director, VHA Office of Mental Health and Suicide Prevention, U.S. Department of Veteran Affairs

Susan Winckler (01:35:07):

But thank you so much. That sets the stage for our final session where we want to talk about this idea. What are the considerations for potential psychedelic use in the real world? And I want to underscore, it is still an open question as to whether any of the products we've been discussing will meet the standard for regulatory approval. But should any products be made available for clinical use, it can be helpful to think about what other constructs or engagement is necessary from the health care system and other regulators. And in addition, as was observed quite frequently in yesterday's chat and the Q&A, there is currently some state authorized use of these products which may provide helpful information.

(01:35:56):

So, the fabulous news for our next discussion is that we have six individuals who are going to help us have this conversation. And so I'll invite our panelists to join me here. So we have Dr. Richard Dart, who is the Director of the Rocky Mountain Poison and Drug Center, also Dr. Mason Marks a visiting Professor of Law at Harvard Law School and the Florida Bar Health Law Section Professor at Florida State University College of Law. Dr. Mark Rapaport is Chairman of the Department of Psychiatry and CEO of the Huntsman Mental Health Institute at the University of Utah School of Medicine. Lisa Robin is Chief Advocacy Officer at the Federation of State Medical Boards. Dr. Marta Sokolowska is the Deputy Center Director for Substance Use and Behavioral Health in CDER at FDA. And Dr. Ilsa Wiechers is Deputy Executive Director in the Veterans Health Administration Office of Mental Health and Suicide Prevention.

(01:36:59):

So, panelists, let's jump into the discussion. Some of you have had the opportunity to listen to some of the sessions and we were speaking earlier about what might the reality be and what's next, should there be a product that navigates the regulatory system here. Dr. Wiechers, I'm going to turn to you first. Yesterday we heard a little bit about esketamine and in particularly to explore some potential learnings that might be helpful in conducting research with psychedelics. And you've been involved in overseeing use of esketamine. What have we learned from administering ketamine and esketamine in a major federal health system?

Dr. Ilse Wiechers (01:37:51):

Yeah, thank you for that question. I think there are a couple really key lessons we've learned at VA in our esketamine and ketamine rollout and that I think can apply to when we're preparing and thinking about potential future clinical implementation of psychedelics. One of the keys to our success has been collaboration early and often across the many service lines at a facility or regional level that need to be involved in standing up the clinical service and at the national level with our program offices. So this involves pharmacy, nursing, mental health, our administrative teams and having key people and stakeholders from each of those at the facility level, the regional level, and the national level involved in our conversation from the get-go is part of what I think led to success, instead of one particular office or one particular service line leading independently.

(01:38:47):

The other thing that I think was important for us with our ketamine and esketamine implementation was a stepwise implementation plan, building upon areas where we had existing expertise. So we had folks in VA who were doing ketamine research before esketamine approval in 2019, and we went to those folks and asked them to help lead the way in our early adopters and be early adopters for esketamine intranasal administration. And we built from there to a next step, working with people who had experience with ECT or RTMS, so really looking at the clinical services in the nation who were the

experts in dealing with TRD, treatment-resistant depression. And so stepwise built up, and then from there began expanding to sites where they didn't really have a TRD expertise or clinic already and they hadn't done ketamine, so we saved them for a little bit later in the implementation, so that we could learn from implementation from people who had existing expertise first, really establish our solid best practices, and then use those and expand those outward.

(01:39:52):

I'll finally say safety and monitoring was first and foremost on our mind. We established a prospective mandatory medication use evaluation within VA for esketamine implementation that went above and beyond what the FDA REMS gathered in terms of both safety data and also gathering efficacy data. So we gathered data points on every veteran treated with every dose at every site across VA for esketamine, and we continue to have that database available to us and that's part of what gave us early feedback that it was actually very safe and being tolerated quite well by our veterans with good effect. And that helped to reassure people who were then second or third round implementers that this was actually going well, and we reassured people along the way in real time. And I will just pause there and I have other things I can say later, but I want to make sure everyone else has opportunity to speak as well. But those are my three top things I'd suggest we think about going forward with psychedelics.

Susan Winckler (01:40:51):

So, if I captured the collaboration, the stepwise, and then your safety and monitoring really built in this learning health system component that you could learn from the experience as you broadened it out. Really helpful. I'll invite, and I should say this is how we're going to run this panel, anybody who wants to jump in, you unmute and you fire away, because we want to have a conversation versus just a series of questions and response. So, Dr. Dart, you're unmuted. Is that intentional, because you want to jump in?

Dr. Richard Dart (01:41:28):

That was because I was unsure, but I do want to jump in.

Susan Winckler (01:41:33):

That's okay. Go ahead.

Dr. Richard Dart (01:41:37):

The ketamine, esketamine perspective here I think is very informative. That is what I do in my life is we do post-marketing surveillance of prescription drugs, and we've done that for many years. Obviously the opioids are the big ones, but amphetamines and esketamine. And the experience is very similar to what Ilsa just described, which is under the framework that FDA has established for use of that drug, and of course in the VA we can be sure that it's very close to that, we really have seen remarkably small signals regarding esketamine, in contrast to ketamine, which safety signals have just increased relentlessly over the past few years. And so it draws a nice dichotomy that is partially relevant to psychedelics in general, because the ketamines are not technically psychedelics. They tend to get lumped, so there's some lessons there. I think the FDA framework has worked pretty nicely, but there's some big differences here too, which is that when psychedelics, if they actually are approved for use, it's going to be one of those all eyes on the U.S. again where everyone will be watching to see what happens with the safety profiles of these drugs.

(01:43:09):

And one thing I'm not hearing, in this meeting I think everything has gone well, but in my outside meetings, what I've been hearing is focused on the person who is taking a psychedelic with intention to improve themselves in some way. Sometimes in a medical setting, but not necessarily. There's religious, spiritual, and many other settings where the person really is, it's that set and setting again, where the person really is trying to address some problem that they perceive and that they want to address. And that's great. So we have three groups here. We've got the FDA group, I call it, that's going to be using the drug like the VA is using it. That was a great example. We're going to have the state programs that you mentioned, and my state is one of those states as is Brian's or Brian's studying Oregon I should say. And so we're going to have that group, which is different, but certainly more controlled. But what we don't talk very much about is the third group, which I think is probably the largest group, and that is the unsupervised and uncontrolled use of psychedelics.

(01:44:22):

Now, FDA has learned a lot over the years and we'll have to see what the data show, but I suspect that we won't see a lot of diversion going on with FDA-approved products. But we will see a lot of confusion among people who are using the drugs, have an adverse event, and whether or not the drug associated with those adverse events were an FDA approved drug, a state approved drug, or a totally unapproved drug. And that's a distinction in post-marketing, in the post-market arena, is going to be very important, because sometimes the press and other interested lay individuals misinterpret the data or make assumptions about data like that a drug had to be from a certain program when that's, what we have found many times, that's really not the case.

(01:45:18):

So identifying those products is going to be really super important I think, and that's what we're really focusing much of our effort on. But with the complication that with the psychedelics, we've got to also identify set and setting. It's challenging, but we've been working on this for several months and I think it is surmountable and a very important possibility to have a drug available or have medications available in one of these programs that actually do improve health if we're looking at the right group, and show us which groups are not benefiting from that, so that we can perhaps change policy to help those groups. So I'll stop there as well, so I don't go on too long, but I've got more to say as well, but we'll see what happens.

Susan Winckler (01:46:06):

Yeah, well actually Dr. Dart, I'm going to... So you flagged for us one of the components that just should be considered that in a world where we may have a product that's approved for use, in the post-marketing surveillance will have this dichotomy, if that's the right word, you would expect that there would be some reports from the product that's approved and a component of the medicine supply and then those that are in the non-medical drug supply, and we'll have to have some distinction. I want to ask you a quick question about what's available now, which is the state sanctions not yet approved drug supply. Are you seeing anything in radars today? And is there anything that we can learn from that? Just do a quick piece on that, and then Dr. Marks, I'm going to come to you to talk about the intersection of various regulatory structures, because it plays into this as well. So Dr. Dart, first to you.

Dr. Richard Dart (01:47:19):

Yeah, sure. Well, at the 30,000-foot level or 50,000, whatever you want, what we're seeing is pretty much in the entire country, an increase in the use of psychedelic medications for sure. It's more dramatic in the two states that have approved state programs, although they're just getting started, but we saw, as soon as the legislation passed, we saw increases. So, the use of illicit drug, if you will, is

increasing even before the program has started, really. And so we're seeing that, and it's more dramatic in the two states, although not necessarily associated with terrible outcomes right now. But the numbers are still fairly small and we're just getting started. So I can't really comment too much on that, except that we're seeing the human behavior we would expect under these circumstances.

Susan Winckler (01:48:14):

Okay. And so maybe we should, just for the purposes of our conversation where we want to distinguish between the psychedelic product use of today and potential psychedelic medication use of tomorrow, should a medication be approved. Maybe that'll just help with our conversation today as I was trying to keep track there.

Dr. Richard Dart (01:48:33):

It's a crucial distinction, so yes.

Susan Winckler (01:48:36):

Okay. And then we'll have to just consider that in future monitoring should that exist. Dr. Marks, I want to turn to you, because you're a researcher and observer of regulatory developments and the intersection of these regulatory structures. Dr. Farchione grounded us in what FDA can do, and then there's bounds there. Are there lessons from other spaces that we could keep in mind here about the potential future use of psychedelics? How should we be thinking about this complex regulatory structure?

Dr. Mason Marks (01:49:16):

First of all, thank you so much for having me, and then as an attorney, I'll say that everything I'm about to say is my own opinion. It does not reflect the views of my employers or anyone else. But yeah, I think I'm going to introduce a little more nuance and maybe even complexity into this distinction between medical versus non-medical. And so I study state-regulated psychedelics, and right now Oregon and Colorado are the two states that have legalized supervised administration of psilocybin by facilitators. Oregon is the only one that's currently open for business, though it opened last summer, and Colorado is still in the planning stages and should open next year. And I think it's helpful to point out some differences between what some people in those states would call medical, though not FDA approved, and that's the added distinction. Dr. Dart referred to licit versus illicit, but we have to realize that they're still illicit from the federal perspective, which is important to note.

(01:50:20):

And so let me just compare what these states are doing to medical cannabis, because I think there are some important differences. So in most states now have cannabis regulation of some form or another. Many have medical cannabis, and in those industries, healthcare providers have very minimal involvement. They don't even write prescriptions. They might write a recommendation. They might evaluate patients and make a diagnosis that qualifies them to receive medical cannabis in that state, but there's no cannabis on site. Patients don't go to a pharmacist except in Georgia, but for the most part, they don't go to a pharmacist. They go to a dispensary. They buy cannabis products. They take them home and use them not under supervision.

(01:51:06):

What's happening in states like Oregon is very different. There, there's a center called a psilocybin service center, where a state licensed facilitator administers or the service center administers this

psilocybin and the facilitator monitors what's called a client for five or six hours. This is very different, because it looks a lot more like conventional health care. The substance is in the room. The health care provider is there with the client or patient. But nevertheless, in Oregon there are some important legal barriers between conventional healthcare practice and psychedelics. For example, these psilocybin service centers cannot operate in a licensed health care facility. The facilitators cannot make medical claims. If they have a health care license, they're not allowed to exercise the privileges of those licenses, so they're not supposed to act as health care professionals in Oregon. It's really what you might refer to as adult use or even recreational use, as some people might put it, but many people and organizations are promoting it as therapeutic, and there are estimates that up to 8 or 900 people so far have come through Oregon. Most of them come from out of state and they're coming for treatment of health conditions like depression or PTSD.

(01:52:32):

So there is some concern, therefore, confusion, consumer confusion about whether they are receiving an FDA-approved product or not, and of course, or not. These concerns are amplified, I think, in Colorado where these distinctions between health care and psychedelics don't exist. So in fact, there's an advisory board, a psychedelic advisory board in Colorado that has recommended that the service centers, or what they call healing centers, are actually treated as licensed health care facilities in Colorado. So it's very different. There's no bar against making medical claims. There's no bar against practicing medicine or treating health conditions. So, really the regulators and this board are framing Colorado's program as a medical program. And so that creates the very real scenario that if the FDA does approve psilocybin, it could be offered in the same office potentially and could be potentially confusing to consumers. So I think there's a role for FDA to play in terms of medical claims that are being made, for example, and if there's a lesson to be learned, one is that this heavy regulation is not financially sustainable. I know one of FDA's priorities is accessible and affordable medicines. In Oregon, that program has gotten millions of dollars over budget. Taxpayers have had to bail it out. And so I just think that is something that can be learned from the state program when FDA does start to think about any restrictions that might be imposed on use. Thanks so much.

Susan Winckler (01:54:07):

So that's really helpful in helping us understand that, in one case, there's this distinct segregation or separation of the state authorized, but still federally not product from the health care system versus an integration, which then makes me want to turn to Lisa and to Dr. Rapaport to talk about that integration with health care. Lisa, in your role at the Federation of State Medical Boards, how are state medical boards thinking about, are they thinking about the Colorado and Oregon situations? Probably are if they're in Colorado and Oregon, but maybe not, but then are they, and how might they be thinking about if there's approval of products at the federal level for clinical use? What's happening in the state medical boards?

Lisa Robin (01:55:15):

Well, I think you have to recognize how the medical boards only have jurisdiction over those individuals, as like physicians or nursing boards, the nurses. And really this is new, and there are just a handful of states that have addressed ketamine, the use of ketamine. And there's a couple of states have guidelines in effect or an advisory caution to physicians. But I think that it has now coming to their attention, and I know that a number of states are putting together study committees to look at what they need to do and to be prepared. I guess they're a little bit behind on some of these... I think their concern comes around some of the clinics and how quickly that they are cropping up. And so I think

you're going to see more activity. So I think it's really, really important to bring those folks into the discussion and to keep them informed of what really is going on and how that fits into, because it created a lot of confusion and when the states began to, with the cannabis and as I said, it's everywhere now, there are policies in place. We have policy on what would be sort of good practice if in the event that they were to receive a complaint.

(01:56:49):

And that's really where that I think you're going to see them look carefully at, it's just all about patient safety. That there's adequate personnel. That the physicians that are involved are certainly up to, that they are qualified to do appropriate evaluation and make sure of who the patient population is and whatever the standard of care is that they comply with that. Because when they get... If there is an adverse event or a patient harm, and they will be called upon to evaluate that claim and then take action if necessary. But I think you're going to see them put some guidance out. I really know that that's ongoing, and I think by summer you're going to see some activity.

Susan Winckler (01:57:44):

Okay. And so that helps us with the... As Dr. Marks mentioned a bit, if we think about the Agency as regulating the product and the information about the product and its availability, and then our state medical boards and state nursing boards, state pharmacy boards are more about the people and the entities that are involved. And then these state sanctioning of products is in the middle there, creating a lot of things for your members to do, Lisa, to think through that. And so, as the state medical boards think through that, I would imagine they may look then at FDA product labeling, but also at clinical guidelines and other things. What should we think about as the inputs that state medical boards think of? And Dr. Marks, I'd welcome you to chime in on that as well if you want to add. But Lisa, what do you-

Lisa Robin (01:58:50):

Well, right, and I think a good example is with opioids. That's a good example of how the boards have had to address, then they've had to look at the REMS programs and model their CME and training requirements around that, and how that they look at practice and they're going to look at an individual's prescribing practices, and that, it may lead to most boards having guidance around prescribing, maybe mirror the CDC guidelines, and that gives them the how they would evaluate an individual's practice. And I think that you're going to see this follow the same path.

Susan Winckler (01:59:48):

Okay, that's helpful, because then it also reminds us that the state medical board has the CME or the continuing medical education is a bit of, "Here's..." Something that you keep pace with, the proactive direction to the providers in the state, and then the illumination of, "Here are things to do," and then there's the, "There's been a patient harm or a complaint." The medical board is involved throughout those. Okay.

Lisa Robin (02:00:20):

Yes.

Susan Winckler (02:00:21):

Okay. Really helpful. Dr. Rapaport, I want to turn to you. So, when we were speaking earlier, I thought, "Okay, so I should introduce you as a psychiatrist who isn't deeply involved in research for psychedelics."

Dr. Mark Rapaport (02:00:37):

That's good.

Susan Winckler (02:00:39):

That then is a great way to speak to how should the broader mental health community be thinking about the current use and the considerations for potential future use of psychedelics?

Dr. Mark Rapaport (02:00:55):

Well, thank you. I look at it as the good, the bad, and the ugly. The good are a couple things. One, if these agents are successful, they're going to help people and also give people and families a lot of hope. The good is that we're learning a lot about the basic biology of both the psychedelics and the entactogens, and we're learning how it may affect neuroplasticity. And also, it's one of the first areas where there's been a healing of the dichotomy that used to exist between psychotherapies and pharmacotherapies, because these agents really facilitate the work done with psychotherapies. So that's all the good.

(02:01:47):

Now, the bad. The bad are a lot of myths or assumptions that people have. One of the myths or assumptions is that, "Oh gosh, these compounds have been used, or variations have been used, in a variety of different cultures for a variety of different culturally syntonic rituals or ceremonies," i.e. then they're safe. That's not necessarily the case at all. And we're not thinking about using any of these compounds in that manner. Another part of the bad is this blanket assumption, and I think Dr. Marks spoke of this that, "Oh gosh, since we've been legalizing marijuana or using medical marijuana, the same type of models and approaches should hold true for psychedelics and entactogens," and that truly may not be the case at all. A third assumption is that, "Oh, well these compounds are being used in other cultures," including Australia and including Switzerland and other places, but the system of care in those environments are very different than the system of care in the United States.

(02:03:19):

Now, the ugly. The ugly is, this is the first time in my career, and I've done a lot of work in psychopharmacology for many, many years. This is the first time where publicity and public discourse around a therapy or treatment has occurred well before the actual data from peer-reviewed studies in the FDA and EMA has occurred. So there's been a tremendous groundswell of enthusiasm, optimism, sort of belief that, “Oh gosh, we need to get these substances out there,” partially because of experiences that had occurred previously in the ‘60s. Partially because of some very well-written and powerful pieces that have been written. But our public acceptance and public interest is ahead of the science, and to me that is very disconcerting and ugly. Another aspect of it is that at least as far as I know, we really don't understand the right dose, the right frequency, the right setting and psychotherapies to use. We don't know how long effects will last and for whom, but we do know that between 2018 and 2022, in California, there was a 54% increase in people with problems who've taken psychedelics showing up in the emergency room. We do know that there has been an increase in admissions people that were taking psychedelics.

(02:05:24):

So from my perspective, my concern is that we may have something that for the right patient used appropriately in the right setting and with the right training, it could be really wonderful and a game changer. But if it is promulgated widely… You know, a year ago, I was in a meeting and an assistant came up to me and she said to me, "Oh, my therapist is hosting a weekend and she wants to take 10 of us

away for the weekend to take peyote. And what do you think? Should I do that?" Of course I said no, but unfortunately this type of discussion is occurring a lot all over the place, and our job is to do no harm. So that's kind of where I'm coming from.

Susan Winckler (02:06:24):

Dr. Rapaport, that was really helpful and particularly I think the order in which you articulated those, right? We've talked a lot about the promise and the good that there absolutely may be some benefit and you have organizations, companies that are pursuing that, but that we need to know more. And I think that's really the goal of a lot of the discussion has been how can we share information about dosing, about constructing these studies, about assessing the durability of response so that we can bring that, that that would be something that would come with the products. But then you also, I think spoke to the need for education to help dispel the myth and perhaps the misunderstanding. And I think… Is it accurate that you were thinking about those are myths that exist amongst healthcare professionals as well as amongst consumers and patients. Is that right?

Dr. Mark Rapaport (02:07:34):

Yes, that's correct. And all of us want the best for people and all of us are enthusiastic. But it's really easy to take some of these arguments and just assume that they're correct without stepping back and looking at them and without understanding the context which some of these substances have been used, be it within health care systems or be it within different cultures where this has been part of a culture for a long, long time.

Susan Winckler (02:08:08):

And that's a good grounding and reminder for us that we are talking about different things and I think that the medical use of the products. Dr. Marks, you unmuted so I'm going to turn to you if you want to jump in there.

Dr. Mason Marks (02:08:30):

Well, I just wanted to point out, and this was raised I think a bit earlier, that some states are creating sort of a task force or work group to study this type of state legislation. But this year, more than ever before, there are more states considering therapeutic programs, whether through the legislature or by voter ballot initiatives. California, Massachusetts, Illinois, Arizona. There's a very long list. And I do think there's something valuable about taking the time to really study state policy before rushing ahead.

(02:09:05):

I'm not actually sure that regulating psychedelics like cannabis would be bad. I actually think, one of my main points is that the way that states are doing it is not like cannabis. They're doing it more like health care, where there is a health care provider or someone acting in that role, treating people and the harm that might result from that misperceptions that stem from that. It may very well be that regulating psychedelics in some ways like cannabis is the right thing to do. I don't think we can prevent people from using them at this point so to the extent that we can educate them and about... And I think FDA has a great role to play there in its information providing capacity.

Susan Winckler (02:09:55):

Well, that actually is a great opportunity. Dr. Sokolowska, we just said FDA. So what… As you think about this from a policy perspective, what would you emphasize from the Agency kind of role and opportunity and maybe potential partnerships and collaboration that would be important?

Dr. Marta Sokolowska (02:10:23):

So first of all, thank you very much for hosting this session. And just wanted to emphasize that from FDA perspective, that's why we had the draft guidance released last year. Our primary focus is on guiding the industry and researchers in studying this product to evaluate the safety and effectiveness, so we can have the data when appropriate for FDA to review if these drugs truly are safe and effective and that the benefits of his medication outweigh the risks.

(02:10:57):

But as it was pointed out throughout this session yesterday and today, there are still tons of questions and it's really important to engage in these discussions. As Dr. Faccioni mentioned today, we have somewhat limited authority in the post-marketing space. So it's really critical for us to engage in these discussions. And obviously we will use the pre-marketing data to help to provide the labels that hopefully the researchers and the clinicians later on will be able to utilize in implementation of these drugs if they are determined safe and effective. But having these discussions really critical because it's their role will be key in safe implementation of these products if they are FDA approved. So I understand that there are a lot of interest in this space, and that's why I really believe that having this discussion and hearing some of these concerns, it's of great value.

Susan Winckler (02:12:04):

And that strikes me then the, we've talked a bit about the importance of education and better understanding and then integration into health care practice. Dr. Wiechers, I want to turn back to you. If you were thinking about implementation of an approved psychedelic, what components from your esketamine, do you think many of those would be applicable? Are there things that you might do differently? Just kind of blue sky with us a little bit in thinking about if the VA were to have this opportunity, say a product were to be approved, and I should say think rather large health system, and there are things we can learn from the esketamine, but what would you perhaps... Are all the things that we just talked about different animating factors or would you stick with the structure?

Dr. Ilse Wiechers (02:13:13):

I think a lot of the underlying structure remains the same. So the idea of broad collaboration at all levels. I think stepwise implementation in an iterative kind of learning environment is going to be critical. And I also think one of the things that a large health system can do is help with some of that post-marketing surveillance. That's exactly essentially what our VA medication use evaluation provided for esketamine, and would hope something similar would be implemented for psychedelics as well and suspect it will. And so that can actually help inform not just FDA, but also other large health systems. I think one of the things that I'll note would be notably different, the esketamine clinical workflow was substantially different from your usual outpatient mental health visit. This will be even more substantially different from your usual standard outpatient mental health visit, right? We're talking about having to identify staffing models and space redesign in a way that really looks different from what most mental health settings look like in an outpatient setting.

(02:14:33):

Now, maybe there's opportunities to do this in residential treatment. Maybe there's other ways we can frame it and think about it. But it's not going to be like what happens typically when FDA approves a

medication, which is it just kind of falls into place in the usual outpatient med visit, right? We've got a structure. We've got RVUs. We've got everything all sorted out, mapped out. We know how to run those clinics. These clinics look remarkably different. And so there's a substantial need for large health systems to think about strategically planning for the resources that would be needed to implement this. And in doing that, to also think if we're taking these resources and putting them over here, we all have finite resources. So what are we taking resources away from if we're implementing the resources to stand up this service? And so that is something in particular that we're thinking very carefully about.

(02:15:25):

I'll also say, this is the type of enterprise that I would imagine can't happen everywhere. There will likely be centers with the expertise in certain parts of the country. I suspect other parts of the country, particularly those more rural with less mental health resources available will have challenges in finding access to the treatments for the people who need it in those places. So we also have to think as a large health system, in particular one that's national. I've got to think about how to get people from point A to point B. And for smaller health systems that are regional, that may be less of a challenge, but there's still the idea of how do we ensure equitable access and ensure that everyone who needs it has access to it regardless of where they live and if they're in a large city next to the treatment center. So those are some of the challenges I think that will be important to take on as we think about any potential future clinical implementation of these treatments.

Susan Winckler (02:16:24):

Yeah. And thank you for giving voice to and reminding us of the resource involvement and that it's not a typical product, and then the complexities that just creates and perhaps perpetuating the inequities and the challenges we already have in reaching traditionally underserved populations. And if we have the good available that it's not just available for those who live close to the good and have access to it.

(02:16:58):

Dr. Rapaport, I want to come back to you with a question as it relates to, you mentioned the public discourse and what I might call the, well, it was called in one of our discussions, the description of these as ‘wonder drugs,’ which we said then they should be called "drugs of wonder" and not miracle drugs. But how should the health care system be thinking about managing patient expectations for these products? Is that an area where we will want to invest preparation of the health care professional?

Dr. Mark Rapaport (02:17:42):

Yeah, we're going to need to. It's going to be critical. Well, let's take two, three steps back. One of the most powerful things in medicine is hope and patient expectations. A lot of the research that we do is confounded by the expectations that patients have of results. And it doesn't matter if we talk about psychotropics or antihypertensives or surgeries. It is promulgated across the spectrum of all research. And it's also such a wonderful, powerful tool to use. But frankly, beginning with the patient advertising that's occurred on television a number of years ago and moving forward, we've been in a unique environment where in a good way patients are advocating for themselves more, but in a bad way, unfortunately they don't have the information and the facts they need.

(02:18:47):

And many times their desire to get better, their family's desire to get better, the hope factor sometimes clouds their understanding of what can go on. And so I do believe that we have a real obligation to be compassionate, yet to be clear, about what's a reasonable expectation and what's not a reasonable expectation. But that also requires our teams to understand that as well. And also it requires our teams

to know how to have that discussion and understand that there will be certain people that will come back with anger, other people that will come back with disbelief, and others that will feel appropriately grateful for what we do. But I think it's really a critical component of what we will need to address with these compounds because public discourse and interests and optimism is so far ahead of the science.

Susan Winckler (02:20:10):

And that's a reminder to you. Like all… most medications, the decision of the appropriateness is at the individual patient level in concert with the prescriber. And that would be true with these products as well. And that, that's a part of the approval from FDA, is that that's with the intervention of a prescriber who would determine that it was appropriate for the individual patient.

(02:20:45):

Let me turn then… Dr. Dart, I want to come back to you and let's think about, so we've been talking a bit deeply about clinical practice and what would need to change there and what do we need to think from a regulatory structure. Let me turn to you and say, as you think about the surveillance system, you already flagged we want to be able to distinguish in the surveillance system between medication and the other. I'll change my language again. But should a medication be approved, that product versus other. What is the component... What are other things that we should be thinking about in a surveillance, I guess I'd say a surveillance system and, as Dr. Wiechers reminded us, a learning health system so that we can continue to learn about products on the market. But what about in a surveillance system?

Dr. Richard Dart (02:21:42):

Well, I think another principle of surveillance is that things change. And we've seen it with every drug. We saw it with the opioids, cannabis. I mean, really it's just a normal human behavior, right? As time goes by, our behaviors change. And so the surveillance needs to be able to adapt to that. There's ways to address that by using, for example, questionnaires that have fixed sections that never change and other parts that do change so you can analyze them separately and consider that data separately. So I think the change is a pretty big one. The other really big one is there's not going to be one answer. And that's one thing that FDA certainly had to come to grips with for the opioids because, depending on where the data came from and the quality of the data, you had so many different answers pummeling them in a sense, and all of us that it became very confusing.

(02:22:43):

So we try to use a multi-component approach, meaning different populations will need to be studied with different instruments, and those aren't all the same. So the VA could be a very good source of data in a more controlled setting. But those other groups I was talking about, then you need other data sources to analyze those. They should all be validated. And that was one of the more striking things I think about the opioids is that it was a huge, it is still a huge problem. But at the time, the problem has shifted from prescription opioids. There's still issues with prescription opioids, don't get me wrong. But now we have the illicit fentanyl, which it overwhelms all of that basically. And so this constant dynamic change needs to be assessed. And the way you do that is with multiple different tools looking at it from different perspectives and then the ability to add questions, for example, or add additional information, follow up with patients.

(02:23:45):

So we did some interesting work. We were actually able to get back to patients to ask them why they were injecting their medication, and the answers were fascinating. Absolutely fascinating. And not what

a lot of the pundits thought that it was. So we're going to see this evolving ecosystem, if you will, or environment after a drug is approved that will be affected by the state programs, getting back to my identity, and able to identify the set and setting and the drug that's being used, and that has to change over time. And if it's thought out, those things are addressable. But it's great that we're starting now instead of waiting until after. Because that was one of the big challenges with the opioids, of course, was that sort of snuck up on society unexpectedly, and the response was vigorous when it finally developed. But it was like an immune response, it took a while for that response to really mature and develop. This way we can try to get at these issues before they're marketed.

Susan Winckler (02:24:53):

Well, and I think to your point, and it might help us in the conversation and the education, is that we'll also continue to learn more. Right?

Dr. Richard Dart (02:25:03):

Yeah.

Susan Winckler (02:25:05):

Part of the surveillance is really, I bifurcated surveillance from learning, but I shouldn't have. That will help us. All of this will help us learn more, and that that's the scientific process, and that we would, in fact, expect our understanding will evolve and perhaps even recommendations about set and setting and durability. There will be what is known at the time a decision is made and then what would be learned after that.

Dr. Richard Dart (02:25:45):

Yeah. Very well said.

Susan Winckler (02:25:48):

Okay. So speaking of learning more, Dr. Wiechers, I want to change again a bit. VA has announced that there will be some funding of research on psychedelics. How would that research complement any possible future clinical implementation or what should we know about that?

Dr. Ilse Wiechers (02:26:09):

Yeah, thank you for that question and prompt to share for those who didn't already know that we released our first request for applications late at the very end of last year. And our office of research development is looking forward to reviewing all the applications that come in and expanding our VA-funded portfolio of psychedelic research. I'll note that we did have a variety of private and principal investigators across VA who were already engaged in psychedelic research on VA campus prior to this RFA, largely funded by philanthropic organizations that have been funding a large portion of the psychedelic research to date. So this is not the first psychedelic research to happen at VA, but it's the first to be funded by VA. The reason why we are excited about this opportunity is because this will allow us to expand what we know about the safety and the efficacy of these treatments in our veteran population.

(02:27:12):

So the veterans who seek care and receive their care at VHA are in many ways unique compared to the general population, especially those that have been in the published literature to date for drugs like

MDMA and psilocybin. Our veterans tend to have a higher medical complexity and comorbidity with multiple mental health conditions as well. And they have, in many instances, uniquely different trauma experiences, combat-related, that actually make them a little bit different in the way that they respond to treatment. So we want to see how these work in our population. Our population also happens to be more diverse in terms of racial and gender background than some of the populations that have been studied before. So we're really looking forward to the opportunity to learn about will this actually help our veterans and the veterans that we treat every day. And so that is one of the reasons why we went down that road.

(02:28:12):

I think, that said, research takes a minute, right? And by a minute, I mean like three to five years. So we recognize that it's going to be a slower process to get the data and the results from those studies then potentially when we will see the timeline or the time horizon on one of the agents in the pipeline with FDA potentially being approved. So we envision that these are parallel processes that, and we have standard processes in place for when new medications are approved. We've got things that kick into gear automatically with our pharmacy benefits management to evaluate the data and determine when and how to use the new medication within VA. Those are all processes that will be in place should something become approved, MDMA or psilocybin in the future. And I already explained that one of the things I can guarantee you we'll be doing if that comes to pass is we'll be implementing a very rigorous safety monitoring program internally regardless of what happens with REMS outside.

(02:29:15):

We will be doing that monitoring internally and that will allow us to learn and do kind of real world data culling to kind of figure out, what are we learning? What's the signal for safety? Is there anything that we need to be concerned about? What's the signal for efficacy in our real world implementation, should that come to pass? And so we'll have the opportunity to learn from both streams of data. And since we like to play and work together in the sandbox, Office of Research Development and Office of Mental Health and Suicide Prevention talk together to ensure we're pulling the same data points using similar metrics across what would be our clinical research trials and then our actual future potential clinical implementation.

(02:29:57):

So we'll actually have a really robust large data set that combines research participants as well as real world clinical practice. And I think that is an opportunity, and one of the great aspects of being a large integrated health system across the nation is that we can really pull that data from our real world clinical experience as well as what we learned from our research trials. So we'll be able to, I think, do the two in parallel, should it come to pass that we're in a position where we need to do clinical implementation, but for now we've got the research is underway. We're bolstering it with VA funding and we're working together to ensure that the research implementation and the way we're doing that kind of syncs up enough so that these data can be meaningful for us if we have to combine the clinical and the research pots.

Susan Winckler (02:30:47):

So that's really helpful and is a component that just helpful in what you're planning to do and then the opportunity to generate evidence outside of… We've spent the last two days talking about generating evidence in clinical trials and you're reminding us of the opportunity and even the responsibility to continue to generate evidence post-clinical trials.

Dr. Ilse Wiechers (02:31:16):

Exactly, yeah.

Susan Winckler (02:31:18):

I want to go back though to, so let me go back to clinical trials, and something that's happening in parallel that you talked about Dr. Marks, which is the continuing state availability, or at least discussions of state availability. How should we be thinking about the effect that increased availability in state programs might have on drug development and data collection for regulatory purposes beyond Dr. Dart's component about tracking what was what. But what would you see on the horizon? Is that something to monitor? How should we be thinking about that state availability and then trying to continue to advance good clinical research to answer some of the questions that Dr. Rapaport teed up?

Dr. Mason Marks (02:32:21):

It's a complicated question. I think there would be some people who would say that state programs might disincentivize people from enrolling in clinical trials. I mean, these are people who would say the same thing about right to try or expanded access. So there may be similar types of concerns, but I do see great motivation for utilizing state regulated programs, sort of mini-FDAs, states as mini-FDAs. There seems to be a great hunger for data. And it's referred to as real-world data, though the FDA typically refers to real-world data as coming in the post-market period after something is FDA approved. Here, people are talking about real-world data as something before FDA approval. And I worry a bit about that.

(02:33:17):

I do also just want to draw, kind of highlight a couple of things were raised in other sessions but haven't really been raised here. One of them was the psychedelic exceptionalism that David Yaden from Hopkins mentioned. There does seem to be an assumption or a tendency to want to apply different standards to these medicines. I think a lot of that does stem from fear from the ‘60s, mistakes that may have been made or the way that research was conducted. But I like to point out that we didn't get the modern era of FDA research until 1963 or ‘62, when the FDA's powers were expanded and the agency was required to test for efficacy. So a lot of that research came in a very different time.

(02:34:06):

But I think there is sort of an assumption that there needs to be different standard. There is an assumption about requiring very specialized centers or maybe restricting only to psychiatry. I think one area that's been overlooked is potential uses outside psychiatry, things that might be handled by neurologists, like headache, different pain conditions that typically fall outside of psychiatry. So I think I agree with Dr. Dart about that there will not be one answer and it'll depend on the patient population and the context. But I also wonder, are we overlooking existing mechanisms for surveillance, like voluntary reporting of adverse events that the FDA utilizes? Are those just being forgotten in favor of starting up very, very complicated surveillance systems that I think have some ethical privacy concerns. We are talking about federally illegal substances and tracking people. I have some worries about that.

Susan Winckler (02:35:15):

Yeah, it's the complexity of that regulatory structure that we talked about, and then the ability to gather the information generated in that complex regulatory environment. Is there anything that folks here would think too, about potentially inclusion or exclusion criteria, if you excluded any individuals with prior use? I would imagine that would be a challenge, where you have more state-approved use. But that, I guess, we would leave to our researchers to navigate. I want to... we have about 20 minutes left here, and I want to make sure that we hear from each of you what you wanted most to underline and

underscore what you think about in considering the potential future use of psychedelics. I'll think through maybe starting with you, Lisa. Is there one thing that you think... it can be more than one, but at least one, thing that you think would be most helpful to your members? To the state medical boards, as they would move to navigate a psychedelic medication, should one be approved for use?

Lisa Robin (02:36:45):

Sure. Yes, and I think what we have learned over time, that it's really very important for them to be informed as to the research, and make sure that these policy decisions are made based on good data. I go back to... we don't want to have happened with this as what we experienced with the opioids. I think that's real important. I think the boards are going to be looking for answers. They're looking now, they're looking for research. They want to know what they're going to have to deal with. It is also, these models are different because it is going to have to be such a team approach, interdisciplinary. What are the criteria of the individuals that are going to be involved? What is the training? And so having them informed, I think the FSMB, that's our role. We are going to be providing some, at least a forum for discussion at our upcoming annual meeting. I think that we will stay in touch with our friends at the FDA.

Susan Winckler (02:38:06):

Fabulous. Thanks, Lisa. That's a good reminder that good policy is informed policy.

Lisa Robin (02:38:15):

Yes.

Susan Winckler (02:38:15):

And you've got to have the information and awareness and understanding and opportunity to discuss that would be helpful for your members. Great.

Lisa Robin (02:38:30):

Yes, and the other... I would just add one other thing. I think it's really important, at the state level, for the boards to be informed from their policymakers, because sometimes they're not necessarily involved in those discussions. I loved the discussion around the public and publicity getting out ahead of the science.

Susan Winckler (02:38:55):

I think you also reminded me, too, that probably a reality of your day job is that you recognize that every state is different.

Lisa Robin (02:39:03):

Yeah.

Susan Winckler (02:39:04):

It's not the state medical board policy, but rather the policies developed by each state medical board.

Lisa Robin (02:39:12):

Correct.

Susan Winckler (02:39:13):

Yeah.

Lisa Robin (02:39:14):

We try to give guidance to that, so there's some consistency and consensus around those policies.

Susan Winckler (02:39:21):

Right, right. But then you could have that, so if it's consistently informed, right, and they're working from the same basis of information, then it can be intentional adaptations and differences.

Lisa Robin (02:39:35):

Yes.

Susan Winckler (02:39:36):

Okay. Let me give you the warning of who I'm coming to next, so you can all be ready with your, what is a piece that I'd like to see. So Dr. Dart, I'm going to come to you next, then Rappaport, Marks, Weekers, and Sokolowska. That's if I can remember the order I just gave you. Dr. Dart?

Dr. Richard Dart (02:39:56):

Well, I think I'd like to come back to the issue that Mason brought up about the basically sensitive data, which is certainly true. I don't see it as dramatically different. It is different, but not dramatically different than illicit use of fentanyl or any other of these psychoactive drugs. It is an important consideration, so our solution to that is to use de-identified data. What's amazing to me, I'm old, and the world has changed dramatically. Our national survey we put out, and we get 60,000 responses. Well, we put out in two phases of 30,000. We'll get 30,000 responses from people within 30 days with questionnaires that go into detail about their illicit behaviors, the drugs they abuse, why they abuse them. It's not just opioids. The drugs they abuse, why they abuse them, what route they use, where they got them. Of course, we can't identify them, because the data comes to us in an unidentified manner.

(02:41:06):

But there's this... the world has just changed. People are willing to talk about these things. And while I understand that Oregon, in particular, has had some serious concerns about that, we need to be able to reassure people. So for example, we get an NIH Certificate of Confidentiality, even though most of our data can't be identified. Even if you had the data in your hands, no one could back figure that out. To reassure everybody as much as possible. Although I think, after these are approved, and they're started to be used in practice, I don't see that being a huge issue in the sense that not a huger issue than their psychological challenges that they're trying to face already, which are also sensitive information, for sure. There are tools, there's ways to address those issues. And so I don't see that as a big barrier as long as we pay attention to it and don't, don’t loosen our control or collect the data in ways that are prone to be misused or perverted.

Susan Winckler (02:42:19):

You would offer that… there are ways to, recognizing the concern that Dr. Marks raised, there are ways to gather and further protect the information and continue to learn from it. Okay. Dr. Rappaport, thoughts on what we can do to amplify the good and minimize the bad and deal with the ugly?

Dr. Mark Rapaport (02:42:50):

Yeah, I've been fortunate to be an NIH researcher for many years, probably more years than some people have been alive, on the panel, to be honest. I think there are a couple of things that I think this is a tremendous opportunity to get the right dose, in the right person, in the right setting, and understanding the right follow-up. What I'm concerned about are the following: I'm really concerned about true believers. Part of the reason for that is people may be well-intended, but you really have to be detached enough from your work to know what the data's saying. I think it's really critical that, in looking at this, we want what's best for our patients and their families. But that also means that we have to have a healthy amount of skepticism about this work and understand the strengths and limitations of it moving forward, because there can be real unintended consequences.

(02:44:12):

The other point I'd make is, and I hate to bring this up, but as we've seen with the opioid crisis, as we've seen with, to a certain extent at times, the growth of ketamine clinics, unfortunately there are some people that are unscrupulous. There are some people that are there for the money. That are not there to help. I think that it's incumbent upon us, as we look at moving forward with these agents, assuming that they are as effective and safe, that we be aware of that. Because unfortunately, that's another component to this picture that one needs to be aware of. Thank you for allowing me to participate in this panel.

Susan Winckler (02:45:15):

Yeah. You remind us that there will be the education requirements and the dissemination, so that this can be done well, and then there will be the compliance requirements of our regulators to pursue those who are not interested in following the structures that have been mandated, or the regulatory environment that's been prescribed. All right. I think my order was Dr. Marks, Dr. Weekers, Dr. Sokolowska. If it wasn't, that's the new order. Dr. Marks?

Dr. Mason Marks (02:45:49):

Thank you. So I don't want to focus on data, but I do disagree with Dr. Dart and a couple of points.

Susan Winckler (02:45:55):

Okay.

Dr. Mason Marks (02:45:56):

I think the work that you do at Rocky Mountain Poison and Drug Safety is very important, and there's a lot of voluntary surveys that are done. That's great, and I support research. I think the problem is when it's forced and that's what's being done in these state programs. It's being done in a way that I think is unethical and, unfortunately, these laws and the data collection requirements are often drafted by cannabis business attorneys instead of people who have knowledge of... there are people who specialize in privacy. I think that the social and legal, occupational risks to people are overlooked. I think there are some concerns with de-identification, but if people voluntarily contribute their de-identified data, I think that's great.

(02:46:44):

But what I really wanted to respond to was Lisa's comment. Here's a problem that I see with these state programs. Sometimes the state medical boards are approached during the drafting of these laws, but they don't want anything to do with it because, of course, because they'll say, "We're waiting on the

FDA," which makes sense, but then what happens is they're left out of the conversation. The people drafting the laws don't really understand the realities of medical practice, and so it's unfortunate. I think it's too bad there's not a broader tent of people working on these problems. Maybe I don't disagree with Dr. Dart as much. I do think you're doing great work out there in Colorado.

Susan Winckler (02:47:30):

Well, I think what you helped distinguish is the voluntary reporting versus the mandatory tracking. That is two very different structures, very different structures. All right. And underscoring again, let's collaborate and work on these things together, which tends to yield better outcomes. Dr. Weekers, coming to you.

Dr. Ilse Wiechers (02:47:56):

Yeah, so I think in closing, I'll just say that my everyday job is ensuring our nation's veterans have access to timely, high-quality, evidence-based mental health treatment. Those three points, just to emphasize, so timely access makes me say, "We really need to be thinking about preparing, and having some of the scaffolding built, so that we know what we need to do, if and when approval or something comes to market." It also speaks to those issues I raised earlier of equitable access. Everyone should have timely access, whether they live in a small town in rural Montana or New York City.

(02:48:37):

The high quality speaks to all of the issues we've been talking about with training, and certification, and making sure that everyone is an adherence to protocols, and setting up standards of care. Then the evidence-based, so and just to echo, I think Dr. Rappaport, we want the science to lead us. We don't want to lead the science. So want to ensure that we've got the data and the evidence to support the treatments that we're offering to folks. Those are, I think, my final reflections. I think it speaks to the many things that we have to be considering as we move forward, and the complexities therein.

Susan Winckler (02:49:18):

Well, and great for reminding us that it's good to work on that scaffolding versus responding in an, "Oh, my goodness, it's here," result.

Dr. Ilse Wiechers (02:49:28):

I've done that before and don't want to do that again. Yeah. Fair enough.

Susan Winckler (02:49:31):

Not so good.

Dr. Ilse Wiechers (02:49:31):

Yeah.

Susan Winckler (02:49:33):

Dr. Sokolowska, I turn to you. I'm reminded that, that 85% of this meeting was about the clinical research and what can we learn and what are the various dimensions that we need to think about in the clinical research to then yield the information upon which FDA would make a decision and then the information that all of these players would use in finding that right dose to the right patient in the right setting for the right purpose. In thinking through your responsibilities, at FDA, and the role of the

Agency, are there things that you would consider or that you would ask of others? Just I'll turn it back to you.

Dr. Marta Sokolowska (02:50:26):

Well, so first of all, this session has been very, very informative. This whole meeting has been very informative, because it helps us to focus on the science. And as mentioned earlier, FDA doesn't control the practice of medicine, but we are hoping that if these drugs are considered as safe and effective, and if they are FDA approved, that science would really inform the medical practice and implementation. And again, thank you very much for all the comments that we've heard throughout these sessions today.

(02:51:01):

It was very interesting to hear some comments regarding the increased focus on and hype, as it was, I think, termed before, regarding the wonder drug, so the drug is of wonder, psychedelics, how they are going to address the mental health disorders. We recognize the impact of mental health disorders, currently in the US population and beyond, and we want to emphasize that, as we are discussing psychedelics as potential one mode, or methodology to address these issues, we really have to focus on further development of additional treatments to really address the broad range of disorders that really plug in this country, because that's definitely part of our mandate.

(02:51:47):

One thing that I found very interesting is the discussion regarding post-marketing surveillance. This is something that we are not doing specifically for psychedelics. We are not specific if they are approved. We are doing routine surveillance of drugs that are under our jurisdiction, that are FDA approved. And hearing some of the concerns, some of the areas that we really have to pay attention, I think is really important. We definitely take that into consideration as we are going forward, how to dissociate these different systems, the different signals from... if psychedelics are FDA approved, the FDA-approved product versus this state-regulated product versus the illicit use of these products. I think these are very important questions that they were being brought up. Furthermore, the issue of the state regulated use, now that psychedelics are somewhat different, as brought up so many times before, with new molecular entities, but not so new, because they are being used by many, many people in the US population, and again, and beyond. So what kind of, particularly the safety issues, we can learn, safety concerns, we can learn from that as we are considering these products. It's also very important to our broader understanding. So overall, again, I just want to say thank you for a lot of the points that are being brought up, and particularly the potential for collaboration with our federal partners. I'm really looking forward to working with VA as well as CDC, and other partners, to truly help to have a better understanding of these different signals that we can take into consideration when potentially reviewing these products and post-marketing if appropriate, so that... Thank you.

Adjourn

Susan C. Winckler, RPh, Esq., CEO, Reagan-Udall Foundation for the FDA

Susan Winckler (02:53:44):

Fabulous. Thank you to each of our panelists who's joined us for this concluding discussion. To all of our speakers in the last two days. We've probed a lot of different components of clinical research involving psychedelics and we couldn't have done it without each of our speakers, our panelists, and our attendees who were providing such rich input, and commentary, and questions, and pieces to pursue. With that, I will say we are wrapping up our meeting. We will be posting a transcript, the recording at

our website reaganudall.org sometime next week. We hope that you have had an opportunity to learn something and use this information in future research. We thank you again for joining us. Take care and we hope to see you soon.