FOOD AND DRUG ADMINISTRATION

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JOINT MEETING OF THE PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE (PDAC) AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)

Virtual Meeting

Thursday, October 8, 2020

10:02 a.m. to 4:38 p.m.

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

LaToya Bonner, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE

MEMBERS (Voting)

Walter S. Dunn, MD, PhD

Assistant Clinical Professor

University of California Los Angeles (UCLA)

Department of Psychiatry

Director, Mood Disorders Clinic

West Los Angeles Veterans Administration

Medical Center

Los Angeles, California

Jess G. Fiedorowicz, MD, PhD

Head and Chief, Department of Mental Health

The Ottawa Hospital

Professor and Senior Research Chair in Adult

Psychiatry, Department of Psychiatry

University of Ottawa

Ottawa, Ontario

Satish Iyengar, PhD

Chair and Professor of Statistics

Department of Statistics

University of Pittsburgh

Pittsburgh, Pennsylvania

Felipe A. Jain, MD

Assistant Professor of Psychiatry

Harvard Medical School

Director of Healthy Aging Studies

Depression Clinical and Research Program

Massachusetts General Hospital

Boston, Massachusetts

Jessica J. Jeffrey, MD, MPH, MBA

Assistant Clinical Professor of Psychiatry

Associate Director, Division of Population Behavioral Health

Nathanson Family Resilience Center

UCLA Semel Institute of Neuroscience and Human Behavior

Los Angeles, California

Sonia L. Krishna, MD, FAPA, DFAACAP

Affiliate Faculty, Department of Psychiatry

Dell Medical School

The University of Texas at Austin

Austin, Texas

Rajesh Narendran, MD

(Chairperson)

Attending Psychiatrist

Re:solve Crisis Network

Western Psychiatric Institute and Clinics

Associate Professor in Radiology and Psychiatry

Psychiatric Molecular Imaging Program

University of Pittsburgh

Pittsburgh, Pennsylvania

Patrick S. Thomas, Jr., MD, PhD

Assistant Professor, Department of Psychiatry

Baylor College of Medicine, Menninger Clinic

Houston, Texas

Kim O. Witczak

(Consumer Representative)

Co-Founder, Executive Director

Woodymatters

Minneapolis, Minnesota

PSYCHOPHARMACOLOGIC DRUGS ADVISORY COMMITTEE MEMBER (Non-Voting)

Robert W. Baker, MD

(Industry Representative)

Vice President, Clinical Program Design

Eli Lilly and Company

Lilly Corporate Center

Indianapolis, Indiana

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE MEMBERS (Voting)

Denise M. Boudreau, PhD, RPh

Senior Scientific Investigator

Kaiser Permanente Health Research Institute

Kaiser Permanente Washington

Professor (Affiliate)

Departments of Pharmacy and Epidemiology

University of Washington

Seattle, Washington

Karim Anton Calis, PharmD, MPH, FASHP, FCCP
Director of Clinical Research and Compliance
Office of the Scientific Director
Eunice Kennedy Shriver National Institute of
Child Health and Human Development
National Institutes of Health
Bethesda, Maryland

Marie R. Griffin, MD, MPH
Professor of Health Policy, Emerita
Department of Health Policy
Vanderbilt University
Nashville, Tennessee

Laurel A. Habel, MPH, PhD
Associate Director, Cancer Research
Division of Research
Kaiser Permanente Northern California
Oakland, California

Sonia Hernandez-Diaz, MD, MPH, DrPH

(Chairperson)

Professor of Epidemiology

Department of Epidemiology

Harvard T.H. Chan School of Public Health

Boston, Massachusetts

Martin Kulldorff, PhD

Professor of Medicine and Biostatistician

Division of Pharmacoepidemiology and Pharmacoeconomics

Department of Medicine

Harvard Medical School and Brigham & Women's Hospital

Boston, Massachusetts

Steven B. Meisel, PharmD, CPPS

System Director of Medication Safety

M Health Fairview

Minneapolis, Minnesota

Lewis S. Nelson, MD

Professor and Chair

Department of Emergency Medicine

Chief, Division of Medical Toxicology

Rutgers New Jersey Medical School

Newark, New Jersey

DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE MEMBER (Non-Voting)

Reema J. Mehta, PharmD, MPH

(Industry Representative)

Senior Director, Head of Risk Management and Safety Surveillance Research

Pfizer, Inc.

North Peapack, New Jersey

TEMPORARY MEMBERS (Voting)

Traci C. Green, PhD, MSc

Professor

Heller School for Social Policy and

Management Director

Opioid Policy Research Collaborative

Brandeis University

Waltham, Massachusetts

Brandon D.L. Marshall, PhD

Associate Professor

Department of Epidemiology

Brown University School of Public Health

Providence, Rhode Island

Christopher R. McCurdy, BSPh, PhD, FAAPS
Director
UF Clinical and Translational Science Institute
Translational Drug Development Core
Professor of Medicinal Chemistry
Department of Medicinal Chemistry
University of Florida, College of Pharmacy
Gainesville, Florida

James J. McGough, MD, MS
Professor of Clinical Psychiatry
UCLA Semel Institute for Neuroscience &
Human Behavior
Los Angeles, California

Philip Posner, PhD
(Patient Representative)
Gainesville, Florida

Jon E. Zibbell, PhD

Senior Public Health Scientist

Behavioral Health Research Division

RTI International

Century Plaza 1

Atlanta, Georgia

FDA PARTICIPANTS (Non-Voting)

Billy Dunn, MD

Director (Acting)

Office of Neuroscience (ON)

Office of New Drugs (OND), CDER, FDA

Eric Bastings, MD

Deputy Director (Acting)

ON, OND, CDER, FDA

Tiffany R. Farchione, MD

Director (Acting)

Division of Psychiatry (DP)

ON, OND, CDER, FDA

Bernard Fischer, MD
Deputy Director (Acting)
DP, ON, OND, CDER, FDA

Judy Staffa, PhD, RPh
Associate Director for the Public Health Initiatives
Office of Surveillance and Epidemiology (OSE)
CDER, FDA

Tamra Meyer, PhD, MPH
Team Lead, Nonmedical Use Team #1
Division of Epidemiology II (DEPI-II)
Office of Pharmacovigilance and Epidemiology (OPE)
OSE, CDER, FDA

Dominic Chiapperino, PhD
Director
Controlled Substance Staff (CSS)
Office of the Center Director (OCD)
CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(10:02 a.m.)

Call to Order

DR. NARENDRAN: Good morning and welcome. I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Lauren-Jei McCarthy. Her email and phone number are currently displayed.

My name is Dr. Raj Narendran, and I will be chairing today's meeting. I will now call the October 8, 2020 Joint Meeting of the Psychopharmacologic Drug Advisory Committee and Drug Safety and Risk Management Advisory Committee meeting to order. Dr. LaToya Bonner is the designated federal officer for today's meeting and will begin with the introductions. I'll hand it over to Dr. Bonner.

Introduction of Committee

DR. BONNER: Good morning. My name is LaToya Bonner, and I am the designated federal officer for today's meeting. When I call your name, please introduce yourself by stating your name and affiliation. Please also state for the record that you

have reviewed the FDA's and Arbor Pharmaceuticals' prerecorded presentations in their entirety. If you have not, please state the extent of your preparation for today's meeting.

We will start with Dr. Dunn. Please introduce yourself and your affiliation.

DR. W. DUNN: Good morning. My name is Walter Dunn. I'm an assistant professor at UCLA. I confirm that I have reviewed the material.

DR. BONNER: Next is Dr. Jess Fiedorowicz.

DR. FIEDOROWICZ: Yes. Hello. My name is Jess Fiedorowicz. I'm with the University of Ottawa and the Ottawa Hospital with an adjunct appointment at the University of Iowa. I have also reviewed the materials.

DR. BONNER: Next is Dr. Iyengar.

DR. IYENGAR: Hello. This is Satish Iyengar. I'm with the statistics department and the Department of Psychiatry at the University of Pittsburgh, and I also confirm that I have reviewed all the materials.

DR. BONNER: Next is Dr. Jain.

DR. JAIN: Hello. This is Dr. Felipe Jain.

I'm a psychiatrist at Massachusetts General Hospital and assistant professor at Harvard Medical School. I confirm that I have reviewed the materials.

DR. BONNER: Dr. Jeffrey?

DR. JEFFREY: Hi, everyone. My name is Jessica Jeffrey. I'm a child psychiatrist at UCLA, and I have reviewed all the prerecorded presentations.

DR. BONNER: Dr. Krishna?

DR. KRISHNA: Hi. This is Sonia Krishna. I'm affiliate faculty at Dell Medical School at the University of Texas, Austin. I have reviewed all the materials.

DR. BONNER: And our chairperson, Dr. Narendran?

DR. NARENDRAN: I'm Dr. Narendran. I'm a psychiatrist at UPMC. I'm also a professor in radiology and psychiatry at the University of Pittsburgh. I have reviewed all the materials.

DR. BONNER: Thank you, sir.

Dr. Thomas?

DR. THOMAS: Hello. I'm Patrick Thomas [inaudible - distortion].

DR. BONNER: Dr. Thomas, there are some audio issues with your introduction, so I'll come back to you.

Next is Kim Witczak.

DR. WITCZAK: Hi. Good morning. Kim Witczak from Minneapolis, consumer rep, founder of Woodymatters, and I have reviewed all the materials.

DR. BONNER: Dr. Baker?

DR. BAKER: Hi. This is Robert Baker at Eli Lilly and Company, where I'm responsible for our clinical trial designs and phase 1 programs. I'm also a psychiatrist. I'm the pharmaceutical industry representative and not voting, but I have reviewed the materials.

DR. BONNER: We're going to go back to Dr. Thomas.

Can you reintroduce yourself, sir?

DR. THOMAS: Hello. Can you hear me now?

DR. BONNER: Yes, I can.

DR. THOMAS: Okay, great. Hi. I'm Dr. Patrick Thomas, assistant professor at Baylor College of Medicine, and I've reviewed the material.

DR. BONNER: Next is Dr. Boudreau.

DR. BOUDREAU: Hi. Good morning. I'm Denise Boudreau, scientific investigator at Kaiser Permanente, Washington and also professor at the University of Washington, Department of Pharmacy and Epidemiology. And yes, I have reviewed all the materials from both FDA and the sponsor.

DR. BONNER: Thank you.

Dr. Calis, please introduce yourself.

DR. CALIS: Good morning. I'm Karim Calis. I'm director of clinical research and compliance at the NICHD in NIH, and I'm also chair of the intramural NIH IRB, and I have reviewed all of the materials.

DR. BONNER: Dr. Griffin?

DR. GRIFFIN: Hi. I'm Marie Griffin. I'm an internist and pharmacoepidemiologist and Professor of Health Policy, Emerita at Vanderbilt University, and I confirm that I reviewed all the material.

DR. BONNER: Next is Dr. Habel.

DR. HABEL: Hi. This is Laurel Habel. I'm an epidemiologist at the Division of Research at Kaiser Permanente Northern California, and I confirm that I've

reviewed all the materials.

DR. BONNER: Dr. Sonia Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Hi. This is Sonia Hernandez-Diaz, Professor of Pharmacoepidemiology at the Harvard Chan School of Public Health, and I have reviewed all the materials.

DR. BONNER: Next is Dr. Kulldorff.

DR. KULLDORFF: Hi. My name is Martin Kulldorff. I'm a biostatistician in the Harvard Medical School in the Division of Pharmacoepidemiology. I have reviewed all the presentations, and I'm a little bit older than that pictures indicates.

DR. BONNER: Dr. Meisel?

DR. MEISEL: Good morning. Steve Meisel. I am a director of medication safety for M Health Fairview integrated health system based in Minneapolis, Minnesota, and I confirm I reviewed the materials.

DR. BONNER: Dr. Nelson was next.

DR. NELSON: Good morning. Lewis Nelson, professor and chair, Department of Emergency Medicine at Rutgers New Jersey Medical School in Newark, New Jersey. I'm the chief of the Division of Medical

Toxicology and senior consultant to the New Jersey Poison Control Center in Newark, New Jersey. I have reviewed all of the materials.

DR. BONNER: Thank you, sir.

Dr. Mehta?

DR. MEHTA: Hi. Reema Mehta from Pfizer, head of risk management and safety surveillance research, and I am the industry rep, nonvoting, and I confirm I have read all the materials.

DR. BONNER: Next we'll have Dr. Green.

DR. GREEN: Good morning. I'm Traci Green. I'm an epidemiologist. I'm a professor at the Heller School for Social Policy and Management and the director of the Opioid Policy Research Collaborative at Brandeis University, and I confirm I have reviewed all the materials.

DR. BONNER: Thank you.

Dr. Marshall?

DR. MARSHALL: Good morning, everyone. This is Brandon Marshall. I'm an associate professor in epidemiology at the Brown University School of Public Health, and I confirm I have reviewed all of the

materials.

DR. BONNER: Thank you.

Dr. McCurdy?

DR. McCURDY: Good morning. My name is Chris McCurdy. I'm at the University of Florida where I serve as director of the Translational Drug Development Core and also as Professor of Medicinal Chemistry and Pharmaceutics in the College of Pharmacy, and I confirm that I have reviewed all the materials for today's meeting.

DR. BONNER: Thank you, sir.

Dr. Posner, please introduce yourself and your affiliation.

DR. POSNER: Phil Posner. I'm the patient with ADD, and I have a courtesy appointment at the University of Florida, College of Medicine in the Department of Physiology and Genetics, and I confirm that I have read all of the materials.

DR. BONNER: Thank you.

Dr. Zibbell?

DR. ZIBBELL: Hey, everyone. I'm Jon Zibbell. I'm a senior public health scientist in the Behavioral

Health Research Division at RTI International in Atlanta, Georgia; also an adjunct appointment at Emory University, and I confirm that I've reviewed all the materials. Thanks.

DR. BONNER: Thank you.

Next, we will have our FDA participants.

Dr. Dunn?

(No response.)

DR. BONNER: Dr. Dunn, please unmute your phone.

DR. B. DUNN: Hello. This is Dr. Dunn. Sorry. I had to unmute things. This is Dr. Dunn. I direct the Office of Neuroscience at the FDA.

DR. BONNER: Thank you, sir.

Dr. Bastings?

DR. BASTINGS: Yes. Good morning. Eric Bastings, acting deputy director of the Office of Neuroscience, FDA.

DR. BONNER: Dr. Farchione?

DR. FARCHIONE: Hi. This is Tiffany Farchione. I'm the acting director of the Division of Psychiatry.

DR. BONNER: Dr. Fischer?

DR. FISCHER: Hi. This is Bernie Fischer. I'm the acting deputy for Division of Psychiatry.

DR. BONNER: Dr. Staffa, please introduce yourself.

DR. STAFFA: Good morning. This is Judy Staffa. I'm the associate director for Public Health Initiatives in the Office of Surveillance and Epidemiology at FDA.

DR. BONNER: Next will be Dr. Meyer.

DR. MEYER: Hi. I'm Tamra Meyer. I'm the team lead for Nonmedical Use Team Number 1 in the Division of Epidemiology at FDA.

DR. BONNER: Next is Dr. Chiapperino.

DR. CHIAPPERINO: Good morning. This is Dominic Chiapperino. I am the director of the controlled substance staff in the drug center. Thank you.

DR. BONNER: That concludes our introductions. I'll hand the meeting back to the chair, Dr. Narendran.

DR. NARENDRAN: Thank you, Dr. Bonner.

For topics such as those being discussed at

today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We're aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

I will now hand it over to Dr. Bonner to read the Conflict of Interest Statement for the meeting.

Conflict of Interest Statement

DR. BONNER: Thank you, sir.

The Food and Drug Administration is convening today's joint meeting of the Psychopharmacologic Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972.

With the exception of the industry representative, all members and temporary voting members of the committees are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the committees' compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of the committees are in compliance with federal ethics and conflict of interest laws. Under 18

U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of the committees have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and royalties; and primary employment.

Today's agenda involves discussion of new drug application 211179, for amphetamine sulfate

immediate-release oral capsules submitted by Arbor Pharmaceuticals, LLC, for the proposed indication of treatment of attention deficit hyperactivity disorder. The product has been formulated with properties intended to deter non-oral abuse, and the applicant has submitted data to support these abuse-deterrent properties for this product.

The committees will be asked to discuss the overall risk-benefit profile of the product, including the potential public health impact and whether the applicant has demonstrated abuse-deterrent properties for their product that would support labeling.

This is a particular matters meeting during which specific matters related to Arbor Pharmaceuticals' NDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the

product at issue.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Robert Baker and Reema Mehta are participating in this meeting as nonvoting industry representatives, acting on behalf of regulated industry. Dr. Baker's and Dr. Mehta's role at this meeting is to represent industry in general and not any particular company. Dr. Baker is employed by Eli Lilly and Dr. Mehta is employed by Pfizer.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the committees of any financial relationships that they may have with the firm at issue.

Thank you. I will now turn the meeting back over to our chair.

DR. NARENDRAN: Thank you, Dr. Bonner.

We will now proceed with the FDA's opening remarks from Dr. Tiffany Farchione.

Dr. Farchione?

DR. FARCHIONE: Great. Thank you.

I'm just looking for my slides.

DR. BONNER: Please stand by just a moment.

DR. FARCHIONE: Thank you.

(Pause.)

FDA Opening Remarks - Tiffany Farchione

DR. FARCHIONE: Good morning, and welcome to this joint meeting of the Psychopharmacologic Drugs and the Drug Safety and Risk Management Advisory Committees. My name is Tiffany Farchione, and I'm the acting director of the Division of Psychiatry here at FDA.

Before we begin, I would like to acknowledge these unusual circumstances. Today's meeting is obviously being held virtually given the ongoing public health emergency. Both the agency and the applicant prerecorded their presentations, and the committee members are expected to have viewed these presentations

in advance of today's meeting, as they confirmed during the introduction. However, before moving on to the clarifying questions, public comment, and discussion, I will begin here with a brief summary of the agency presentation, and the applicant will follow with a brief summary of their materials.

The purpose of this meeting is to discuss a new drug application submitted by Arbor Pharmaceuticals for AR19, an immediate-release amphetamine sulfate product formulated with properties intended to deter non-oral abuse.

The committees will be asked to discuss the overall risk-benefit profile of the product, including the potential public health impact and whether the applicant has demonstrated abuse-deterrent properties for their products efficiently to support inclusion of language describing those properties in the labeling. If language describing these properties is included in labeling, this product would be the first stimulant with such abuse-deterrent labeling.

AR19 was developed under the 505(b)(2) pathway. This means that the applicant is relying, in

part, on the agency's findings of safety and effectiveness for a previously approved amphetamine product to support this application. In this case, the approved product is indicated for the treatment of ADHD in pediatric patients with a maximum recommended total daily dose of 40 milligrams. It's administered once in the morning, followed by a second dose 4 to 6 hours later; in other words, 20 milligrams twice per day.

The applicant has conducted a relative bioavailability study comparing AR19 to the previously approved drug, as well as the randomized, fixed-dose, double-blind, placebo-controlled safety and efficacy study in adults with ADHD.

Based on these studies, the efficacy of AR19 for the treatment of ADHD is not in question and will not be a focus of this meeting. Rather, this meeting will focus on the product's proposed abuse-deterrent properties; whether the benefit-risk assessment for the drug supports approval of this new formulation; and the role of abuse-deterrent stimulants more broadly in addressing the public health problem of stimulant nonmedical use.

Before we really begin, I'd like to define some of the terms we will be using during today's meeting. In general, FDA has defined "misuse" as the intentional use for therapeutic purposes of a drug in a manner other than as prescribed or by an individual for whom it was not prescribed.

We have defined "abuse" as the intentional non-therapeutic use of a drug, even one, for its desirable psychological or physiological effects. However, it can be difficult to differentiate between misuse and abuse in epidemiologic data, therefore when discussing epidemiologic data, the term "nonmedical use" refers to both misuse and abuse.

We recognize that language can perpetuate stigma and negative bias towards individuals with substance-use disorders and create barriers to effective treatment. FDA is committed to reducing stigma, expanding therapeutic options, and ensuring access to evidence-based treatments for individuals with substance-use disorders.

We also recognize that the term "abuse-deterrent formulation" may be misunderstood to mean

abuse or addiction-proof formulation. Although we will use that term today, the agency is currently engaged in rigorous mixed-method, multiphase research on healthcare providers' perspectives on issues related to abuse deterrence, including the terminology for describing these products.

Returning to the application at hand, because there's no established pathway for developing abuse-deterrent stimulants, the applicant has based their development program on agency guidance for developing abuse-deterrent opioids.

In the absence of class-specific guidance, this is not an unreasonable approach. The scientific principles governing assessment of a product's ability to deter abuse are the same. However, because the patterns of misuse and abuse, morbidity, and mortality associated with prescription stimulants are different from those associated with prescription opioids, we have remained agnostic on the applicability of opioid abuse-deterrent guidance to the development of abuse-deterrent stimulants.

AR19 is an immediate-release product with

proposed strength originally ranging from 2.5 to 40 milligrams, although we acknowledge that the AC materials note the applicant is now seeking the maximum strength of 30 milligrams.

Although the most frequent route of abuse for prescription stimulants is oral, this product was not designed to deter abuse by the oral route. It is only intended to deter abuse via the intranasal and intravenous route. The committees will be asked to comment on the data presented by the applicant to support these abuse-deterrent claims, as well as the agency's perspective on these data.

Although there are no formulation-specific safety concerns when this product is administered via the intended oral route, abuse-deterrent formulations are also evaluated for potential risk secondary to manipulation for use via unintended routes of administration.

The prerecorded presentations included information about two of the excipients in this formulation that may present safety concerns when the product is manipulated and also about the potential

public health impact of abuse-deterrent stimulants.

Dr. Ponta's presentation outlines the results of the laboratory manipulation and extraction studies, otherwise known as category 1 studies. Physical manipulation studies aim to manipulate capsule contents to reduce particle size to produce a powder amenable to insufflation. Extractability and syringeability studies are performed to determine whether a syringeable material can be produced.

The physical manipulation studies show that roughly 82 to 98 percent of non-abuse-deterrent amphetamine can be reduced to an insufflatable particle size without pretreatment. By contrast, 75.6 percent of the contents of the 40-milligram AR19 capsule can be reduced to an insufflatable particle size with pretreatment.

I would note that there was a typo in the FDA presentation related to the amount that could be reduced to less than 1000 microns, but without pretreatment, the percentage of AR19 particles that could be reduced to less than 1000 microns is actually 98.8 percent, not 88.8 percent as described.

With regard to extractability and syringeability, up to 90 percent of amphetamine can be extracted from non-ADF formulations without pretreatment. Based on the applicant's studies, only about 15 percent of the amphetamine can be extracted from an AR19 capsule without pretreatment and about 50 percent can be extracted with pretreatment.

They also showed that extraction from multiple capsules was largely not feasible. However, since recording the prerecorded session, we received the results of extraction studies conducted by our own lab and are no longer sure we agree with these conclusions. It appears that it may be possible to extract up to 40 percent of amphetamine without pretreatment, and under certain conditions, it may be possible to extract more than 50 percent of the amphetamine from multiple capsules.

Dr. Bansil's presentation outlined the pharmacokinetic and human abuse potential studies, also known as category 2 and 3 studies conducted as part of the development program. Starting with studies examining intravenous abuse potential, we note that

human abuse potential studies to evaluate the abuse-deterrent effects of manipulated product administered by the IV route could not be conducted for safety reasons; for example, concerns related to excipient in this product. Therefore, the evaluation of abuse-deterrent effect by the IV route is supported by in vitro syringeability studies.

This evaluation required an understanding of the dose-response curve for reinforcing effects to determine the minimum reinforcing dose. Based on data from the literature, our controlled substances staff determined that a reasonable minimum reinforcing dose would be 10 milligrams of amphetamine administered in a small volume over a 1-minute period. In vitro manipulation studies demonstrated that it is possible to obtain a solution for intravenous use that contains 10 milligrams or more of amphetamine.

The applicant performed an intranasal human abuse potential study, and I'm going to spend a bit of time here because the methods and terminology are not as familiar as our usual clinical trial. It's also important to explain why you heard different

interpretations of the overall conclusions in the agency and the applicant presentations.

To summarize, the primary analysis looking at drug liking in the prespecified completer population failed the validation test. Failing validation means that the responses of the subject population taken as a whole do not provide reliable results because the subject did not respond as one would expect to the positive control relative to placebo. In other words, you'd expect subjects to report liking in the positive control and neutrality for placebo, and you expect the mean difference in the maximum drug liking, between the positive control and placebo, to reach a certain threshold; in this case 15 points.

Looking at the 37 subject completer population, their study failed the validation test. In their slides and briefing materials, the applicant presents only results that include all 37 subjects in their analyses, but we already know that analysis of that population did not result in a validated study. Once you determine that the subjects' responses are not reliable, it is not appropriate to conduct further

analyses on this population. This is not a matter of removing outliers for post hoc analyses; this is a matter of the appropriateness of conducting further analyses on an unreliable population.

The only post hoc results that should be considered reliable would come from a population that does pass the validation test. Prespecifying criteria to remove subjects who are responding unreliably was an option but was not done in this case. However, removing subjects with unreliable responses from the completer population post hoc at least allows a reasonable approach to conducting further post hoc analyses of primary and secondary endpoints in the modified completer population.

To consider a product's ability to deter abuse based on these endpoints, Arbor presented data in their application with a single subject removed. We don't agree that removal of that single subject resulted in a validated study, and they did not present those analyses in their background materials, so I won't discuss them further.

FDA conducted analyses with four subjects with

unreliable responses excluded, and this modified completer population did pass the validation test. However, with this more reliable subject population, the study still was not able to detect a nominally significant difference by the prespecified margin between manipulated AR19 and amphetamine. So an abuse-deterrent effect for AR19 for the intranasal route was not established.

That was a lot of information packed into those last couple of slides, so let me quickly summarize the take-home point. AR19 is not intended to and will not deter abuse by the oral route. Even though you can extract less amphetamine from AR19 than from non-ADF formulations of amphetamine, in vitro manipulation studies demonstrate that it is feasible to obtain a solution for injection containing a reinforcing dose of amphetamine.

The intranasal HAP study does not provide convincing evidence that the formulation employed for AR19 has significant abuse-deterrent effects as compared to amphetamine sulfate when administered by the intranasal route.

Moving on to the nonclinical findings, as Lieutenant Commander Matthew noted, there are no formulation-specific safety concerns when this product is used as intended, however, abuse-deterrent formulations are also evaluated for potential risk secondary to manipulation for use via an unintended route. Her presentation included information about two of the excipients in this formulation that may present safety concerns when the product is manipulated, high molecular weight polyethylene oxide, or PEO, and talc.

If AR19 is manipulated in a manner that results in some syringeable high molecular weight PEO, we cannot rule out the possibility of thrombotic microangiopathy. On the other hand, talc exposure via injecting or snorting manipulated AR19 likely poses a similar risk to other non-ADF formulations that contain talc.

I also want to note here that the applicant did request a correction to the FDA presentation regarding the amount of unknown material in the Condition 8 extract. The FDA background document and presentation noted that approximately 15 percent of the

material is of unknown chemical composition.

We would like to note that based on our assessment of the data submitted by the applicant characterizing the chemical identity of the material in the Condition 8 extract sample, approximately 15 percent of the mass of the extracted material is not accounted for as either PEO, PEG, TDA, talc starch, or amphetamine. However, we acknowledge that of that 15 percent, approximately 3.4 percent of that unknown mass has been characterized as amphetamine-related impurities, although the exact chemical identity of these amphetamine-related impurities was not reported.

Dr. Shearer's presentation outlined the potential public health impact of AR19 and of abuse-deterrent stimulants in general. For opioids, the agency has explicitly stated that we will consider the broader public health risks of the drug related to misuse, abuse, opioid-use disorder, accidental exposure, and overdose in both patients and others, as well as any properties of the drug that may mitigate such risk. Considering public health in our benefit-risk assessment will also be useful for

evaluating the potential impact of ADF stimulants.

We recognize that an abuse-deterrent formulation of a single product will likely have little impact on the overall problem of prescription stimulant nonmedical use, but it is also important to consider the broader question of whether effective abuse-deterrent formulations of prescription stimulant products in general have the potential for public health benefit.

To their credit, the applicant submitted multiple reports containing results from original studies and analyses of other available data intended to outline the scope and pattern of nonmedical stimulant use in the United States. Because this is the first stimulant application seeking abuse-deterrent labeling, the agency's prerecorded presentations included a lengthy discussion of the epidemiologic data submitted by the applicant, as well as data generated by FDA related to nonmedical use of stimulants and the potential public health impact of abuse-deterrent formulation.

Rather than present a summary of Dr. Shearer's

comprehensive presentation, I've listed here a few of the unanswered questions that may serve to spur some discussion this afternoon, which brings me to today's agenda.

You have already had an opportunity to view presentations from the applicant and the agency. The applicant will also present a brief summary today followed by an opportunity for the committee members to ask clarifying questions. We will then hear public comments before moving on to the questions for the committee.

Today, you will be asked to address these questions and points of discussion.

1) Considering the patterns of prescription stimulant nonmedical use in the United States, please discuss the potential public health impact of prescription stimulants formulated to be abuse-deterrent.

2) Based on the information provided, including the intranasal study comparing this product to amphetamine sulfate, has the applicant provided adequate evidence that the formulation of AR19 would

deter intranasal use?

3) Based on the information provided, including the syringeability study, has the applicant provided adequate evidence that the formulation of AR19 would deter intravenous use?

4) Based on the information provided, has the applicant adequately characterized the safety of AR19?

5) Discuss whether the benefits of AR19 outweigh the risks for the proposed indication.

6) What, if any, additional data are needed to address outstanding issues?

Finally, on a practical note, I would like to alert you to the different processes FDA will be using to internally confer when needed, particularly when addressing questions from the committee.

Our advisory committee staff has done a wonderful job of harnessing technology to allow us to still have public meetings like this, and I would like to acknowledge their support throughout the process of planning and executing this virtual meeting. However, we have a large group of multidisciplinary scientists and leadership across CDER involved in this meeting,

and there may be slight delays in our responses as we confer virtually to make sure we identify the optimal respondent to your question.

I thank you in advance for your patience as we all learn together how to make this work. And with that, I will turn it over to the applicant. Thank you.

DR. SCULLIN: Thank you. I'll wait for slides here.

DR. BONNER: We will now turn the meeting over to the chair, Dr. Narendran.

DR. NARENDRAN: Thank you, Dr. Farchione.

I just want to read this statement.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including Arbor Pharmaceuticals' non-employee presenters, to advise the committee of any financial relationships that they may have with the

applicant, such as consulting fees, travel expenses, honoraria, and interest in the applicant, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with Arbor Pharmaceuticals' summary presentation. Thank you for the summary presentation.

Applicant Presentation - Evan Scullin

DR. SCULLIN: Thank you and good morning. My name is Evan Scullin. I'm the vice president of medical affairs at Arbor Pharmaceuticals. As you've seen, the FDA posted an errata to correct several inaccuracies related to Arbor's clinical and nonclinical data. When the FDA issued its errata, they added the statement related to impurities in our nonclinical extract, which was also incorrect.

In the FDA's presentation, we had to suggest additional corrections, however, the FDA informed us no additional corrections would be made. These inaccuracies and misrepresentations are regrettable in the light of the complex issues you are being asked to consider today. We will do our best, in this presentation and in our Q&A period, to present the data accurately and transparently.

AR19 is the first immediate-release ADHD prescription stimulant formulated with physical and chemical barriers designed to resist manipulations required for snorting, smoking, and injecting. AR19 is a pellets-in-capsule form of amphetamine sulfate and could be used for any patient for whom an immediate-release amphetamine medication is indicated.

We agree with the FDA that AR19 meets the standard for approval in pediatric and adult patients with ADHD. We have proposed the term "manipulation resistant" to describe AR19's formulation rather than "abuse deterrent" since it may stigmatize patients and lead to the false perception that the medication is abuse proof.

We think manipulation resistant conveys what this medication does. It imposes barriers to conversion for non-oral use. We've surveyed more than 700 physicians, and the vast majority recognize the need for an option like AR19 that would provide protection for at-risk patients.

We originally formulated AR19 in 7 dose strengths to provide clinicians flexible dosing options. Based on FDA's concern regarding the highest dose strength, Arbor proposes to eliminate the 40-milligram dose. This would leave 30 milligrams as the highest strength.

Finally, Arbor is committed to ensuring patient access to AR19. One of the primary concerns expressed in public comments at the Federal Register is that sponsors price these medications so high that access is very limited. We intend to price AR19 consistent with currently marketed prescription stimulants.

Thank you. I'll now turn the presentation over to Dr. Faraone.

(No response.)

DR. SCULLIN: Dr. Faraone, I believe you're on mute.

Applicant Presentation - Stephen Faraone

DR. FARAONE: Thank you. I am Stephen Faraone, vice chair of research and professor in the Department of Psychiatry at SUNY Upstate Medical University. I am a paid consultant for Arbor Pharmaceuticals.

I'll provide my views on question 1 regarding patterns of prescription stimulant nonmedical use and the potential public health impact of prescription stimulants with barriers to non-oral use. The FDA's materials have focused extensively on comparisons between opioids and stimulants. An important topic for the focus today will be the harms of non-oral use of prescription stimulants.

Epidemiologic data have improved our understanding of both the most vulnerable target populations and the target medications most attractive or abused. Older adolescents and young adults with ADHD have the highest prevalence of misuse and abuse. In fact, the prevalence of non-oral use is highest

among college students with ADHD. Forty-five percent of those prescribed a stimulant had snorted it. Also, immediate-release medications are more likely to be misused or abused than extended-release products. Amphetamine is more frequently misused or abused than methylphenidate.

Among those who have ever used a prescription stimulant, non-oral use is surprisingly high, about 1 in 7 adolescents, 1 in 5 college students, and 1 in 6 adults. Across all age groups, snorting was the most common route by far, followed by smoking, and injecting. This is alarming because the risks for major medical effects and death are substantially higher for non-oral than oral use. The relative risk for life-threatening events was nearly 3 times greater for snorting and more than 7 times greater for injecting. The relative risk for death were even higher.

As the FDA stated, the absolute rate of adverse harms is higher with oral nonmedical use, but since harm reduction is fundamental to public health, it would be irresponsible to ignore the known risks of

non-oral use even though it's less common. Snorting, smoking, and injecting CNS active drugs leads to faster or greater effects. The drug enters the brain more quickly, which accelerates and intensifies its effects. As a result, non-oral routes put users at a higher risk for compulsive use and addiction.

This pathway to addiction has been so well documented that it is described in professional guidelines and psychopharmacology textbooks. To summarize, the target population of older adolescents and college students is not orally using prescription stimulants at alarming rates, especially immediate-release amphetamine. Nearly half of college students with ADHD report snorting their medicine. Younger individuals dismiss these risks because they are using a medicine prescribed by a doctor, but the risk of serious medical harm is much greater with snorting or injecting.

Non-oral use also predisposes individuals to compulsive use and addiction. Today, all IR stimulants are easy to manipulate and use by these more dangerous routes. Prevention and harm reduction should be the

goals. Manipulation-resistant formulations will provide us that opportunity.

Thank you. I'll now turn over the presentation to Dr. Setnik.

Applicant Presentation - Beatrice Setnik

DR. SETNIK: Thank you. I'm Beatrice Setnik, the chief scientific officer at Altasciences. I am a paid consultant for Arbor Pharmaceuticals. I'll be discussing the evidence showing that AR19 can be expected to reduce nasal use. All immediate-release prescription stimulants today offer no barriers to snorting. AR19 imparts meaningful barriers to both manipulation and abuse potential. I'll start by describing barriers to manipulation.

Scientists at DRUGSCAN performed a large battery of tests to evaluate possible methods a person might use to prepare AR19 for non-oral use. They selected 7 tools for extensive evaluation. This chart will show the percentage of particles reduced below the threshold that FDA considers amenable for snorting.

All tools reduced Evekeo to a snortable form in less than 1 minute. For AR19, most tools were

completely ineffective. For Tools 4 and 6, most material remained larger particles. Pretreatment did not have a significant impact on particle size reduction. Therefore, DRUGSSCAN scientists had to modify a tool to get the majority of AR19 pellets into small particles. After several weeks of experimentation, they identified an optimized 20-minute, multi-step procedure that required modifying Tool 7 and applying select accessories.

This is a complicated method that is unlikely to be performed in the real world. Furthermore, even with all the time and effort required, AR19 could not be reduced to a fine powder. In contrast, Evekeo could be crushed into a fine powder in just 30 seconds.

Next, I will review the intranasal human abuse potential study. HAP studies only evaluate the second barrier because trained pharmacy staff prepare the drugs for subjects using the optimized method. HAP studies are evaluated based on the pattern of findings across all of the measures.

Prior to initiating the study, the protocol and statistical analysis plan were submitted to the FDA

for review, and we incorporated all the recommendations. Consistent with good scientific practice, I'll be showing these prespecified analyses, which include all completers, accounting for the totality of the data. The FDA has chosen to present post hoc exploratory analyses, which excludes several subjects.

Let's start with the pharmacokinetics. Intranasal API was associated with a rapid increase in plasma concentration. In contrast, intranasal AR19 led to a more gradual rise that did not reach the levels associated with API. These results confirmed that the inability to reduce AR19 to a fine powder reduces intranasal bioavailability.

This slide will show the results for the primary endpoint of drug liking Emax, the maximum liking score observed during the entire study. 100 represents strong liking, 50 is neutral, and 0 represents strong disliking. Placebo was close to neutral. Amphetamine had a maximum score of 78. AR19 was 9 points lower than amphetamine. The p-value with a superiority margin of 10 percent narrowly missed the

threshold for significance of 0.025 with a p-value of 0.026.

The rationale for snorting a stimulant is to achieve a quick effect. In the first 15 minutes, AR19 was indistinguishable from placebo. At most time points, the drug liking for AR19 was about half that of API. The totality of the data on the prespecified analyses of the secondary endpoints show a very consistent pattern. All endpoints showed that AR19 has a lower abuse potential than API. This includes take drug again, which is probably the most important endpoint for a drug that is intended to prevent repeated use.

To summarize, AR19 is difficult to manipulate and less rewarding to snort. AR19 could not be prepared for snorting with common household tools. Even with a modified tool, specific equipment, and considerable time and effort, AR19 could not be reduced to a fine powder. Based on this barrier alone, it is unlikely that a typical individual would be able to prepare AR19 for snorting. Even when optimally manipulated, subjects experienced lower drug liking and

high over time and expressed a lower willingness to take AR19 again. Taken together, these multiple barriers can be expected to reduce snorting with AR19.

Thank you. I'll now turn the presentation to Dr. Kinzler.

Applicant Presentation - Eric Kinzler

DR. KINZLER: Thank you. My name is Eric Kinzler. I'm an independent consultant and the study director for in vitro testing at DRUGSCAN. I'll now review the data demonstrating that AR19 can be expected to impede intravenous use.

Intravenous users are looking to inject a dose that will achieve a desired effect. FDA referenced an article that stated 10 milligrams is a minimum reinforcing amphetamine dose, meaning the lowest dose that could be differentiated from placebo. But the reason people inject drugs is to achieve an immediate and profound effect. They're not looking to just feel a difference from nothing at all.

Therefore, 10 milligrams is not a relevant dose for intravenous drug use in the real world. Rather, the literature and postings on drug abuse

websites show that IV users initiate with doses of 20 to 40 milligrams, and when they become experienced, their doses may escalate up to 100 to 300 milligrams per injection with multiple injections per day.

A product's ability to reduce the incentive for injection depends on two factors. The first is the input, which is the amount of time, effort, and materials required to prepare a product for injection. The second is the output, which is the IV dose they can achieve from those conditions. We tested real-world techniques of IV users, as well as advanced laboratory techniques.

To summarize our findings, we found that it was not feasible to prepare AR19 for injection using standard methods. From the hundreds of conditions evaluated, most yielded trace amounts of amphetamine or none at all.

We found one method from AR19 40 milligram that provided a maximum recovery of 20 milligrams or 50 percent. This advanced laboratory procedure took an hour and required manipulation with modified Tool 7, pretreatment, vigorously agitating and extracting at

near boiling temperatures for an extended period of time, and syringing with a relatively large needle through a laboratory filter. We also found that extracting multiple AR19 capsules for injection is not feasible.

The sponsor has decided not to market the 40-milligram dose, which would reduce the maximum recovery possible from AR19. Given what we know about the doses sought for injection, we can conclude that it is not feasible to produce a highly rewarding dose for injection with AR19.

Thank you. I'll now turn the presentation over to Dr. Dillberger.

Applicant Presentation - John Dillberger

DR. DILLBERGER: Thank you. I'm John Dillberger. I'm a pathologist and toxicologist with more than 30 years of experience in evaluating the nonclinical safety of new drug products, and I'm a paid consultant to Arbor. I'll review the information characterizing the safety of AR19.

As Dr. Farchione noted in her summary presentation, there are no safety concerns with AR19 19

when it's taken as intended by the oral route. All its excipients are included in other FDA-approved medications. The FDA has highlighted two specific excipients of concern for unintended routes of administration, high molecular weight PEO and talc.

Both excipients are contained in many of the most commonly prescribed prescription stimulants. For example, PEO 7 million is a primary excipient in Concerta. While we know Concerta's injected, there have been no reports of PEO-related toxicities despite more than 85 million prescriptions dispensed. Also, like AR19, both Ritalin and Adderall XR contain talc. The literature suggests AR19 would have to be snorted or injected thousands of times to cause talc toxicity. Therefore, PEO and talc in AR19 do not pose a unique risk.

To summarize our findings, there was no evidence of meaningful in vitro hemolysis with any AR19 extract. While it's impossible to evaluate every nonmedical use scenario, we designed our in vivo studies to evaluate the extract with the highest amphetamine content because it poses the greatest risk

for repeat use.

Our pivotal study tested this extract in an exaggerated scenario that assumed a person would take the one hour of time and effort with laboratory equipment to manipulate and extract an AR19 40-milligram capsule, do this 3 times per day, and repeat that lengthy and complicated procedure every day for a week. Even in this exaggerated scenario, AR19 was well tolerated. Therefore, the safety of AR19 has been well characterized for both oral and non-oral routes of administration.

Thank you. I'll now turn the presentation over to Dr. Rostain.

Applicant Presentation - Anthony Rostain

DR. ROSTAIN: Thank you. My name is Anthony Rostain, and I'm the chair of psychiatry and behavioral health at Cooper University Healthcare, and I'm a paid consultant for Arbor Pharmaceuticals. I'm pleased to discuss the benefit-risk profile of AR19.

Let's begin with an understanding of what AR19 can be expected to do and also what it can't. It can't prevent oral misuse or abuse, and it is not abuse-proof

by any route. But it can make manipulation difficult, reduce the positive reinforcement of non-oral routes, and reduce their harmful medical outcomes. Taken together, AR19 would be a harm reduction strategy that makes non-oral use more difficult and less rewarding.

As detailed in my recorded presentation, this is exactly what AR19 does for all non-oral routes of administration. The physical and chemical barriers makes snorting, smoking, and injecting more difficult and less rewarding. Perhaps the most important public health concern is that a manipulation-resistant formulation could lead individuals to seek illicit stimulants.

Researchers from the National Institute on Drug Abuse have stated in the New England Journal of Medicine that there is no consistent evidence linking the introduction of abuse-deterrent opioids to an increase in use of illicit opioids. It's also important to underscore that stimulants and opioids are different. Opioids may cause physical dependence; stimulants do not.

Motivations for nonmedical use are also

distinct, pain relief and euphoria for opioids and primarily performance enhancement for stimulants. AR19 would also be an option among many, not a reformulation of the entire immediate-release amphetamine market.

The at-risk population of older adolescents and young adults feel comfortable non-orally using stimulant medications because they were prescribed by a doctor and are perceived as safe. The likelihood that AR19 would prompt them to initiate use of illicit stimulants is low because they are street drugs and are perceived as dangerous.

In summary, no IR amphetamine products impose barriers to reduce the harms of non-oral use and prevent progression down a path of more dangerous drug-taking behaviors. That is why those of us who are treating physicians see AR19 as a needed treatment option that could provide extra levels of protection for our patients with ADHD.

Thank you. Dr. Evan Scullin will now moderate the Q&A period.

DR. SCULLIN: Thank you, Dr. Rostain. I'll turn it to the chair. I'm happy to take any questions.

Clarifying Questions to Applicant

DR. NARENDRAN: Thank you for the summary presentations. We will now take clarifying questions for Arbor Pharmaceuticals. Please use the raised-hand icon to indicate that you have a question and remember to put your hand down after you have asked the question. Please remember to state your name for the record before you speak and direct your question to a specific presenter if you can. If you wish for a specific slide to be displayed, please let us know what the slide number is if possible.

Finally, it will be helpful to acknowledge at the end of your question with a thank you and end of your follow-up question saying that this is all the questions you have so we can move on to the next panel member. Because it's a big panel, and a lot of you may have questions, I'd like to give everybody a chance, first, who hasn't asked a question, so try to restrict it to a single question.

If you have a related follow-up question that comes up, please feel free to go ahead and ask it. However, please don't string two or three questions

back to back, which would mean it would take away from the other panel members who may have questions, so please be cognizant of that.

We'll go ahead. The first panel member, Dr. Dunn, ask your question.

DR. W. DUNN: Thank you. This is Walter Dunn from UCLA. My question is for Dr. Kinzler and Dr. Dillberger.

Can you comment on the different extracts that were manipulated in the in vitro studies, specifically Conditions 1, 2, 6 and 9. It appears that these -- or the other extracts, other than 8 that were syringeable or injectable, can you talk a little bit about how difficult they were to create in relation to Extract 8? You mentioned that Extract 8 took approximately 1 hour of laboratory processes. But as far as the other conditions, 1, 2, 6 and 9, were they less difficult, more difficult?

Then as a related follow-up question, in a real-world situation, of those injectable formulations, what would be the most likely that someone trying for the first or second time, which of these extracts would

they come up with? Thank you.

DR. SCULLIN: Yes. Just to remind the committee that we selected Extract 8 because it had the highest PEO and highest API content, I'll ask for Dr. Kinzler to comment on your question in regards to Extracts 1, 2, 6 and 9.

Dr. Kinzler?

(No response.)

DR. SCULLIN: Dr. Kinzler, you're on mute.

(No response.)

DR. SCULLIN: Okay. We also have Dr. Dillberger.

Dr. Dillberger, can you provide some comments in relation to these extracts and the in vitro and in vivo studies that were conducted?

Dr. Dillberger?

DR. DILLBERGER: Right. Well, I can speak to the in vitro studies, the in vitro hemolysis study. We did evaluate all of those injectable extracts. None of them produced clinically meaningful hemolysis. They weren't meaningfully different from the water control as opposed to the PEO 7 million, which produced a

concentration-related hemolysis in vitro.

Dr. Kinzler will have to speak to the details of preparation that you were asking about.

DR. KINZLER: Yes, a technical issue. My apologies.

Eric Kinzler. Extracts 1, 2, 6 and 9 were all less complicated to do, other than, let's see, 2, 6, and 9 were not manipulated with the optimal procedure, so they are slightly less complicated. However, what we found in those, in 1, 2, 6 and 9, is that the amount of API that's actually recovered is way lower than what we got from Extract 8, so they're not likely to be repeatedly used.

DR. SCULLIN: And just to remind the committee, we agreed to eliminate the 40-milligram dose. So with the 30-milligram dose, this would be lower than the FDA identified threshold for a reinforcing dose.

DR. NARENDRAN: Does that answer your question, Dr. Dunn?

DR. W. DUNN: Yes. Thank you so much.

DR. NARENDRAN: Okay. Thank you.

Next question, Dr. Kulldorff?

DR. KULLDORFF: Yes, thank you. This is Martin Kulldorff. This is maybe a question both for the sponsor and FDA.

The sponsor is asking for up to 30 milligrams, but not 40 milligrams, so why are you presenting the data in this slide from 40 milligrams? Or if you want to put the same question another way around, if the data presented, if it was convincing for 40 milligrams, why are you not asking for 40 milligrams, but only 30 milligrams and less?

DR. SCULLIN: Forty milligrams was selected in the dose selection phase of the human abuse potential study as a distinguished dose from placebo, so that was brought into the main study. As it relates to the 30 milligrams, the proportion of excipients in that dose would be similar to the 40 milligrams. So you would have the same manipulation resistance as the 40 milligram or the 30, just a lower API yield.

Then finally, we know that users who snort will typically go from an oral dose that they're familiar with, say, 20 or 40 milligrams, and use it via

their non-oral route. So someone might be using two 20 milligrams, so this would be more material and more work, time, and effort to get to that, which is highly unlikely due to the manipulation resistance and what is required to get to the modified Tool 7. So that information for the 40 milligrams translates to two 20 milligrams as well.

DR. KULLDORFF: Does FDA have a comment on that?

DR. NARENDRAN: Dr. Kulldorff, can we wait for the FDA's presentation question time to answer that question --

DR. KULLDORFF: Okay. Thank you very much.

DR. NARENDRAN: -- to be more efficient? Thank you.

Next question is Dr. McGough.

DR. McGOUGH: Thanks. It's Jim McGough from UCLA. My question is for primarily Dr. Faraone and maybe perhaps Dr. Rostain. I was struck by the statement that 45 percent of college students snort their medication, and I'm a little puzzled by this. I respect the source that you got that from.

Then there's also the implication that those snorting the medicine go on and have serious addiction problems, et cetera, but I'm not aware of any study or signal that's ever suggested people who are treated with their ADHD medicine have higher rates of addiction. In fact, if anything, we argue that proper treatment of the condition mitigates the risk for substance abuse.

So I'm struck a little bit by this disconnect between the reported high rates of non-oral abuse and the implications of greater risk for substance abuse and the dire medical outcomes that Dr. Rostain mentioned, but yet we don't see that. And then, in general, again, if anything, people argue that proper treatment has never been associated with increased risk of substance addiction, and if anything, it actually decreases it.

So can you just comment on that? Because this seems to not quite gel with our other information.

DR. SCULLIN: Yes. I'd like to get feedback from Dr. Faraone and Rostain in a moment. If we can present AM-17, please? Thank you.

So your statements are correct. Patients treated with ADHD stimulant medications have a lower risk of substance-use disorder, but as we know, and as the FDA affirmed in their presentation, ADHD patients have a higher risk of nonmedical use versus non-ADHD patients, so that's inherent with the condition. But if its treated, if the condition's properly treated and managed, that risk is reduced. So this really displays the medical need to protect these ADHD patients.

I'll ask for Dr. Faraone to respond in relation to the 45 percent, but the FDA has stated in the Federal Register notice last year that between 10 and 30 percent of college students snort their medication, and as much as 50 percent, so this data actually aligns.

Dr. Faraone, can you please comment on that as well?

DR. FARAONE: Sure. Dr. McGough is absolutely correct. Appropriate treatment of ADHD reduces the risk for substance-use disorders. I've published meta-analyses on that. But the point is that many of these college students are not appropriately using

their medication. They will, for example, snort their medication, save it up and snort it so they can stay up late and study. So it's this inappropriate use that we're concerned about, not the appropriate use.

DR. SCULLIN: Thank you.

Dr. Rostain, can you please comment on what you see in your clinical practice that relates to non-oral use, particularly snorting?

DR. ROSTAIN: The past several decades that I've been working, prior to coming to Cooper, I've been at the University of Pennsylvania for 40 years, and over the last 20 years, I've seen a substantial rise in both patients reporting non-oral uses and also from our own internal surveys, as well as published surveys. It's now become a rather routine part of college life that if you want to get studying quicker, you just grind up your immediate-release stimulant and you snort it.

The concern we have is that this is a growing phenomenon. So, yes, it may seem like a high number, that data that was reported by the Inflexxion study, which is really catching what the trend has been over

the last several decades. I believe it is a major health risk. Not to say that they all go on to become substance users; it just says right now they are exposing themselves to potentially catastrophic medical complications, and I've had a few patients end up with both hospitalizations for medical and psychiatric serious morbidities having snorted, essentially, their medication.

DR. SCULLIN: Thank you. While we acknowledge that oral is the most common nonmedical use, the FDA has affirmed that non-oral use is associated with the greatest risk of harm. So AR19 would address this need to address this potential for harm. There have been over a dozen stimulant medications approved by the FDA in the past decade. None of them have any properties that would mitigate this type of non-oral use, so this would be the first for immediate-release stimulants, which there are no manipulation-resistant products today.

DR. NARENDRAN: The next question is Dr. Hernandez-Diaz.

DR. HERNANDEZ-DIAZ: Hi. Thank you. This is

a question probably for Dr. Setnik. I was wondering since the viability is similar to the oral route unlike the opioids, what are the incentives to use snorting or injection? We have discussed a little bit of that already, but I was specifically wondering whether there are comparisons of the liking effects over time between the intranasal AR19 and the oral formulation, if you can expand on that comparison of the liking effects with the oral formulation.

DR. SCULLIN: Thank you. The human abuse potential study really evaluated comparing non-oral of the API from our current product Evekeo versus AR19. So we did not have an oral comparator. But I will show -- if we can pull CO-45, please?

To your question, the motivation for someone to use non-oral, and particularly for snorting in relation to HAP study, it's a rapid and profound effect. So they're looking for an effect within the first 15 minutes. As you can see at the first 15-minute time point, AR19 is indistinguishable from placebo, and you see distinct differences across all time points versus API for AR19.

So it's this early onset that people are looking for, but this is true across all the measures that we saw. These were prespecified analyses that were consistent across all pharmacodynamic measures. You can see here for mean high, good effects over time, as well as -- if we can show CO-48, please?

As Dr. Setnik shared in her presentation, across all the prespecified pharmacodynamic endpoints, we saw significant differences for AR19 versus API, and this is a consistent pattern on the prespecified analysis that the FDA provided input and we took on board.

DR. HERNANDEZ-DIAZ: Thank you. You would think that the oral effect will take more than 15 minutes, so it's a question of time --

DR. SCULLIN: Correct.

DR. HERNANDEZ-DIAZ: -- from intake. Okay. Thank you very much.

DR. SCULLIN: They're looking for a faster and more profound effect.

DR. HERNANDEZ-DIAZ: Thank you.

I have another question, but it's unrelated,

so I will go back online.

DR. NARENDRAN: Thank you, Dr. Hernandez-Diaz.

Next question, Ms. Witczak?

MS. WITCZAK: Hi. My question is I'd love to know a little bit more about the people that were in your study, a little bit about their background. I know you use a 40 and I know the FDA took out some of the outliers, but who were they? Tell me a little bit about them.

DR. SCULLIN: So you're referring to the study population in the HAP study.

MS. WITCZAK: Yes.

DR. SCULLIN: I'll ask Dr. Setnik to respond to your question in terms of the HAP study population.

Dr. Setnik?

DR. SETNIK: Yes. This is Beatrice Setnik. The study population is a face-valid population that's routinely used for human abuse potential evaluation. This included healthy male and female subjects. These were non-dependent, so these subjects were not physically dependent on drugs or alcohol, but they were current stimulant users who used stimulants for

recreational, non-therapeutic purposes, and they had to have had at least 10 times in their lifetime experience with stimulants and at least a recent time once in the past 12 weeks. They also had to have had intranasal experience for drug use with recreational, non-therapeutic reasons.

MS. WITCZAK: Just to follow-up, what's the age group, the ages that were in that?

DR. SETNIK: It was 18 to 55 years old.

MS. WITCZAK: Okay. And pretty even with men or male/female?

DR. SETNIK: There were more males than females in the study, as is typical of these types of studies.

MS. WITCZAK: Thank you.

DR. NARENDRAN: Next question, Dr. Jeffrey?

DR. JEFFREY: Hi there. Thank you. Jessica Jeffrey from UCLA. I have a question about the intranasal study. How long did it take to manipulate AR19 with Tools 4 and 6, and did you use common household tools to manipulate AR19 in 4 and 6?

DR. SCULLIN: Thank you. I'll ask for

Dr. Kinzler to respond to your question.

Dr. Kinzler?

DR. KINZLER: Sure. Eric Kinzler. Tools 4 and 6 actually do take quite a bit less time, but you get a meager reduction in particle size. Neither resulted in the majority of particles less than 500 microns, which is FDA's definition of insufflatable.

So really, the question is, could a user insufflate with Tools 4 and 6? The answer's probably yes, but the particles will be much larger. They would have quite a bit less surface area, which would inhibit intranasal absorption, which results in lower plasma levels and ultimately lower drug liking relative to the data that were presented today for the human abuse potential study.

DR. JEFFREY: Thank you. And the second part of my question, were those manipulated using common household tools?

DR. SCULLIN: Dr. Kinzler?

DR. KINZLER: Yes. The way that we do these studies, actually, with this product specifically, we tested more than 20 household tools. In the case of

AR19, none of them successfully reduced the majority of AR19 particles below 500 microns, which is why we actually had to create a new tool for AR19, which we've never done before.

So this modification was non-intuitive. It requires consistent maintenance. In other words, if you don't continually maintain this tool, it becomes ineffective, and even then, this physical manipulation process was physically demanding. It takes about 20 minutes, and actually it takes some skill and dedication by our laboratory scientists to actually get it into a consistent and reproducible powder.

DR. JEFFREY: Thank you.

DR. NARENDRAN: Next question, Dr. Meisel?

DR. MEISEL: Steve Meisel with Fairview in Minneapolis. I don't remember what slide it was, but it's figure 8 of the sponsor's briefing document, going back to the primary endpoint. I'd like to focus on that a little bit if we can get that slide up. It talks about the primary endpoint, and sponsor knows which slide I'm talking about.

DR. SCULLIN: Yes, we have that for you.

DR. MEISEL: There we go. Perfect. Thank you.

So as I read the briefing documents from both the agency and the sponsor, the target here was a 10 percent reduction, yet all we have here is a 9 percent reduction. I know we've got a PO [ph] of 0.026 and that sort of thing. But if we fail the primary endpoint, why does the 9 percent matter and why did the second endpoint matter, if we failed the primary endpoint?

DR. SCULLIN: Yes. Thank you. The reduction drug liking was consistent with reductions across the pharmacodynamic findings on the secondary endpoints. This 69, this will not be obtained by any other method and is highly unlikely to be attained with modified Tool 7. There is no established clinically meaningful threshold for a margin for the stimulant class. This is the first prescription stimulant to be evaluated with a margin, and for this reason, this narrowly missed by 0.001.

For this reason, we take in the totality of the data, and this is what the FDA has stated in their

guidance, that we take into account the totality of the data to consider the evaluation of the product from a human abuse potential standpoint.

DR. MEISEL: Okay. Thank you.

DR. NARENDRAN: Next question is Dr. Nelson.

DR. NELSON: Thank you. Lewis Nelson from Rutgers New Jersey Medical School. I think this is a question for Dr. Kinzler, again, about manipulation. We learned a lot from the manipulation postmarketing of OxyContin, and it became pretty evident that people in the real world became very skilled and creative at getting oxycodone out of the abuse-deterrent formulation.

I know you used a number of tools, you said 20, and you came up with the one that worked the best of the 20, and I know you're not allowed to give us the actual information on what these tools were. But did you go and look online, on blogs, on Reddit, on other places to find out what had been used for OxyContin and try to apply those to this product, or did you use just a standard battery of assessment tools that would normally be used for this determination? Thank you.

DR. SCULLIN: Thank you.

Dr. Kinzler?

DR. KINZLER: Yes. Eric Kinzler. That's exactly what we do. We start with our standard battery of tools. You can imagine we start with simple things, spoons and credit cards. If that doesn't work, we iteratively go to something that's more difficult, hammers, coffee grinders, that such a thing. If that doesn't work, then we go up even further and try different types of coffee grinders, spice grinders, whatever that happens to be. And if none of those are effective, we actually have to create a new tool.

So basically, all of our experiments are based upon what is actually done in the real world. I guess the one thing that I will say is that most of our experiments that we presented, showing today tools 1 through 7, are the best of the best, so it is very unlikely that somebody in the real world is going to come up with a better particle size reduction method. Then even if they did, with optimal physical manipulation, AR19 showed a reduction in human abuse potential study.

DR. NELSON: Thank you. I don't want to beat a dead horse, but those that failed the study history, you know that old expression. When OxyContin was originally introduced, I think we, they, you did the same sorts of studies and showed that it was not manipulatable to release a substantial amount of oxycodone, and post-release, it became apparent that there were ways to do it.

So I guess my question is whether you specifically looked for those other ways, as street pharmacologists, to figure how to do this, and try those on your own?

DR. KINZLER: Yes, thank you for that. You are absolutely correct. We found out two or three weeks ago that category 1, 2, and 3 testing were pretty predictive of a reduction in real-world abuse for OxyContin. What's important to realize about that conclusion is that OxyContin was a first-generation ADF. It, frankly, can be defeated by simply manipulating with a very simple household tool for a couple of minutes, and that's still resulted in significant reduction in non-oral use.

This is simply not the case with AR19. It is very difficult to manipulate. It takes a whole lot of time, effort, and, frankly, some skill and dedication if you really want to get into it. And even then, if a recreational was able to manipulate it, it'd still result in less drug liking than anything else on the market.

So again, if you were going to compare OxyContin to this, there's no comparison, in my opinion. With roughly 10 years of manipulating these products, the data we've generated strongly support that this product is manipulation resistant, and we would hope that it has a decrease in non-oral use in the real world.

DR. NELSON: Thank you.

DR. NARENDRAN: Thank you.

I have four more questions and five minutes. If you guys can keep it really short, the answers and the questions.

Dr. Jain was next.

DR. JAIN: Hello. This is Dr. Felipe Jain. My question

pertains to the 10 percent reduction in drug liking that was chosen as the primary outcome. What I believe I heard in response to the question by Dr. Meisner [ph] was that no clinically relevant threshold has been established. I wonder if we could have some comments regarding any prior literature that would inform the choice of a primary endpoint for a stimulant deterrence study. Thank you.

DR. SCULLIN: Thanks. I'll ask for Dr. Setnik to respond here. This was a 10 percent margin for the primary endpoint of drug liking that was applied, so there's no precedent for this.

Dr. Setnik?

DR. SETNIK: Yes. The 10 percent margin came out through the 2015 opioid guidance, and this is what was applied for the amphetamine. Typically, drug liking has been one of the key endpoints of interest, but generally these types of studies have always historically been interpreted in the entirety of their data, the totality across endpoints. So we always look at patterns and the responses across different measures, which was what was presented today.

So as Dr. Evan had mentioned, this is the first time that this margin has been applied to the analysis, which was narrowly missed by 0.001 of a p-value.

DR. JAIN: Thank you.

DR. NARENDRAN: Next question is Dr. Zibbell.

DR. ZIBBELL: Hey, everybody. Thanks. This is Jon Zibbell, RTI International. I think this question is for Dr. Kinzler. I was looking over the two documents, the two presentations by Arbor, one and two, in the email that we got, and I just have a question about the syringeability study, specifically, the heating.

If I read this correctly, you said that your findings -- I think it was 3, 4, and 5 -- were not injectable or syringeable because of the heating element, and they congealed after they were heated, so they might have turned into a liquid in some type of cooker. But it congealed too quickly to either be pulled into the syringe or congealed into the syringe, making it non-injectable.

Can you just explain a little bit the congeal

aspect quickly? Thanks.

DR. SCULLIN: Thank you. I'll ask for Dr. Kinzler to respond. Can we have DS-10, please? Thank you.

Dr. Kinzler?

DR. KINZLER: Yes. Eric Kinzler. You're absolutely correct. Everything on that chart, Extracts 1 through 9, were all done in a laboratory setting, first of all. It's possible, I suppose, that an IV user might be able to repeat those, but probably very unlikely.

What you see here is Extracts 3, 4, 5 and 7 are the ones that are not syringeable. So the way that these are done, as those are manipulated, again, with the 20-minute procedure, then they're pretreated, and then they're put into a water bath at near boiling temperatures for an extended period of time. So by the time we get those out of those water baths, we are able to pull those into a syringe for a very short amount of time. But by the time it would cool off and an IV user would try to inject it, it becomes impossible to push it back out.

DR. SCULLIN: Thanks, Dr. Kinzler.

And just to remind everyone, this was with manipulated AR19, so they would have had to identify modified Tool 7, which Dr. Kinzler described earlier.

DR. ZIBBELL: Thank you.

Clarifying Questions to FDA

DR. NARENDRAN: I think that's all the time we have, unfortunately. I want to hand it to the agency so they will get their 30 minutes, and then if there is extra time, we can come back to the pending two questions to Arbor.

So again, the same. If you have questions, please raise your hand icon. Please remember to put your hand down after the question has been answered. Please remember to state your name for the record and specify for a direct presenter, and the agency can pick who would be the right person to answer.

I'll now hand it over to the agency. Anybody have questions?

(No response.)

DR. NARENDRAN: Anybody have questions for the agency please raise your hand.

I'll start with Dr. Marshall.

DR. MARSHALL: Hi. Brandon Marshall, Brown School of Public Health. I had a question for the FDA regarding a statement in the regulatory history. There was a statement that the prescriptions could be restricted to newly diagnosed or naive patients, or perhaps patients currently receiving the standard product could be prohibited from switching.

I thought that was an interesting approach, so I just wanted to know a little bit more about what that would look like. Is that conditional on approval? Would that be a labeling guideline? How much was that discussed with the applicant and as an option for this product?

DR. FARCHIONE: Sure. Just quickly -- this is Tiffany Farchione -- can you point to which page? I have the background document open, and I just want to make sure I'm referring to the correct --

DR. MARSHALL: Yes. That was at the bottom of page 16 in the FDA briefing document.

DR. FARCHIONE: 16.1-6.

DR. MARSHALL: Yes.

DR. FARCHIONE: Right. Actually, this I think would be most appropriate for Dominic.

Dominic, this is in the CSS comments about developing abuse-deterrent products.

DR. CHIAPPERINO: Hi. I'm sorry. I'm not familiar with the paragraph you're talking about. I don't have -- can you read the statement in question?

DR. MARSHALL: Sure. It says, "Prescriptions of AR19 could be restricted to newly diagnosed or stimulant-naive patients who presumably are less likely to have already begun abusing stimulants. Established patients currently receiving amphetamine could also be prohibited from switching to AR19."

It sounded like that was a suggestion made to the sponsor, and I just wanted to know more about that, to the extent which that was discussed or how that would work in practice.

DR. FARCHIONE: Right.

Dominic, I can give you a little bit of context, too. It's in the extensive comments that we made regarding the overarching comment on developing of an abuse-deterrent stimulant and the appropriateness of

looking at the opioid guidances for reference. The paragraph starts with, "Your NDA submission should consider this impact on public health and explain how you will mitigate." I think that in this section we were just providing some examples of potential options that they could consider for how you would mitigate the adverse events for those already abusing stimulants, if you want to add more to that, Dominic.

DR. CHIAPPERINO: Yes. I don't think that those particular comments originated with the controlled substance staff. For the postmarket setting, I don't think that those comments originated with the controlled substance staff. I'm sorry.

DR. MARSHALL: Okay. No problem. Thank you.

DR. NARENDRAN: Dr. Staffa has a question, so I'm going to pass it to her first, before we take further questions.

Dr. Staffa?

DR. STAFFA: Yes. This is Judy Staffa from the Office of Surveillance and Epidemiology. I don't have a question, but I know a question that came up for the sponsor, that was also directed to FDA staff, was

about the 45 percent prevalence of snorting, and I was going to ask Dr. Joe Shearer to comment on FDA's interpretation of the epidemiology data on that issue.

So Joe, can you provide some insight of our thinking on that point?

DR. SHEARER: Yes. Thank you, Judy.

The finding that we're talking about with the 45 percent among people with ADHD, it's also important to note that this is among people who have reported lifetime nonmedical use of prescription stimulants. Also, it's talking about snorting for across a lifetime. If you look at snorting within the last year among this population, it's actually around 25 percent within the last year.

So I think it's important to note this isn't just among people with just ADHD, but it's among people with ADHD and a history of nonmedical use, and it's also reported for lifetime snorting. So I just wanted to make those two kind of clarifying points. Thanks.

DR. NARENDRAN: Thank you for that clarification.

Next question is from Dr. Jain.

DR. JAIN: Thank you. Dr. Felipe Jain, Massachusetts General Hospital. The sponsor has implied that the primary outcome, that there's no evidence that it's clinically meaningful and that a more appropriate clinically meaningful outcome is the subject's willingness to take the drug again.

I wonder if the FDA could comment on the primary outcome and is clinical relevance, and whether or not it agrees with the sponsor. Thank you.

DR. CHIAPPERINO: Hi. This is Dominic Chiapperino --

DR. FARCHIONE: Thank you, Dominic.

DR. CHIAPPERINO: -- for the controlled substance staff. Regarding the primary endpoint of drug liking, Emax of drug liking, we do not agree with the sponsor's interpretation of their data. I think it was very important that Dr. Farchione highlighted the issue with the validation test and the completer population in this HAP study.

All of the sponsor's reported results were using the full 37-subject population, so they talk about the primary endpoint and it being a near miss for

statistical significance. But really, the FDA analysis modified the completer population in the way that we think is more appropriate to look at the primary and secondary endpoints in the study. And when you look at that modified completer population, they did miss on the drug liking endpoint, primary endpoint.

I think our presentation does acknowledge some positive results across the study when using the adjusted completer populations, but there was no question that the primary endpoints of drug liking Emax and also the responder analysis did not meet their endpoints.

DR. JAIN: I'm clear on that point, but I'm not clear on the clinical meaningfulness of the primary endpoint.

DR. CHIAPPERINO: With respect to the 10 percent reduction?

DR. JAIN: Yes.

DR. CHIAPPERINO: So in all of these studies, we try to have an endpoint that we think would be predictive of the real-world effects. We actually do not have confirmatory evidence for many ADF products

that have been on the market. We certainly don't have any results for a stimulant because there are no stimulant ADF products on the market. So all of protocol design features, including the 10 percent reduction endpoint, are intended to be predictive of real-world abuse.

We don't think a 10 percent margin is actually a very large margin to beat, but it is reasonable to set an endpoint such as 10 percent reduction, and even doing so with a relatively low margin, the study did not show statistical significance for that endpoint.

DR. JAIN: Thank you.

DR. NARENDRAN: Next question is Dr. McGough.

DR. McGOUGH: Thanks. Jim McGough, UCLA. I understand Arbor's data to show that the compound is not practically manipulatable and extractable, and it is not syringeable, but the FDA study seems to come to a different conclusion. I'm not sure if there's some magic in the FDA labs or what reason.

I would like to ask the FDA, can you provide any explanation as to why you found in contrast to the Arbor data that you could actually extract it and you

could administer an abusable dose of the medicine? Do you have any explanation as to why their studies are coming out one way and you were able to find something different?

DR. PONTA: Hi. This is Andrei Ponta, interim product reviewer. I guess there are a couple of things to note here. The data presented in the presentation was actually the sponsor's data. So when we say that 50 percent of the drug product was able to be syringeable with Condition 8, that was data that was provided by the applicant, and I don't think we disagree on that.

Where there might be some disagreement was the difficulty of the extraction and the condition, and we do not agree that the conditions to extract an injectable dose was only achievable in a laboratory. We think that this can be done in the home setting. Our laboratory also tried different ways to do the extraction syringeability studies, and they did find that there were other ways that the applicant did not attempt, and they were able to get, for example, amphetamine from multiple capsules.

I did want to mention that these studies are done with common household solvents and using common household tools. Again, these are not things that need a laboratory to be accomplished for the extractability.

DR. McGOUGH: So basically, FDA employed somewhat a different method and they were able to get a different result.

DR. PONTA: The method variation was slight, as they were still using the same tools, so there were no new tools used by the FDA. So the same tools, the same type of treatments, and a slight variation to those. The laboratory did try -- like I said, a slight variation to those, and they were able to get a different amount extracted.

There were also differences in the particle size reduction that we saw. So again, the applicant stated that no common household tool could get AR19 to a snortable form. Again, we do not agree with that assertion. Multiple tools were able to reduce AR19 capsule content to a size amenable to insufflation. Two tools reduced close to 50 percent of the drug product to a size of less than 500 microns. This

required no pretreatment and only a short preparation time.

Additionally, that one tool reduced 76 percent of the drug product to a size of less than 500 microns. This is what the applicant refers to as Tool 7. We disagree with the applicant's statement that this toolkit had to be created. This is, again, another common household tool. We do not consider this a complex tool that's found in the laboratory. This tool was modified by the applicant, but this modification can be done in almost any household, and it was performed with something that is readily available.

DR. McGOUGH: Okay. Thank you.

DR. NARENDRAN: Next question, Dr. Jeffrey. We have a lot of questions, so if you guys can be very focused again in questions and answers.

Dr. Jeffrey?

(No response.)

DR. JEFFREY: Sorry. No questions. Dr. McGough asked a question similar to what I was going to ask. Thank you.

DR. NARENDRAN: Thank you, Dr. Jeffrey. I

appreciate that.

Next question, Ms. Witczak?

MS. WITCZAK: Yes. Kim Witczak. As somebody who has spent their career in marketing and the power of words, I'm curious what you think of the sponsor's term using "manipulation resistant" as opposed to "abuse deterrent." I'd just be curious if that's something -- because I could see it being a big potential marketing ability to the doctors and the public, so I'm curious what your opinions are on that.

DR. STAFFA: This is Judy Staffa from OSE. We see that that's certainly a suggestion, and as we had mentioned at the meeting about a month ago, we had quite a lot of input on the use of what kind of terminology we should be using, and we heard a lot of folks concerned about the use of the term "abuse deterrent" and how confusing it can be, and we are actively discussing that. So I think this is something we can clearly consider, but we have not made any decisions about that as of yet.

DR. NARENDRAN: Thank you.

Next question, Dr. Calis?

DR. CALIS: Yes. Thank you very much, and I appreciate the responses so far. My question has to do -- and I think it might have been asked earlier but not answered yet, but as it relates to commenting on the risk associated with AR19 in terms of abuse potential for manipulation as it relates to availability of a 30-milligram dosage form rather than the previously proposed 40-milligram dosage form. I'd just like to get FDA's thoughts on that.

DR. CHIAPPERINO: Hi. This is Dominic Chiapperino for the controlled substance staff. Regarding the fact that most of the category 1 through 3 studies were conducted with 40 milligram, we do not have a complete set of data for 30-milligram capsules relative to a comparator.

The sponsor did mention the ratio of excipients and active ingredient in lower strength tablets, so that would be something to consider, and maybe lower strength capsules would present challenge for manipulation, but we do not have a full set of data for lower strength tablets.

I don't know if our OPQ colleagues would like

to also comment on that question.

DR. CALIS: Thank you.

DR. PONTA: Hi. Yes. This is Andrei Ponta. What I would like to say is just a couple of different things. Between the 40 and the 30 milligram excipient-wise, they are proportional, so I think you can more or less take the data from the 40 milligram and apply it to the 30. But the applicant also performed studies with some of the lower strength, especially the particle size reduction studies, and most of the results were fairly close in line when you went down in strength.

So I think you can apply the 40-milligram data mostly to the 30 milligram as well.

DR. CALIS: Okay. Thank you.

DR. NARENDRAN: Thank you.

Next question, Dr. Thomas.

DR. THOMAS: Hi. Dr. Patrick Thomas, Baylor College of Medicine. In the FDA's presentation, there was some new, recent data about being able to get usable amounts from multiple capsules.

Can the FDA speak to where that data is and

what it looked like compared to the applicant's data related to multiple capsules? Because there was a difference in terms that they decided they couldn't get multiple capsules and what they think that difference might be.

DR. PONTA: Hi. This is Andrei Ponta again. The data, we sent out samples to our laboratory, and they were only able to finish the studies I think early this week or late last week, so we weren't able to include it in the presentation. I tried to address this a little bit earlier. There were differences in some of the ways that the study was performed for the multiple capsule studies and whether or not amphetamine could be extracted and be syringed for multiple capsules.

I guess I'm not a hundred percent sure how much I can say about this, so I'll try to stay a little bit general so there are no details on how to manipulate the product. I think the deputy labs might have a couple of tools instead of just a optimal tool that the applicant suggested, and you can use maybe a variety of different extraction volumes rather than a

constant extraction volume, as the applicant shows.

DR. THOMAS: Thank you.

DR. NARENDRAN: Thank you.

Next question, Dr. Green?

DR. GREEN: I had a question about the HAP studies and whether for the insufflation methodology, whether insufflation of liquids and a solution, for instance, the multiple capsule solution would have been considered? Therefore, how much of the safety data that is derived from the syringeability and insufflation studies can we use to inform route of administration like that?

DR. CHIAPPERINO: Hi. This is Dominic, controlled substance staff. Are you asking if it was considered whether a liquid form or a gel-like preparation from AR19 could have been used as one of the treatments in the HAP study?

DR. GREEN: Yes. I'm thinking about a common practice we see with people insufflating solutions of drugs that may be -- or medications that have abuse potential and are prepared as a solution and then sniffed, as opposed to just powder. Maybe the form of

the drug is a film for instance and that is the pathway for taking. It's made into solution and then sniffed. It strikes me that this might be a medication, and we should consider that pathway, too.

DR. CHIAPPERINO: Yes. I can't speak to what people might do with the formulation if it were out in the real-world setting, but we did consider the powdered form of AR19 to be the most ideal to use in this HAP study. We do think there is a well-established pattern in the community abusing drugs by the intranasal route of snorting a powdered form, and I think that the sponsor did you use an appropriate form for the AR19 treatment.

DR. JEFFREY: Okay. Thank you.

DR. NARENDRAN: Next question is Dr. Iyengar.

DR. IYENGAR: [Inaudible - off mic] -- or adding. Removing or including a couple of subjects changes the conclusions qualitatively. How exactly was the sample size of 37 chosen for the HAP study, and did you consider increasing it to get some more clarity?

DR. CHIAPPERINO: This is Dominic Chiapperino for controlled substance staff. HAP studies have

generally been acceptable for anywhere between 35 and 45 completers. The studies have not traditionally been larger than that. It is difficult to enroll subjects sometimes from this population, and we do think that the statistical analyses that have been done to support the powering of the study indicates that this small study population can still provide some meaningful results.

DR. IYENGAR: Thank you.

DR. NARENDRAN: Thank you.

Next question, Dr. Nelson?

DR. NELSON: It's Lewis Nelson from Rutgers. I withdraw my question. Thank you.

DR. NARENDRAN: Thank you. Appreciate that.

Next question, Dr. Griffin?

DR. GRIFFIN: This is Marie Griffin. My question was about the 30-milligram dose, and it was answered.

DR. NARENDRAN: Thank you again; much appreciated.

Next question, Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz,

brief question follow-up to the sample size that was being discussed regarding the different interpretation from the intranasal-deterrent properties. Was the problem, the size of the effect or that the p-value didn't cross the threshold after excluding the patients and having that smaller sample size?

DR. CHIAPPERINO: This is Dominic Chiapperino, controlled substance staff. It was the latter. There was not a statistically significant result even with the modified completer population.

DR. HERNANDEZ-DIAZ: But the size of the effect, if the p-value had been significant with a larger sample size, the size of the effect was considered appropriate or meaningful?

DR. CHIAPPERINO: You're asking if they had gotten a statistically significant result on the 10 percent reduction margin, would we have considered that meaningful.

DR. HERNANDEZ-DIAZ: Yes. If the size of the estimate would have been the same but the p-value had crossed the threshold, would you have considered that result meaningful?

DR. CHIAPPERINO: Well, we would have considered that they met the prespecified endpoint and, yes, we would have considered it meaningful as much as we're able to say that such a reduction in drug liking is meaningful. We still don't know how a formulation that would have that differentiation from the positive control, how that might modify abuse patterns in a real-world setting. That would be established by postmarketing studies.

DR. HERNANDEZ-DIAZ: Okay. Thank you.

DR. NARENDRAN: Thank you.

Next question is Dr. Meisel.

DR. MEISEL: Hi. I withdraw my question. Thank you.

DR. NARENDRAN: Okay, Dr. Meisel.

Another question from Dr. Dunn.

DR. W. DUNN: Walter Dunn, UCLA. This is a question for Dr. Mathew from the FDA.

Regarding your prerecorded presentation slide 9, on the last column about number of milligrams of the PEO, if my interpretation of that is correct, there's actually different limits of detection for each of

those conditions that were tested. For example, for Condition 2, it was below 3.9 milligrams, so it's possible that there was PEO excipient greater than a million dalton at 3.8 milligrams. And if that's true, the difference in the limits of detection, is that a function at all of how large the PEO excipients were present in those conditions?

LCDR MATHEW: Hi. This is Lieutenant Commander Shiny Mathew. Thank you for the question, and I agree that this is based on the analytical method, the sensitivity of the analytical method. And you're correct in saying that for number 2, we may accept that there is up to 3.8 PEO greater than 1 million dalton. At this time we don't know the various molecular weights that are present in that category, so all we can say is that it could be higher than 1 million daltons in size.

Did you need further clarification?

DR. W. DUNN: Yes, just a quick follow-up. So the difference in the limit of detection, is that a function at all of how large the excipients are present or do we not know that?

LCDR MATHEW: We don't know that, and as far as I understand, they used molecular weight standards of less than 1 million and more than 1 million, and they categorized based on that. So at this point, we don't know what exactly it is that is higher than 1 million.

DR. W. DUNN: Alright. Thank you.

DR. NARENDRAN: Thank you.

Another question from Dr. Mehta.

DR. MEHTA: Hi. Reema Mehta from Pfizer, industry representative, and a question for FDA. In terms of the data that was presented in the start of the presentation and in your prerecorded presentation comparing the sponsor's product to opioid abuse and misuse, recognizing that I think the opioid rates of abuse and misuse represent one end of the spectrum given the opioid crisis, I was curious what FDA thoughts were from the other side of the spectrum in terms of what the lower end of the thresholds would need to be around rates of abuse and misuse and whether it's in a particular modality of abuse or misuse to be demonstrative of benefiting from an ADF formulation.

DR. STAFFA: This is Judy Staffa from OSE. Can you repeat the question? I'm not sure I'm following exactly what you're asking. I know you're talking about trying to understand misuse or nonmedical use of stimulants in the context of opioids, but could you clarify what you're asking us to speak to?

DR. MEHTA: Sure, sure, and apologies if it wasn't clear. I was trying to understand -- since one of the questions that's posed to the panel is trying to understand if there is a public health benefit to having this ADF formulation for the amphetamine class, and if I understood correctly, the context that was provided by FDA was a comparison with opioids, my thought was that the comparison with opioids represents some of the most concerning end of the spectrum with respect to a public health benefit.

I was curious if on the other end of the spectrum, if FDA had certain thresholds in mind that would need to be in the data, from the standpoint of abuse and misuse, as levels that would be demonstrative of benefiting from an ADF formulation for this particular class.

DR. STAFFA: I see. Thank you very much for clarifying. I think I understand your question. This is Judy Staffa again. I think that's exactly one of the questions that we've posed for the committee to discuss, actually. Just to be clear, the sponsor followed the guidance for developing abuse-deterrent formulations of opioids because that was the only guidance available, but that's not to say that that's what the agency thinks. I think that's one of the issues that is challenging here to discuss because of the differences that you see between the epidemiology of the nonmedical use of each class of products, as well as the consequences of those.

So we don't really have a specific threshold in the opioid era, which I think is described in the guidance why we did not set thresholds, and I think that is one of the issues that makes it difficult to make policy decisions about. So I think what we are looking for this afternoon is a discussion of exactly that point. So I think I'll leave that there.

DR. NARENDRAN: Thank you.

Dr. Boudreau?

DR. BOUDREAU: Hi. Denise Boudreau. I was wondering if the agency could comment on the appropriateness and representativeness of the age of the population given the motivation for this abuse-deterrent, manipulation-resistant -- whatever you want to call it -- seems partly motivated by the higher rates of misuse and abuse in the adolescent and college population. My second part of that question is I realize the sample size is small, but whether you would expect drug liking to differ by age and if that was looked at all. Thank you.

DR. FARCHIONE: So you're asking specifically about the population that was used in the HAP study or are you asking about the potentially indicated population in an eventual label if the product was approved?

DR. BOUDREAU: Specifically about the HAP study and the representativeness of that, like what the market is for the product.

DR. FARCHIONE: In that case, I will pitch it to Dom.

DR. CHIAPPERINO: Yes. Hi. This is Dominic

Chiapperino. I don't think that the study protocol differed from typical HAP studies in the inclusion criteria with respect to age. It is true that there seems to be more manipulation going on, based on the epi data that was discussed today, in the younger age population, but we did not advise to enrich the enrolled population with respect to a particular age category, I believe it was 18 to 55, and I'm afraid I don't have an age breakdown. Maybe the sponsor would like to comment, if they would, on the actual age range of their subjects.

DR. SETNIK: Yes. The age range --

DR. SCULLIN: Sorry. Go ahead. Is that Dr. Setnik?

DR. SETNIK: Yes.

DR. SCULLIN: Okay. Thank you.

DR. SETNIK: The age range was -- it's a prespecified range -- 18 to 55. The range in the study was 18 to 50 with a mean age of 34.6. We can give a further breakdown of that, but those are the high level summary for the demographics.

DR. NARENDRAN: Thank you.

This is Raj Narendran. I have a question for the agency. How often does a positive control validation fail in a HAP test, in your experience? I mean, is this quite often in stimulants, opioids, and other substances that are tested in these HAP tests?

DR. CHIAPPERINO: This is Dominic Chiapperino. Yes, that's a very good question. The validation tests generally do not fail very frequently. It happens occasionally. There may be some differences with respect to drug class, and sometimes some of the drugs under investigation do not have quite the reinforcing effects as other classes of drugs. I think opioid HAP studies tend to validate more easily than some other classes of drugs.

This is the first NDA for an ADF stimulant, and most of these drugs have been scheduled long ago. They are sometimes used as positive comparators for new molecular entity stimulants, and they do not tend to fail validation tests, generally.

DR. NARENDRAN: Thank you.

I think the only person I have on my list -- I'm not sure.

Dr. Dunn, do you have a question? And I think that would be the last question if you do.

DR. W. DUNN: Oh, sorry. I forgot to put my hand down.

DR. NARENDRAN: Okay. So I think we could -- I'm sorry. Does Dr. Calis have a question?

Dr. Calis?

DR. CALIS: No. I'm sorry. I probably should adjust my hand raise. I'm sorry.

DR. NARENDRAN: Okay. I'm only 7 minutes over time, so I think we can now break for lunch. I want to thank the agency and the sponsor for answering and clarifying our questions. We can reconvene in one hour at 1 o'clock.

Panel members, please remember that there should not be any chatting or discussion of the meeting topics with other panel members during the lunch break. Additionally, you should plan to rejoin at around 12:45 p.m. to ensure that you're connected before we reconvene at 1 o'clock so we can get the OPH session started on time. Thank you.

Any other things, Latoya? Dr. Bonner, any

closing comments before lunch?

DR. BONNER: Nothing for me. Thank you, sir.

DR. NARENDRAN: Okay. We can now break for lunch. Thank you.

(Whereupon, at 12:08 p.m., a lunch recess was taken.)

A F T E R N O O N S E S S I O N

(1:02 p.m.)

Open Public Hearing

DR. NARENDRAN: We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of expenses in connection with your participation in the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose

not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, your audio is connected now. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record.

MR. CATTOI: My name is Robert Cattoi. I'm representing CHADD, Children and Adults with Attention-Deficit/Hyperactivity Disorder. We

appreciate the opportunity to comment on the development and evaluation of abuse-deterrent formulations of central nervous system stimulants. Founded in 1987, CHADD is a national nonprofit dedicated to the mission of improving the lives of people with ADHD. As home of the CDC-funded National Resource Center on ADHD, CHADD is the trusted source for evidence-based information in attention deficit hyperactivity disorder.

An estimated 4.4 percent of U.S. adults meet the criteria for ADHD in the U.S. based on clinical interview. ADHD is estimated to affect nearly 10.5 million adults in the U.S. While ADHD is recognized as a neurobiological condition that causes significant impairment, it's important that ADHD must be viewed as not just a mental health disorder that is a specific domain of mental health and special education, but as a public health problem, producing a substantial impact on the health quality of life and economic viability of the U.S. population.

Research shows that individuals with untreated ADHD are at a greater risk than unaffected individuals

for eating disorders; obesity; diabetes; sleep disorders; dental issues; substance-use disorder, including smoking; unemployment; academic underachievement; accidental injury; teenage pregnancy; sexually transmitted diseases; depression, suicide; and premature death.

The economic cost of ADHD in the United States ranged from 143 to $266 billion annually. This makes ADHD a far too costly disorder to continue to be undertreated or even ignored not just in mental health settings, but especially by primary care, government public health programs, third-party payers, particularly among adults.

Fortunately, ADHD is a condition for which we have viable treatments. The multimodal treatment approach using medication and behavioral therapy has been shown to reduce symptoms of impulsivity, inattention, and hyperactivity. Treatment allows individuals to focus, work, and to learn. Stimulant medications are generally the first-line treatment for ADHD because they're highly effective at reducing symptoms. Although highly effective, problems of

nonmedical misuse and abuse of prescription stimulants among adolescents, college students, and adults has become evident.

Estimates of nonmedical use of stimulant medications vary widely, depending on the definitions in different studies. The population-based estimates of the National Survey on Drug Use and Health reported that approximately 5 million adults had engaged in nonmedical use of stimulant medication at least once in the last year. This nonmedical use places a substantial burden on healthcare facility use. Data from 2005-2010 show an increase between 67 to 156 percent in the number of emergency room visits for nonmedical use of stimulant medications.

CHADD applauds any steps that reduce misuse and abuse of these medications without impeding access and affordability for those who require different treatment. We recognize the development of abuse-deterrent formulations of stimulant medications provide a means, albeit limited, of reducing abuse. Research suggests that between 550,000 and 2 million U.S. adults snort stimulant medications each year, and between

50,000 and 550,000 don't smoke or inject stimulant medications each year.

Data from poison control centers revealed that the odds of dying from nonmedical use of stimulants is 13 times greater for nasal abusers and 22 times greater for intravenous abusers than for oral abusers. While ADFs may help reduce abuse to snorting, smoking, or injection, it's important to recognize the majority of abuse of stimulant medications is due to an oral route, which will not be deterred by ADF. But given that 38 to 40 percent of stimulant misusers are doing so via intranasal and intravenous use, we support the development of a stimulant that has abuse-deterrent physical features. This would be a very helpful addition to the repertoire of ADHD medications prescribed to high school and college students, those at the highest risk for abuse.

It's CHADD's position that all individuals with diagnosed ADHD should have access to the full range of safe and effective prescription medications indicated to treat ADHD. In light of rampant misconceptions about ADHD treatment, the statements

around the disorder, and other external pressures, individuals with ADHD often face significant barriers to accessing prescribed medication.

We respectfully urge the FDA to consider these systemic burdens on the ADHD population. Any steps to reduce stimulant abuse must not be taken at the expense of ADHD patients' access to required medical treatment. Individuals with ADHD often experience great hardship with timely and affordable access to prescribed medications. It's imperative that the FDA's actions to reduce stimulant abuse, including approval of abuse-deterrent formulations of prescription stimulants, not exacerbate current coverage and access hardships. Thank you for allowing us to comment on this issue.

DR. NARENDRAN: Thank you. Speaker number 2, please step up to the podium.

MS. SEYMOUR: Hi. My name is Kristin Seymour. I'm an advanced practice nurse and I have no financial disclosures with any parties involved in this testimony. I appreciate the opportunity to share my experience as an ADHD patient and as an ADHD coach.

I'm an advanced practice registered nurse in a

large tertiary hospital, and I've practiced in cardiovascular nursing consistently since 1995. I currently also have a side practice, robust side practice, coaching ADHD teens across the globe since 2016. I have lived with ADHD since childhood, which went long undiagnosed until 1991, at age 19 when I was evaluated and diagnosed by a neurologist. I was treated with stimulant medication, which drastically changed my life for the better.

The goal of all healthcare practitioners is to ultimately treat patients and reduce the risk of harm. To date, there is not a manipulation-resistant ADHD formulation or medication available to providers. Prescribers and clinicians must weigh all actual and potential risks and benefits when implementing stimulant medication therapy. Further, clinicians must consider the family members and friends around that patient who also may have access to the stimulant medication.

Teens today can easily access and misuse drugs faster than they can have a pizza delivered. Social media, such as Snapchat, Instagram, Facebook, and

Twitter, are all sources of how teens access and share medication. Parents are often unaware their team may be involved in selling, abusing, or sharing their stimulant medication, as the teens exchange the stimulant for food delivery apps to home or school. This way, there's no cash supply to trace.

Stimulant misuse and abuse is definitely present in our communities and we need to take action. There has never been a medication that is as difficult to manipulate or abuse before the inception of AR19.

Many teens perceive stimulant medication prescribed by a, quote, "physician" and person their mother took them to see, and that the stimulant was given by a trusted parent, as safe. Therefore, the patient will share the stimulant to, quote, "help a friend" with a test or concentration, or rather that teen likes how the medication makes them feel, so they take more of it, not as prescribed. This is particularly true with impulsive ADHD teens.

For the younger population we are talking about today, their brain is not developed enough to know how to handle medication. Even if prescribed, the

medication is perceived as safe because it's a prescription and one their parent administered to them. Two trusted sources, parents and physicians are involved in the administration of the medication, so minors feel it's not something that can hurt them.

Teens base risk on someone they know having a bad outcome. Mortality is based on what they witnessed to be a risk. Countless patients age 12 to 20 years old have confided in me that they have been solicited to give or sell their stimulant medication to a friend for various reasons. Most teens who admitted this in sharing, practice, or being solicited to misuse stimulants are so they can stay up longer, party harder, drink more, or recover faster the next morning from a late night.

This medication, if approved, would reduce the risk of harm for most of the kids we're discussing today because they can't break it down easily to abuse, misuse, or share for a high. The effort someone would have to pursue in order to get this medication to a state of abuse and danger is beyond the ability of the young people and teens we are discussing today, those

of whom this medication would be prescribed and benefit from. They are not a sophisticated user, and this is an important and needed first step. Thank you for your time and consideration.

DR. NARENDRAN: Thank you.

Speaker number 3?

DR. COTTLER: Hi. I'm Linda Cottler. I'm associate dean for research, dean professor, and former founding chair of the Department of Epidemiology at the University of Florida. I have conducted every aspect of research, starting as research coordinator, and I've been funded as principal investigator by the National Institute on Drug Abuse continuously since 1989, and been funded by other NIH Institute foundations and agencies. I'm a psychiatric epidemiologist and my work has involved primary data collection with people 4 to 96 years of age. Most of my research has focused on community dwelling populations.

Today, I offer comments based on my team's research on the critical need for a manipulation-resistant ADHD formula for youth. The preteen age is critical and often overlooked in

studies, as are details on the patterns of use and diversion. My comments are based on findings of two multi-city cross-sectional studies focused on prescription stimulant misuse among youth. The first was funded by Pinney Associates, the second by Arbor Pharmaceuticals. Neither had a role in the conduct of the study or the reporting of the findings.

The National Monitoring of Adolescent Prescription Stimulants study, N-MAPSS, was conducted from 2008 to 2011 across 10 U.S. urban, rural, and suburban cities. 11,048 youth, 10 to 18 years of age were included. 14.8 percent of youth reported using prescription stimulants in their lifetime. Past 30-day use was 6.6 percent with 17 percent reporting any non-oral use; 96 percent was by snorting or sniffing, a result of manipulation.

Non-oral users overwhelmingly got their pills from peers or at school and were over 24 times as likely to say they used to get high and 13 times as likely to report history of illicit drug use than medical users. Sixty-three percent of youth reported that prescription stimulant use was a moderate to large

problem among youth.

N-MAPSS' youth were asked at the end of the interview, "If you ran the world, how would you stop kids from taking other people's prescription medicines?" A large proportion of youth mentioned creative ways to stop misuse, showing that even the 10- to 12-year-old group understands the need to reduce the ability to misuse.

Next, the Study of Non-Oral Administration of Prescription Stimulants, SNAPS, was conducted in fall 2018 across 6 cities in California, Texas, and Florida. SNAPS included 1777 youth, 10 to 17 years of age. Eleven percent reported prescription stimulant use in their lifetime and past 30-day use was reported by 7 and a half percent. Among those users, 20 percent reported non-oral use with 88 percent reporting snorting, sniffing, injecting, or smoking. Both past 30-day and non-oral use rates were higher here than in N-MAPSS.

Diversion was high. 11.4 percent in N-MAPSS was the most common pattern involving buying or getting a stimulant from someone else. In SNAPS, 12.7 percent

diverted with the least common pattern involving buying or getting them. More youth sold or gave away their pills. Among non-oral users, the rate of diversion increased to 70 percent versus 37 percent of oral-only users and 9 percent of non-using youth.

Manipulation-resistant formulations like AR19 are just one strategy in an overall public health harm-reduction approach for non-oral use. This new formulation would minimize tampering so that youth could not snort, sniff, smoke, or inject these stimulant pills. Manipulation-resistant ADHD medication is not currently available, but we have seen from N-MAPSS, and more recently in SNAPS, that it is needed.

We need to reduce the risk of non-oral use, especially now during the current COVID pandemic when youth are bored, impulsive, and seeking recreational activities, and when the FDA could be in the spotlight for not doing all that it could to reduce the harm associated with these controlled substances. Thank you.

DR. NARENDRAN: Thank you.

Speaker number 4?

MR. BORGSCHULTE: My name is Luke Borgschulte. I'm 29 years old and I have no financial disclosures. I was first diagnosed with ADHD in 2014 after my fourth year in college. I wish I had been diagnosed earlier in life, as it could have helped me understand what I was going through and to get the treatment that was right for me. Instead, I turned to friends, acquaintances, and really anyone who could help get ADHD drugs that would help me to deal with the things I was experiencing, and it was easy.

These ADHD drugs are really available from doctors, parents, medicine cabinets, and even kids who needed the meds would sell them for a fast buck. After experimenting with these drugs orally, I was introduced by a friend to snorting them and injecting stimulants to get a bigger and a faster rush. Other kids in college were using them like this, too, at crunch times to get through finals, to party at tailgates longer, and recover to study again.

I don't think about the risk of snorting these stimulants when I was doing it because no one I knew

had anything bad happen to them. That's the way kids in college think. They just aren't intimidated by the risk involved in snorting drugs because most of us never experienced someone overdosing, or dying, and getting sick is sort of just brushed aside as kind of expected, like being hungover after a night of drinking.

I believe this is a problem in most colleges because of what kids saw and learned before they came to campus. The internet highlights some of these stupid behaviors by broadcasting videos of them on Facebook, Instagram, Snapchat, and most kids get a laugh by watching them. It's not taken seriously.

I think a manipulation-resistant stimulant, like the one you are looking at today, could help a lot of kids avoid the slippery slope that comes with snorting or injecting these medications. These kids don't know any better, but you do. You can make a decision today that would help a lot of kids reduce the risk of snorting it or injecting these drugs.

Thank you guys very much. I appreciate it. You have a great day.

DR. NARENDRAN: Thank you.

Speaker number 5?

DR. CHILDRESS: Thank you for the opportunity to speak today. I am Dr. Ann Childress, child adolescent and adult psychiatrist practicing in Nevada. Treatment of ADHD is my area of expertise. I've been in practice for 28 years and conduct pharmaceutical trials for ADHD and follow the subjects after they complete clinical trials.

I've worked with most of the FDA-approved medications in clinical trials and have treated thousands of patients with ADHD. As disclosures, I have been paid as a researcher, consultant, and advisor by most of the companies with branded ADHD products on the market, including Arbor for work with Evekeo and AR19.

Some of the patients I've treated I continue to treat for more than 20 years. Many of these kids began treatment before age 8, so I continue to see them as teenagers and adults. Today, I am speaking on behalf of my patients and their peers in support of the abuse-deterrent amphetamine formulation AR19, and I am

not receiving any compensation for my testimony today.

Most of my patients are treated with stimulants, including amphetamines, because we know the data show stimulants are more effective than other medications for the treatment of ADHD. I try to avoid prescribing immediate-release stimulants whenever possible for a number of reasons. One, I prefer to treat patients with extended-release medications, however, many need a shorter-acting or a booster dose because the extended-release medications often do not provide all-day efficacy for their particular situation.

Some of my college student patients have classes both early in the day and in the evening, and their symptoms can't be managed with just one extended-release medication. Other patients work full-time and attend school in the evening. Some of my high school students have jobs that they have to drive to after school.

However, whenever I write a prescription for an immediate-release stimulant, especially an amphetamine, for adolescents and young adults, I do

with a great deal of forethought and some trepidation. I discuss proper use and misuse with my patients and tell them that sharing their medication with another person is a felony.

The conversation starts with my early adolescent patients. When treating my patients who are about to leave for college, I advise them to lock up their medications and not let classmates know that they're taking medicine for ADHD. I tell them I won't fill prescriptions early no matter what the excuse, however, I know that my counsel may not prevent patients from sharing their medication.

I'm familiar with the literature for nonmedical use and know that misuse and abuse of stimulants is a significant concern with college students and young adults. In that comprehensive meta-analysis, Benson, et al. found that students misuse stimulants primarily for academic reasons, and the most common source for obtaining stimulant medication is from peers with prescription.

I also have concerns about the route of ingestion. In a survey by White, et al., more than

16 percent of students at the University of New Hampshire reported nonmedical use of stimulants and almost half reported misusing or abusing at least 2 or 3 times a month or more. For more than 40 percent, the preferred method of misusing was snorting, and that's why it's so important for me to educate my patients. My patients have had a thorough medical history, and weight and blood pressure and pulse are checked at every visit. Individuals who misuse the medications may not have been evaluated medically and are at increased risk for adverse cardiac effects.

I don't know how often my patients attempt to divert or misuse stimulant medication because I don't find out unless they're caught. One patient with ADHD recently was expelled from high school after giving some of her immediate-release methylphenidate to a friend. I had another teen with ADHD who was on a non-stimulant, who wound up in the emergency room with dystonic reactions after snorting his little brother's immediate-release methylphenidate. Now I advise parents to lock up all the medications in the home and to always supervise dosing.

So if nonmedical use is occurring with my patients, and I'm careful, I worry what is happening with most of my colleagues who don't have the time to educate their patients. I urge the committee to support the approval of AR19 to help deter nonmedical stimulant use. Being able to prescribe an amphetamine formulation that will deter non-oral routes of administration will give me peace of mind when I'm treating my teens and young adults, and it may save someone else's life. Thank you very much.

DR. NARENDRAN: Thank you.

Speaker number 6?

MS. BUCKNER: Thank you for the opportunity to speak with you today. My name is Julie Buckner and I am not receiving any compensation for the testimony. I am here because six years ago, I received the most horrific news that any parent could hear, that my 22-year-old son, Josh Levine, died from acute alcohol intoxication, which was exacerbated by having started an ADHD stimulant that had not been prescribed to him.

Josh was not an addict or an alcoholic. He was a promising young man who had just graduated from

the University of Michigan, where he was a full-time student and the student manager of the football team. He was a loving son and kind of a mama's boy, whose last words to me the day before he died were, "I love you too, Mom."

I was aware of the misuse of stimulants as a study aid, but I was completely ignorant of the misuse of snorted stimulants with alcohol as a party drug until after his death. It wasn't until the coroner called me with questions regarding whether or not he had ADHD because of the presence of stimulants in his system that I began to learn of this practice among college students and others.

On college campuses and elsewhere, stimulants have been co-ingested with alcohol for the purpose of being able to drink more without falling asleep or passing out since the stimulant keeps one awake. With that, the stimulant also lessens the visible effects of the alcohol, so the person can keep drinking without feeling as drunk as what the alcohol is processing within the body.

It's common on a college football Saturday for

students to snort an ADHD stimulant to be able to drink excessively and still be awake for the game and beyond. They have no idea of the serious repercussions that can happen from hospitalization to death. Because these drugs are sold or shared by students who have a proper prescription, people without a prescription think it's a risk-free drug to use recreationally with no thought of dangers.

So in Josh's case, he kept drinking without realizing his blood alcohol was rising dramatically, until he collapsed on the sidewalk as he was walking to his apartment, only to be resuscitated and declared brain dead at the hospital. The person who supplied the stimulant at the private party he attended was a college friend, not a stranger. The medication was prescribed not from the black market. By all accounts of speaking with his friends, this was not a behavior in which he regularly engaged.

Since Josh died, I founded the Joshua Levine Foundation to raise awareness of the dangers of co-ingesting stimulants with alcohol, along with the perils of binge drinking, by speaking with high school

and college students as well as others. Arbor Pharmaceuticals is aware of this problem, and that is why they have been working on AR19. I definitely believe that a manipulation-resistant stimulant to treat ADHD could help prevent tragedies like I've experienced.

Many high school and college students would not go to the black market; they would simply rely on friends to share or sell their prescribed ADHD meds. If there are more manipulation-resistant ADHD meds on the market, it could help prevent this practice, which would help prevent near-fatal and fatal events like the ones that my family has experienced. I wholeheartedly support the approval of AR19, and I thank you so much for your time.

DR. NARENDRAN: Thank you.

Speaker number 7?

DR. GREENBERG: This is Dr. Doris Greenberg, and I thank you for letting me speak today. I have been asked to be an advisor for Arbor recently for a panel to discuss drug misuse. I've been a doctor for a long time, 55 years, and a developmental pediatrician

for 50 years, and actually I care for ADHD patients from childhood through adult years because of the difficulty finding adult physicians who would like to take on ADHD adults.

Stimulant medications have had a wonderful effect in treating these patients, and when used appropriately under medical supervision, they have really improved the lives of countless patients, so much so that I have over 250 grand-patients whose parents were my patients years ago with the same. Unfortunately, some of the medications, especially the short-acting forms of amphetamines, and less often the methylphenidate, have been misused, especially in the nasal respiratory or IV route. This happens mostly in college students and young adults and older adolescents.

Over the years, there's been a "don't ask/don't tell" culture amongst teens and young adults about the misuse of stimulant medications. Teens and college students rarely bring this up in my office. Physicians have not been made aware of the dangerous intranasal, injected, or smoked stimulants until

recently when surveys were taken and published, showing that this is an extraordinary danger.

When asked directly about their use in the office, in the presence of their parents, I've heard how common it is, for college students especially, to have been approached to sell or give their legitimately prescribed short-acting amphetamine to study or party so that they could drink more. But most of the time, it's not forthcoming, and the parents look at me as if to say, "Why are you asking my son about this?" Unfortunately, the non-oral use, as you have just heard, can be fatal, especially when mixed with other drugs or alcohol. Street-wise young people have experimented with many ways to use these stimulants non-orally.

We counsel our patients regularly to prevent misuse of their prescribed medications, but parents are still very naive about the street use of the stimulant medications and they think this just doesn't happen in their home. We role play what would they say if someone approaches them to divert their medicine. Intranasal, smoking, or IV use has made the legitimate

prescribing of these medicines more difficult, as we worry that we could cause serious harm.

It is hard to believe that up to 40 percent of college students have experienced such situations, and the most abused prescription stimulation medicine is Adderall in a short-acting form, the mixed amphetamine salts. The extended-release formulations have been helpful in reducing misuse, however, longer acting extended-release medicines, even generic, have become prohibitively expensive and are frequently denied by insurance plans. As a result, more short-acting forms are being used for economic reasons.

Young adults don't have 12-hour days. They need short-acting doses of their medications in the evenings for driving, for work, or for study. Long-acting medicines used during the day simply do not last into the late evening. Adderall or other short-acting amphetamines are more likely to be misused by adolescents than adults. A formulation that is resistant to manipulation for non-oral use would be a great way to reduce dangerous snorting or IV use.

Those of us who see ADHD treated adequately

with stimulants can attest to the great improvement in quality of life of those treated. They drive better, they stay in school longer, they stay out of the criminal justice system, and they become much more productive adults. They have a much lower incidence of lifetime substance-use disorders. Please help us to prevent dangerous misuse to allow the patients who really need their medications to overcome their ADHD difficulties with appropriate and cost-effective treatment. I thank you.

DR. NARENDRAN: Thank you.

Speaker number 8?

DR. WOLFE: Can you hear me?

This is Sidney Wolfe. I am the physician from the Public Citizen's Health Research Group. I have no financial conflicts of interest. Next slide, please.

The purpose of this slide is to show that ADF opioid prescriptions are a tiny fraction, 1.8 percent as of last year, only 2.7 million out of 154 million prescriptions, and recently, after 10 years on the market, there is no meaningful evidence that there's a reduced overall abuse.

Next slide, and then the one after that also. One more slide to summarize what's on the previous one. Yes.

This is from the recently released 2019 data from NSDUH, and we're looking at comparison in 18 to 25 year olds, the group that everyone has agreed is certainly a major target of prescription stimulant misuse. What you can see is that between 2017 and 2019, there were large statistically significant decreases in misuse of not only stimulant misuses but also opioid misuses. Again, there is no opioid- or stimulant-deterrent product that really has been shown to have an effect. This is due to other kinds of things such as the things that some of the previous speakers have described.

The next slide is the FDA summary verbatim. You've heard this a bunch of times, but I think it gets to the point. What you've been hearing is that there is manipulation resistance, and that certainly would be, if it were true, something to be hoped for, but it doesn't look like it's true. In vitro manipulation studies demonstrated that it is feasible to obtain a

solution for injection containing a reinforcing dose of amphetamine under the conditions reported by the applicant, and the intranasal human abuse potential study does not provide convincing evidence that the formulation AR19 has significant abuse-deterrent effects as compared to amphetamine sulfate when administered by the intranasal route.

So this is really the discussion that's going to happen in an hour or so and some of the questions, and I just want to review what we have seen and, in a sense, some of the things we've just heard. The only way the committee could vote, based on the evidence, that the benefits outweigh the risks is to disregard FDA's conclusion that AR19 is not expected to reduce injection and intranasal abuse.

The second one really is an issue of whether there would be, if it were approved, a dangerously false sense of security. I think what we've heard from some of these people who are sincerely involved in taking care of patients, in some cases doing studies, is they seem to equate manipulation resistance with what this product would deliver even though their

evidence is not very good.

The situation is painfully reminiscent of the Opana ER tragedy in which a reformulated version of Opana ER was approved in 2011, but eventually a ban was purported to have physical chemical properties expected by the company to deter abuse by intranasal and intravenous routes.

This new version was shown too late and caused serious injection harms, hepatitis and HIV, in many people despite the pre-approval in vitro evidence, similar to what you've seen today; that it can still be redacted, the detail of the method, cut, and become readily abusable by ingestion and intravenous injection, and even possibly still by insufflation. So you had evidence before this, and yet it was approved. What happened?

The major difference between what we're looking at today and Opana ER really has to do with a couple things; one, the National Academies report that came out showing that there was not a sufficient focus by the FDA on public health. There was supposed to be an advisory committee on this drug, Opana ER, and it

was canceled -- I was actually on the Drug Abuse Advisory Committee at that time -- because in the words of the head of this part of the FDA, "There were no unusual concerns regarding efficacy or safety of a reformulated opioid."

Your committees have seen the evidence and will hopefully provide support for the analyses the FDA has provided. I'm sure that if you had seen the data back then, Opana ER would never have been approved. Thank you very much.

DR. NARENDRAN: Thank you.

Speaker number 8? I'm sorry. Speaker number 9?

DR. ANTSHEL: Hi. I'm speaker number 9. My name is Kevin Antshel, and I'm a professor of psychology and the director of the clinical psychology doctoral program at Syracuse University. For the past 25 years, I've been actively involved in ADHD clinical practice and research. More recently, I have focused my clinical and research activities on college students with ADHD. I am not receiving any compensation for my testimony today.

There are nearly 20 million college students in the United States and roughly 16 percent of college students report engaging in nonmedical use of stimulant medication. This equates to over 3 million college students engaging in nonmedical use. The most troubling to me as a clinician is that the nonmedical use of stimulant medication occurs more frequently in college students with ADHD.

In addition to the sheer volume of nonmedical users, both with and without ADHD, nearly all of the research on nonmedical use of stimulant medication has found that nonmedical use is associated with lower academic performance and worse academic outcomes. Thus in this case, college students' perceptions of ADHD stimulant medications clearly do not match the reality associated with these outcomes.

Research, as well as my own personal experience, indicates that college students see little potential risk, yet high potential benefit to engaging in nonmedical use. College students often engage in what has been termed "compare and contrast." College students compare and contrast ADHD stimulants with,

quote, "party drugs," end quote, such as cocaine, methamphetamine, and Ecstasy. The college students create an artificial dichotomy in their own minds between the good prescription stimulants and these bad illicit substances.

Stimulants are also viewed as coming from the medical establishment and having no internal or physical side effects. This unfortunately is contrasted with the well-publicized negative side effects of street narcotics such as brain damage, addiction, death, crime, et cetera.

College students also believe that they are engaging in nonmedical stimulant use for the, quote, "right reasons," end quote. For example, stimulants are being taken to promote a positive outcome, i.e., to get better grades and not negative outcomes, i.e., to get high. This serves to only reinforce and strengthen this good versus bad dichotomy that college students have.

Nonmedical use of stimulants is perceived by college students as having no external or societal side effects. Quote, "It helps me and hurts no one," end

quote. College students also view their nonmedical use as one of moderation. They are strategic about when and why they use it and engage in downward comparisons to substances such as alcohol that are used more excessively. And finally, college students frame stimulants as harmless, benign, and socially acceptable, anti-fatigue, and equal to socially acceptable caffeine in all its forms.

For all of the above reasons, college students who engage in nonmedical use of stimulants see very little risk and much potential benefit. A sizable proportion of college students who engage in nonmedical use engage in non-oral routes. This college student non-oral route of administration subgroup is unfortunately increasing in prevalence.

Also unfortunately, many of the stimulant medications, especially the immediate-release formulations, are easily manipulated and permit non-oral routes. Nasal insufflation or snorting is a particular common non-oral route on college campuses, both with and without ADHD. Here again, the goal of these college students is the quicker onset of the

effects to obtain academic performance enhancement.

As noted above, yet bears repeating now, the accent [indiscernible] data clearly do not support that nonmedical use of stimulant medication leads to improved outcomes. In fact, the data suggests quite the opposite. More disturbing, however, is that non-oral routes of administration are associated with troubling outcomes well beyond lower GPAs. These outcomes include acute cardiac events, increased likelihood of requiring admission to a healthcare facility, increased risk for polysubstance abuse, and dependence and increased risk for death.

In conclusion, stimulant medications are efficacious and help college students to manage college and they help college students with ADHD to better manage college. However, the medications carry risk, especially in college students. College students believe that stimulants are an academic steroid associated with low risk. Unfortunately, this perception is not accurate.

I fully support efforts to develop an abuse-deterrent formulation, particularly as it applies to

non-oral abuse. In my opinion, the potential public health impact of this effort is high. Thank you for allowing my testimony today.

DR. NARENDRAN: Thank you.

Speaker number 10?

MR. EWALD: Hello. My name is Andrew Ewald, and I am not being compensated to speak today. I'm currently 22 years old. I was first diagnosed with ADHD when I was 11 years old, and I've been taking stimulants my doctor has prescribed ever since then. This medication has helped me in many ways, such as improved focus during work and school, as well as organization of my thoughts, among many others. I believe the benefits of stimulants outweigh the negatives, but I have seen with my own eyes how stimulants can be misused in high schools and especially colleges, both orally and when they're snorted.

I am sharing my story about stimulant use today because I believe many people are in need of this type of medicine, but may not receive it due to doctors being concerned about prescribing it. To understand

how they're being misused, you must understand the way kids think about stimulants.

Stimulants are part of the equation of success, especially in college. If you want to get ahead, you take a stimulant, and because no one you know has died or had a bad experience with the drug, you think it is okay to share with friends or get it from others. Sometimes to get that extra bump for an exam or term paper, you start snorting it. Snorting it is an easy and common way people will share their stimulants, especially in a party environment, so they can keep partying longer.

When stimulants are not used for studying, they are typically used to drink and party. This becomes even more dangerous because when taking a stimulant and then drinking, you feel like you can drink forever. Another reason people will snort their stimulants is so they can make the pill last longer for more intense use.

I personally knew someone who decided to snort a 30 XR Adderall before going out to the bars. That type of Adderall is in a capsule with beads, and he did

not crush the beads up before snorting them. I remember talking to him a few days later, and he mentioned how he had felt some of the beads still in his nose and how awful it felt. But again, because no one you know has gotten hurt and the pill comes in a bottle that your parents got from your doctor, what is so bad about that?

Having been lucky enough to intern for ADHD specialist, Kristin Seymour, I have been able to use my own personal experience with ADHD and stimulant drugs, as well as what I've observed with friends and others on how people treat and view ADHD and stimulants. What I've learned the most about stimulants is that people do not view them with any sort of danger. Stimulants are always seen as an advantage.

I've also seen how people start to believe they cannot get something done if they don't have a pill to pop before. If someone has a paper to write, they will casually say, "Oh, yeah. I'll pop an Addy and finish it really fast." It is treated as a superpower, not a prescribed drug. It is a dangerous game that is being played far too often.

Again, I believe stimulants can really help people with ADHD, especially in college. Having something like AR19 that could reduce the risk of kids abusing stimulants is an important step to making them safer. Thank you.

DR. NARENDRAN: Speaker number 11?

DR. SEYMOUR: I am Dr. Meg Seymour, a senior fellow at the Center. Our center analyzes scientific and medical data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

Our center strongly supports research and programs to improve the safety and appropriate use of stimulants. All drugs that the FDA considers for approval should be held to a high standard of safety and effectiveness, but the standard for drugs with a high abuse potential needs to be even higher. We all know that ADHD medications are widely misused, and we share many of the concerns expressed by FDA scientists about this application.

Since there are currently no established pathway for developing abuse-deterrent stimulants, the applicant has applied abuse-deterrent guidance for prescription opioids. However, the abuse-deterrent definition of opioids has been widely criticized since the term has been applied to opioids that are difficult to crush but not so difficult to abuse. If an ADHD drug is merely difficult to smoke or inject, it should be labeled as such, not as abuse deterrent. "Abuse deterrent" is a misleading term.

Research shows that patients, family members, and healthcare providers often misunderstand the meaning, thinking it means less addictive. FDA should not make the mistake of using such a widely misunderstood term again, especially since the approval of the stimulant as an abuse deterrent will set a precedent for approving future stimulants.

In addition to the problems with the term "abuse deterrent," the research presented does not even demonstrate that AR19 adequately deters intranasal or intravenous nonmedical use or abuse. The sample in the intranasal abuse study is strikingly small, only about

40 patients, and makes any claim of deterrence even more questionable. We agree with the FDA's scientific assessments that the drug could actually lead to an increase in nonmedical use and abuse, given the high dose per capsule. Even worse, there is no assessment of how to deter oral abuse, which is the most common method for abusing stimulants.

We also share the FDA scientists' concerns over the risk of nonmedical via IV. Talc has been shown to be contaminated with asbestos in previous research and there are also unidentified impurities present in the syringeable material. Both of these pose serious health risks to those engaging in IV nonmedical use of the drug. The applicant's claims of safety do not account for high talc exposures, from high exposure to AR19, or to accumulation from continued use.

It is past time for the FDA to retire the term "abuse deterrent" for opioids, and it could be a disaster to using it for stimulants. We respectfully urge you to listen to the concerns expressed by FDA scientists, who point out that AR19 has no properties

to mitigate the most common form of abuse. Instead, the drug should be labeled with an accurate description of its properties, not as abuse deterrent, so that patients, family members, and healthcare providers do not erroneously assume the drug is less addictive. Thank you.

DR. NARENDRAN: Thank you.

This concludes the open public hearing portion of this meeting and we will no longer take comments from the audience. The committee is expected to now turn its attention to the task at hand, however, I've been told that Arbor, the sponsor, would like an opportunity to discuss a couple of points that were raised by the agency.

So I've decided to give Arbor maybe five minutes to address these comments, and I wanted the agency to have another chance to rebut whatever these new comments are. I'm hoping that there will not be any questions on this new information.

With that, I'll turn it over to the sponsor.

DR. SCULLIN: Thank you. This is Evan Scullin at Arbor Pharmaceuticals. In a moment, I would like to

respond to FDA's introduction of new information today, but first I will ask Dr. Beatrice Setnik to provide a clarification on the prespecified statistical analyses for the human abuse potential study.

Dr. Setnik?

DR. SETNIK: Thank you. This is Beatrice Setnik. To clarify, I'm projecting a table, and I wanted to simply outline that the margins shown by the red dotted lines in this table do not reflect the mean differences. To clarify, the 10 percent margin or the 15-point margin refer to the lower confidence bounds that you see in this table.

For the placebo adjusted difference and drug liking Emax, the mean difference for AR19 relative to API is actually about 45 percent. As you can see, the prespecified analyses for Emax were very near significance, where the lower confidence bound fits at or near the margins as indicated by this red line. But the important point is that this is the first stimulant in this class, and a 15-point validation margin and a 10 percent abuse-deterrent margin are not based on data or clinical relevance as it applies to amphetamines

per se.

This is why we think we have to consider the totality of the data and the pattern of the results overall. In terms of the clinical significance, AR19 is difficult to manipulate and less rewarding overall even when optimally manipulated. Thank you.

DR. SCULLIN: Thank you, Dr. Setnik.

We would like to clarify that Arbor did not have access to the FDA presentation until it was posted two days ago for the public meeting. Once we did, Arbor sent the FDA factual corrections related to their presentation. The FDA did not address all of these. FDA only corrected the error that was one that we submitted that was not in Arbor's favor. The FDA agreed that pretreatment did not impact particle size reduction in their briefing document. Our results agree with that. However, the agency has introduced new information contrary to this. We are committed to showing the factual results.

In addition, it is very surprising that the FDA has introduced new information in this forum that is in direct conflict with the conclusions from their

briefing document and presentation without any data that the committee can examine. Their new information suggests that multiple capsule extraction is possible.

Confusion was also introduced by the FDA around the manipulation resistance of lower dose strengths, which were thoroughly evaluated in our program and submitted in our NDA. Our data showed that standard IV methods were not possible. Laboratory methods were required to achieve a low dose of IV amphetamine. Multiple capsule extraction was not possible with or without pretreatment.

We cannot comment on this new information that FDA has brought up today. We don't know what FDA did or what the relevance is to real-world use. We're happy to assist the committees to provide any clarification needed in relation to data from our program. Thank you.

DR. NARENDRAN: Thank you.

I'd like the agency to maybe take a few minutes, if you desire to address this for the committee. Thank you.

DR. FARCHIONE: I can start. This is Tiffany

Farchione. Actually, we did debate whether or not to present the new information given that we did just receive it from our labs and that it conflicted with findings presented in the briefing document. This is, obviously, new information to us as well, and it's something that we're going to have to consider in our review. But given that the results were different, we felt that it would be important to at least mention it in the presentation.

I don't think that this is something that -- I think as part of the totality of information that we are reviewing today, it's just one more piece in the very complicated picture, but we did feel that it was important to mention. And just to note that, again, it will be a review issue as we dig into those results a little bit further.

I'm not sure if maybe our chemistry team wants to comment further on that.

DR. PONTA: Hi. This is Andrei Ponta, CNC. Like Dr. Farchione just said, this is information for the applicant, but I just would like to bring the focus back to the results that are not under debate. What

the applicant showed is that without pretreatment, up to 76 percent of the AR19 product could be reduced to particles less than 500 microns using a common household tool. And again, two other tools were able to reduce close to 50 percent of the product particles less than 500 microns.

With respect to the extractability and syringeability, up to 50 percent or 20 milligrams of amphetamine sulfate was extracted from AR19 capsules after pretreatment. This is likely to hold true for the 30 milligrams strength; 50 percent or 15 milligrams of amphetamine sulfate is expected to be extracted under the same conditions. This is all data provided by the applicant, which has not been debated. I would just like to make sure that it was said.

DR. CHIAPPERINO: Hi. This is Dominic Chiapperino, CSS. I just want to ask Dr. Bansil to respond to Dr. Setnik's comment.

DR. BANSIL: This is Shalini Bansil from the controlled substance staff. I'm a medical officer. I want to respond to the relevance of the validation part of the human abuse potential study that was conducted

by the sponsor.

Validation is a key part of assessing how valuable a human abuse potential study is, and the margin of 15 that was being debated is really not a matter of debate. It was mentioned in the prespecified analysis by the sponsor. A margin of 15 points for validation is typically used in all HAP studies, whether they're abuse-deterrent studies or new molecular entities, comparing with all kinds of positive controls, and they are very focused on that margin to evaluate whether a study is valid. Thank you.

DR. DANG: Hi. This is Qianyu from biostat, also FDA. I just wanted to say that the study and the completer population failed the validation test. It is a closed testing procedure. Once you fail the validation test, you've used all your alpha, so from that point, any more analysis are all ad hoc. So in that point, the more tests on the completer population with a p-value of 0.026 are also part of the ad hoc analysis because you don't have any alpha to do more tests. Thank you.

DR. NARENDRAN: Are there any further comments from the agency?

DR. FARCHIONE: No. Thank you.

DR. NARENDRAN: Okay.

Dr. Shalini, do you have a comment?

DR. BANSIL: No, sorry. I already spoke. Thank you so much.

DR. NARENDRAN: Okay. Thank you.

DR. BONNER: Dr. Shalini, can you please lower your hand?

DR. BANSIL Yes. Sorry about that.

Questions to the Committee and Discussion

DR. NARENDRAN: So I guess we would proceed to our next section, which is we will proceed with the questions to the committee and committee discussion.

I'd like to remind the public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording, then we will open the question for discussion.

I'll read question number 1. Considering the patterns of prescription stimulant nonmedical use in the United States, please discuss the potential public health impact of prescription stimulants formulated to be abuse deterrent.

Are there any questions about the wording of the question from the panel members? Dr. McGough?

DR. McGOUGH: Yes, thank you. Jim McGough. My sense is, first of all, the proposed product does nothing for the great proportion of nonmedical use of the stimulant, which is basically oral. I think the problem of non-oral use is really in a small group of individuals who have multiple risk factors for bad outcomes or multiple risk factors at least associated with bad outcomes that go beyond their simple nasal use of the medication.

Additionally, I think, at best, I see that there's perhaps a marginal benefit with this product compared to other products. So in terms of the overall totality of the problem of stimulant nonmedical use, I see very little impact on the problem.

One other aspect that was alluded to in the

briefing documents but hasn't at all been discussed here, racemic amphetamine, which in its former life was known as benzedrine, was the first medication serendipitously found to be helpful for ADHD back in 1937, but over the ensuing decades, L-isomer was removed because it was felt that it had more cardiovascular effects than cognitive effects. So basically, dexedrine and then mixed amphetamine salt, which has a small proportion of the L-isomer, came into use.

I have no doubt that should this be approved as a manipulation-resistant compound, there will be a push to market this as the preferred IR stimulant, and all the other IR stimulants are generic, so that's a whole other issue. But I think what would happen, then, if this succeeded in gaining market share is we would be returning to a form of amphetamine that was rejected for safety reasons 70 years ago, and I think that's part of the risk-benefit equation that we haven't really considered.

So I think on the potential benefit side, I think there's, at best, a marginal effect on a very

small aspect of the problem, but on the risk side, we risk reintroducing a compound that I think the document said is now used in 0.3 percent of prescriptions, but correct me if I'm wrong on that. We have the potential, though, to making this a dominant force in the marketplace with unknown safety risks, so I don't see that this solves any problem, and it certainly doesn't meet a standard of benefit over risk.

DR. NARENDRAN: Dr. McGough, sorry, but I think we were more concerned about whether there's any questions about the question.

DR. McGOUGH: Oh, gosh. I'm sorry. Well, you heard my discussion.

(Laughter.)

DR. NARENDRAN: I think you definitely started the discussion.

DR. McGOUGH: That was all I had to say about this, so I will clam up right now. Thank you.

DR. NARENDRAN: Before we open it up for discussion, are there any questions about the question that is unclear?

I'm assuming, Dr. Meisel, you have something

about the question.

DR. MEISEL: Yes. Thanks, Rajesh.

Steve Meisel with M Health Fairview in Minneapolis. We're using the term here "abuse deterrent," but the applicant is not asking for a label of abuse deterrent; they're using the term "manipulation resistant." We talked about this a little bit earlier today.

I think it's important for us to just clarify what we mean by the phrasing of this question here. Are we really talking about something that's abuse deterrent or are we talking about something that is manipulation resistant? And if it's manipulation resistant, what's the definition of that? Because I don't think we have a -- it sounds good, but it's like a lot of the stuff you see in the supermarkets with all sorts of claims that have no scientific or standard definitions.

So I'd like for the agency, before we move into the discussion here, to help us ground in what we mean by the term "abuse deterrence" and whether we should use that synonymously with manipulation

resistance.

DR. NARENDRAN: Dr. Farchione, the agency?

DR. FARCHIONE: Yes. This is Tiffany Farchione, and I can take a first stab at that; then if Dr. Staffa wants to follow up if I miss any important points, we can do that. But essentially, we obviously have not yet reviewed or endorsed the term "manipulation resistant."

When these options were brought up during the review cycle, during development, we talked about the methods that they used to reach this proposed terminology. The agency is currently engaged in actually looking at alternative terminology that would be more precise and more understandable, but that research is ongoing.

I think that for the purposes of this discussion, we should defer comments on potential labeling language, whether it would be abuse deterrent, or manipulation resistant, or whatever, and just focus on exactly what it is that are the properties of the product itself and whether or not you can derive an insufflatable product or whether you can derive

something that can be used intravenously. The end result that we're talking about is the same, but the terminology that we're using versus what they're using may be different. It's a matter of semantics.

DR. MEISEL: Okay. Thanks.

DR. NARENDRAN: Dr. Shalini Bansil for the agency?

DR. BANSIL: Yes?

DR. FARCHIONE: You might still have your hand raised, Shalini.

DR. BANSIL: Oh, I thought I put it down. I'm sorry. Just ignore it because still I'm having problems with my computer maybe.

DR. NARENDRAN: Okay. Thank you.

DR. BANSIL: Is it down now?

(No response.)

DR. NARENDRAN: So is there any other questions from the members about the question? It sounds pretty clear that this question is mostly asking whether this is any -- considering the patterns of prescription stimulant nonmedical use in the United States, please discuss the potential public health

impact of prescription stimulants formulated to be abuse deterrent.

So we're not talking about the specific product at this point; we're just talking about whether there's any public health impact in having an abuse-deterrent formulation stimulant.

Is that correct? That's like an open question at this point, correct?

DR. STAFFA: This is Judy Staffa from FDA. Yes, I think that's the way to interpret this question. This is not specific to this product. This is the more general concept. So if you think about it as the potential public health impact of prescription stimulants formulated to deter non-oral abuse, maybe that's the way to think about that and to have that discussion.

DR. NARENDRAN: Perfect.

So I would like the panel to -- that crystallizes it nicely. So in general, is there a large public health impact in having an abuse-deterrent stimulant? I guess that clarifies my question about the question.

Any other concerns about the question? If not, then I would suggest you raise your hand, and then we could call upon people to give their thoughts one at a time.

Does anybody want to go first? Dr. Hernandez?

DR. HERNANDEZ-DIAZ: Hi. Sonia Hernandez-Diaz. I can go first. First, I agree with the applicant and the FDA on the change of a term to something like manipulation, deterrence, and so forth, so I think that's a great discussion, and I congratulate the FDA for contemplating that.

I think the company is presenting a product that does what they say, though the benefits might have been exaggerated in the presentation. But whether it is 25 to 75 percent harder to abuse via non-oral routes, I think that it will probably deter the abuse through these routes. If the point is often to get faster effects, then what would be the point of spending 20 to 60 minutes manipulating when there are other pills that are available? And I'm focusing more on the most likely size of the effects than about crossing an arbitrary p-value cutoff point with a

sample of 33 subjects.

However, a few pieces of evidence makes me think there could be limited public health impact for this formulation based on just approving this formulation alone because it has been said oral misuse is the most common route.

We were presented estimates from 6 percent to up to 20-30 percent of snorting use and little for other routes and because non-oral misuse often starts with oral misuse. If non-oral use is more difficult for this product, patients will use it orally, given their oral availability, or will get prescriptions for other amphetamines and other similar products, as we have seen for opioids if the price is lower for other products more so.

So from a public health point of view, this approach will make sense if manipulation resistance is really working very well and the only available amphetamine type.

Finally, I think that because it's going to be indicated for high-risk patients, the pills will get still to college kids for concentration and for

partying through all the regular indications. So I think to prevent the epidemic of amphetamines used and abused, as we learned from opioids, we have to start with reducing prescriptions to patients with a clear indication because it seems like a high proportion of pills end up with friends for nonmedical use, so diversion is way too common, and opioids are the same.

So yes, I think this formulation may be a step in the right direction. I think it's the last line of defense and not the first step and that plan A for regulatory agencies and public health agencies is, I think, to put the brake on the epidemic before we are dealing with one of the opioid dimensions ten years from now, acknowledging that these are not opioids, and there are many bad things about opioids.

So I think the label of all amphetamines, including this formulation, is to clearly indicate the risk of abuse and death for the patients and their parents. If, really, 45 percent of non-oral use is being -- used through the non-oral route, I mean, this is alarming. And if we really were to believe that we are close to 45 percent, maybe things will not be

mitigated without supervision.

Finally, public health officials should look at the prescribers, and some of them are around this online table -- making friends here -- and other institutions that are in the position to help for relief. We are thinking public health actions -- for example, closer supervision and education to patients and their families that do need the treatment and maybe mandatory screening at colleges around exams to incentivize the youth to improve performance -- because I think once some kids use it, it's unfair for others, and they are going to start using it because it's perceived as safe.

If we could promote this message that doping is cheating and that selling drugs is a felony that can kill a friend, as we have heard today, I think that would be more useful from a public health point of view than changing the formulation. Thank you.

DR. NARENDRAN: Thank you, Dr. Hernandez.

Dr. Baker?

DR. BAKER: Thank you, Dr. Narendran.

I think one of the things you'd expect in my

role coming from industry is to raise points that might be more broadly applicable to other parts of the industry beyond the sponsor, and one of those I think came up a couple times in the agency's briefing document. It was a concern that successfully deterring abuse might channel people to more dangerous routes such as illicit stimulants.

I think the agency was raising that more as a question than as a showstopper because at its extreme, it would mean if we had a fully manipulation-resistant product, it actually wouldn't be approvable or might have questions about its approvability because of that concern of making the public health impact worse. I doubt that that's where we are, but if that is the spirit of the committee, it would be really useful to hear that for other companies that might be thinking about trying to pursue these kinds of formulations. Thank you for the time.

DR. NARENDRAN: I'm trying to see if there's anybody else. Because there's nobody else, I'm going to fill in. I kind of would like to echo Dr. Sonia Hernandez's comments.

I'm not really sure an abuse-deterrent formulation really provides the kind of deterrent. I think the goal should be, really, to reduce the number of scripts. My concern with an abuse-deterrent formulation or providing a manipulation-resistant formulation is that the people this is going to be prescribed is going to be higher risk individuals, like people with polysubstance abuse.

Although it is a good thing that the company wanted to target it towards college kids, it may end up being prescribed to people in prisons or people with polydrug abuse. It may end up having the unintended impact that people think, oh, this is abuse deterrent or manipulation resistant; I can write it for my substance abusers who use cocaine and stuff, and then it could end up with a lot of illicit substances being mixed with it and cause more harm.

So I think it was a little bit evident with OxyContin and how it was prescribed, like widely. An abuse-deterrent formulation in itself to address a couple of routes that are not really the primary route used, of abuse or misuse, would be more concern I would

think. So I'm not really completely sold on the concept of this being very helpful.

I'm looking for raised hands. Ms. Witczak?

MS. WITCZAK: Yes. Kim Witczak, consumer rep. In theory, it sounds like a great idea to have something that would -- but I think it's going to have limited public health impact. Once again, it always seems like we're trying to solve a bigger societal problem with another medication solution. From a company point of view and going in and marketing for doctors and all of that, it seems like, sure, if you're able to sell it, maybe this would be the prescription, but at the end of the day, if there's a will, there's a way.

I still think it's not going to probably make the -- in concept, I don't think it's going to make the big dent like we were hoping it did for the opioids, and I think the same with the stimulants. It seems like most of it is on the oral, and this I don't think is really going to impact the bigger problem that we have with stimulant abuse.

DR. NARENDRAN: Dr. McGough?

DR. McGOUGH: I'm sorry. I don't think my hand was raised again. But the comments I raised before, inappropriately, are sustained. I agree. I see minimal benefit from a public health perspective and maybe some more risks.

DR. NARENDRAN: Dr. Meisel?

DR. MEISEL: Steve Meisel with Fairview, Minneapolis. I'll take a slightly counter-review. If you're thinking about the casual user, the person who for the first time doesn't know quite what they're doing, and they try to crush something up to snort it and so on, you make it a little bit harder and you might deter somebody, from that point of view, from that first experience there. So there may be some value in that really narrow population.

But if you're around other people and you're doing this, I can guarantee you, within a month of a product like this thing on the market, there will be a bajillion websites where people can go look and find out how to do this in a way that it's going to work, so it would be short-lived. But if you're one of those really casual folks and you're not around those kinds

of groups and fraternities, or whatever, it might have some impact at the margins of somebody going ahead and snorting this stuff.

DR. NARENDRAN: Thank you, Dr. Meisel.

Dr. Marshall?

DR. MARSHALL: Yes. Brandon Marshall, Brown School of Public Health. I agree with Dr. Meisel. I think of this almost as like an incident versus prevalent case issue where there may be some benefit for someone newly being prescribed this medication that might be just difficult for them to start crushing, so perhaps that prevents that progression. That's why I asked about that restriction to people newly being prescribed this medication.

But we also have this huge prevalent pool of people who are already nonmedically using these substances, so in that population there could be all sorts of adverse consequences, shifts to other illicit drugs, and switching to increased oral dosing. I guess I had a question maybe from my clinical colleagues on what some of the adverse side effects are of just consuming higher doses orally versus snorting a lower

dose.

I agree. I might see some marginal benefit in an infinite group of patients perhaps more than offset by harms in people who are currently nonmedically using these sort of prescriptions.

DR. NARENDRAN: Thank you.

Dr. Green, you're next.

DR. GREEN: Thank you. Traci Green from Brandeis. I agree with the previous two speakers, especially with considering the potential health impact of prescription stimulants and an abuse-deterrent formulation as a design intervention and as a public health pathway for preventing further harm.

One of the many lessons we've taken from the ADF guidance and the different formulations that have developed and have been approved, and many not marketed through this pathway, is really thinking about those unintended consequences. It's very hard to set side by side the prescription opioid epidemic and the prescription stimulant products and the nonmedical use epidemic that we're describing here. They're quite different. Their pathways, their initiation, their

cessation patterns, their trajectories over time, and the burden of death are completely different, and I think it may behoove us as a country to think about different guidance in these instances rather than applying one to the other.

If we could do that in a thoughtful way, and if there were some guidance from FDA in this area to perhaps take the moment to consider what are those unintended consequences and perhaps more specifically thinking about the routes of administration that changed -- smoking, snorting, and multiple-dose episodes -- things that we've learned from watching what happened with Opana, to fail to learn from these experiences is truly the tragedy.

So an emphasis perhaps on better and different guidance to help ADFs should be developed in the future for prescription stimulants that are more appropriate for stimulant medications and the stimulant problem that we've been exploring, and emphasizing perhaps also the opportunity to think about better prescribing, prescribing efforts that are focused on prescription stimulants.

We heard clinical presentations and practices from the public testimony of, really, thoughtful clinicians who've taken the time of patients who are very communicative, who think about supervision and monitoring, and talking and involving parents and families in safer use. This has been something we've learned from prescription opioids as a really important component to successfully reducing misuse and preventing overdose. This is probably the time to think about applying that to prescription stimulants as well, not just ADF design modifications.

DR. NARENDRAN: Thank you.

Dr. Boudreau, did you have a comment?

(No response.)

DR. NARENDRAN: If you don't have a comment, please --

DR. BOUDREAU: Sorry. I was muted. Denise Boudreau. I had lowered my hand just because some of what I was going to say was covered. But I just wanted to emphasize that I know the medications are quite different from opioids in many ways, but one of the impacts of the abuse-deterrent opioids, in addition to

people going to different opioids and going to illicit opioids, was also simply changing their preferred route of administration, so going from an injected and inhaled to oral route.

So while I commend the effort, and I think until there's probably changes in practice patterns and also having the market predominantly have abuse-deterrent formulations, I don't think that this will move the needle much in a public health impact way.

DR. NARENDRAN: Thank you.

Dr. Green, I think you lowered your hand, too.

Please don't forget to lower your hand if your question has been answered.

Any other -- my psychiatry colleagues who want to weigh in on this general question? Dr. Calis, I see your hand up there.

DR. CALIS: Okay. I think I just unmuted. Thank you very much. I agree with the general sentiment that we've heard so far. I think that prescription stimulant abuse is a real public health problem. It's a dilemma that we should take seriously. I think that, in this case, the method the applicant

has developed, certainly from what we've seen so far, is not foolproof, but I think the applicant should be really congratulated for trying to move the needle forward. It represents the first step in that direction where there are no other plausible options.

The difficulty here is that there are a lot of limitations in the data that's provided, and I think that unless we have something that moves the needle a little bit further and really gives us more concrete evidence that this product will do what it's stated to do, I think that we can create some misimpressions about it. I think that getting the distinction of being the first abuse-deterrent stimulant, if that were to happen, I think would give many a false sense of security, and I think that would be a potential problem that we should really consider as well.

DR. NARENDRAN: Thank you.

Dr. Thomas?

(No response.)

DR. NARENDRAN: Dr. Thomas, are you there?

(No response.)

DR. NARENDRAN: Well, I'll move to

Dr. Zibbell, and then I'll come back to Dr. Thomas.

Dr. Zibbell?

DR. ZIBBELL: Hey. Thanks, everybody. I'll keep this short. I'm Jon Zibbell, RTI International, Emory University. I wanted to just briefly talk about the injection-related harm and some of the concerns I have. I do agree that it just seems there will be just a marginal effect given the smaller number of the population that's actually injecting stimulants. I think we still don't know the relationship between iatrogenic use and transitioning to more illicit forms.

One of the things that does give me concern is that it seems that you are able to manipulate the products, to insufflate them and inject them, albeit with different types of manipulations and different difficulties. One of the things that concerns me in the report was that some of the tools that were used to manipulate and get into a solution, that larger syringes were actually needed in order to inject this.

This is the same thing we saw with Opana, that the hydroxyethyl cellulose for the extended-release excipient caused the medication to gel, and how folks

overrode the gelling is they just added more water to it. So they made a bigger solution, but the problem was those bigger solutions needed bigger syringes, so bigger solutions mean they can be shared.

Bill Zule at RTI has shown that larger syringes, when they're shared, hold more of what's called dead space, where the needle attaches to the hub of the syringe and more liquid is left over there post-injection. So my fear is that people will figure out how to inject these, and using in a larger syringe, as we know, is a risk for HIV and hepatitis, so that really gave me a pause.

The second thing that gave me pause is the congealing of the substance. You can heat it up under high temperature, get it in a solution and pull it into the syringe, and then it congeals, so you can't push it out. There's evidence from the UK in the early 2000s where there was some prescription opioids that had a kind of congealing mechanism, and it really caused a lot of vein damage, where once you pull that in the syringe and it's heated, people are going to try to get it out of there before it cools or before it congeals,

or they inject it and it congeals when it's already in you. Of course that wouldn't be like a thrombosis with clots or anything but more of a vasculitis and other vein-related damage.

So both the congealing once it's already in the syringe gives me really great pause for injection-related harm, and then the larger syringes being used in order to inject the material also gave me harm with the evidence that that is related to HIV and hepatitis transmission. That's just the injection route, but I just wanted to offer those two because those are two potential public health impacts that we did not see with Opana, and that did happen with Opana, albeit there were other factors involved in that as well. Thank you.

DR. NARENDRAN: Thank you.

Dr. Calis?

DR. CALIS: Hi. Sorry. I just kept my hand raised. I apologize. I'll change it now.

DR. NARENDRAN: Thank you.

Dr. Nelson?

DR. NELSON: Thank you. Lewis Nelson from

Rutgers New Jersey Medical School. I just want to reiterate what I brought up earlier. This might be a different discussion if we were having an advisory committee to evaluate the first ADH med or the first amphetamine that we were going to be discussing to release on the market and the benefit of making that formulation abuse deterrent to tamper resistant or whatever we'd like to call it. But at this point, the horse is out of the barn, and I'm not sure we're really going to get much benefit from closing the barn door.

I do think that we need to study the history of abuse-deterrent formulations and ask if this drug class is really that different and if this population is really that different than what we've seen in the past. I tend to think there are probably some differences but, overall, substance of use that interacts with the reward system in the brain and engenders the feelings that it does, whether it's for one benefit of stimulation or another benefit of sedation, or whatever you'd like to compare the two class of drugs as, reward is reward, and I'm just concerned that we need to look back at what's happen

with the opioids. Thank you.

DR. NARENDRAN: Thank you.

I don't see any other hands raised. This is Raj Narendran. I think talking in terms of just not abuse-deterrent formulations but also other paradigms to kind of reduce the number of scripts and track the number of pills, I know the agency has approved medications for schizophrenia, where they can take a pill and then look it up on your iPhone and see how many pills they took or how compliant the patients have been, and they can send it to their pharmacist, or family member, or a physician.

So to think outside of just deterrence and just in terms of tracking might be another way to avoid harm in college kids; did they really take 30 pills or did they pass 10 to their friends at a frat party? So I think I would urge industry to think large and use other more novel methods to address this horrible problem.

I think that concludes our discussion for question number 1. In terms of trying to summarize, I've heard a lot of comments related to the public

health impact in itself might be limited. Many members seemed to voice that, and they were unclear how an abuse-deterrent formulation in itself may aid.

Although trying to reflect back on the Opana ER and the opioid epidemic seemed to provide some guidance of how things could play out, some people thought maybe it could have a narrow impact in reducing substance-use transition to more harmful ways in the newly prescribed group. I liked the comments where they talked about the incidence, that maybe a small incidence could be benefit, but the larger prevalence of people using amphetamine and other stimulants for misuse could be harmed by a product like this.

I also heard some comments that the agency has to work to maybe include other stakeholders like family members and prescribers and come up with a specific guidance, perhaps, of how an abuse-deterrent formulation should look for stimulant abuse. But overall, it sounds like a lot of people were concerned that this in itself may not be enough to change the course of a horrible addictive process.

DR. NARENDRAN: Does the agency feel like they

got enough comments on this issue? Are we ready to move on to the next question?

DR. FARCHIONE: This has been very helpful. Thank you. This is Tiffany Farchione.

DR. NARENDRAN: Thank you.

I'm going to hand it over to Dr. Bonner, the DFO, because question number 2 through 5 are voting questions, so she can provide us with a framework of how it's going to work.

Dr. Bonner?

DR. BONNER: Yes. Hi. This is LaToya Bonner, DFO for this AC meeting. I will go over the voting instructions to the panel.

Questions 2 through 5 are voting questions. Voting members will use the Adobe Connect platform to submit their vote for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you will be moved to a voting breakout room. A new display will appear

where you will submit your vote. There will be no discussion during the voting. You should select the radio button, that is this round circular button, in the window that corresponds to your vote; yes, no, or abstain. You should not leave the no-vote choice selected. Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed.

Once all voting members have selected their vote, the DFO, myself, will announce that the vote is closed. Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record, then the chair person will go down the roster and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did if you choose. We will continue in the same manner until all questions have been answered or discussed.

Are there any questions about the voting process before we begin?

(No response.)

DR. BONNER: I will turn the meeting over to the chair.

DR. NARENDRAN: Question number 2. I'll read the question. Based on the information provided, including intranasal study comparing this product to amphetamine sulfate, has the applicant provided adequate evidence that the immediate-release oral formulation of amphetamine sulfate, AR19, would deter intranasal use?

Are there any questions about the question? Please feel free to raise your hand electronically so we can get clarification.

(No response.)

DR. NARENDRAN: I don't see any hands.

DR. BONNER: Neither do I.

DR. NARENDRAN: Okay.

DR. BONNER: Okay. We will now move --

DR. NARENDRAN: Go ahead, LaToya.

DR. BONNER: -- to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. BONNER: This is LaToya Bonner again, DFO. I will speak these votes into the record. For question 2, 4 yes; 19 no; zero abstained. I will turn the meeting back over to the chair.

DR. NARENDRAN: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification for your vote if you wish to. We'll start with the first person on the list.

Dr. Nelson?

DR. NELSON: Yes. Hi. This is Lewis Nelson from Rutgers New Jersey Medical School, and I voted no. I think that the product does not meet even the weak criteria set for it, a 10 percent reduction in drug liking, which is a questionable clinical value. It's unlikely, based on what we know about the opioids and the ADF opioids, that once this formulation's marketed, it will have better than expected outcomes, and it's more likely that it will have unexpected or unpredicted effect.

I understand the concerns of the public speakers who really would like to see some product that has abuse-deterrent formulations for all of the right reasons, but this product seems to be of marginal value, and I don't think that the data support its beneficial effects. Thank you.

DR. NARENDRAN: Dr. Griffin?

DR. GRIFFIN: Marie Griffin. I voted no, and I focused on adequate evidence. I think there was some evidence for some barrier to use, but I don't think the evidence presented was adequate.

DR. NARENDRAN: Dr. Iyengar?

DR. IYENGAR: This is Satish Iyengar from the University of Pittsburgh. I also voted no. I'm sort of echoing what Dr. Nelson said. I, too, was very moved by the public testimony, but I just did not think that the data bore out the claim that it would deter intranasal use. Thank you.

DR. NARENDRAN: Dr. Green?

DR. GREEN: Traci Green. I voted no for the reasons previously stated. I did not see a meaningful clinical reduction. There were one too many

manipulations for my level of comfort to agree that there was intranasal abuse deterrence reached. I think that while there may be room for an ADF for prescription stimulants, especially for the nasal route, it did not appear that this was it. Thank you.

DR. NARENDRAN: Ms. Witczak?

MS. WITCZAK: Kim Witczak, Woodymatters, consumer rep. I voted no. I didn't feel -- when I look at the word "adequate" evidence, I think, especially if this is the first of its kind in this new class, we need to have standards that are even higher. Thank you.

DR. NARENDRAN: Dr. Calis?

DR. CALIS: Hi. This is Karim Calis from the NIH, and I voted no as well. I agree with the general sentiment so far. I don't believe that there is compelling evidence to support an intranasal abuse-deterrent claim.

DR. NARENDRAN: Dr. Dunn?

DR. W. DUNN: This is Walter Dunn from UCLA. I voted no. I interpreted the question as can this product deter intranasal use to a clinically meaningful

degree. When considering deterrence, I also took into account the two aspects of reward versus effort, and I think based off of the human abuse potential studies, the results of that were weakened by the failure of the validation component, and therefore not entirely clear to me if intranasal use would result in a highly rewarding use.

The second component was the effort. It sounds like, based off of the FDA finding, that there are some conflicting evidence about the ease of manipulation through an insufflatable form. So given the fact that it may be easier to get it through an intranasal formulation and the fact that it can still be highly rewarding, I did not believe that the sponsor was able to demonstrate that it would deter intranasal use to a clinically meaningful degree. Thank you.

DR. NARENDRAN: Dr. Meisel?

DR. MEISEL: Steve Meisel with M Health Fairview in Minneapolis. I also voted no for the reasons that Drs. Nelson and Dunn articulated very nicely. When you set up a study and you have an endpoint, and you fail to meet the endpoint, to me

that's pretty telling that there is not adequate evidence that it's going to do what you say it's going to do. So I think the evidence is far from adequate. Thank you.

DR. NARENDRAN: Dr. Posner?

DR. POSNER: Yes. Philip Posner. I voted yes, and that was based upon my interpretation of the question. To me, deter the use of this compound as an intranasal access, I was quite convinced that what they have done in their formulation makes it much more difficult to use this than anything else that's on the market. So I don't think it will deter people from abusing this particular type of stimulant, but I think it will deter them from using this particular stimulant.

I understand what the people are saying about not meeting the endpoint, but when you compare this product with everything else that's on the market, or what students or abusers or users can get elsewhere, I take Occam's razor; they're going to take the easy way out. They're not going to go through the excess work of having to empty the capsule, crush the tablets, and

put them in a powder form that they can snort. So I think it will deter the use of this particular compound.

DR. NARENDRAN: Thank you.

Dr. Zibbell?

DR. ZIBBELL: Hey. This is Jon Zibbell, RTI International. I voted no, and the key for me was based on the information provided. And based on the information provided, I just couldn't vote yes. The sponsor's evidence just does not show that it deters intranasal use. In fact, it showed there was still likeability. I just want to stress, again, it was based on the information that was provided. Thanks.

DR. NARENDRAN: Dr. Fiedorowicz?

DR. FIEDOROWICZ: Yes. I went yes, although it was a soft yes because I went back and forth on this. Like Dr. Meisel, I was concerned about not meeting the primary endpoint, but ultimately what I thought was a totality of the evidence, I ultimately went with yes. I think making it harder to snort should deter such intranasal use and found the argument, considering both input and output, to be

somewhat compelling, although the output evidence here was certainly marginal. Thank you.

DR. NARENDRAN: Dr. Jeffrey?

(No response.)

DR. JEFFREY: Dr. Jeffrey, are you there?

(No response.)

DR. NARENDRAN: Maybe I'll move forward and come back to Dr. Jeffrey.

Dr. Boudreau?

DR. BOUDREAU: Denise Boudreau from Kaiser Permanente Washington, and I voted no, based on what I saw as marginal effectiveness of an endpoint, where the clinical relevance was also questionable.

DR. NARENDRAN: Dr. Jeffrey, are you there? Can you unmute yourself?

DR. JEFFREY: Yes. Hi. I'm here. Sorry about that. I was unmuted, but I'm not sure what happened.

Can you hear me now?

DR. NARENDRAN: I can hear you now, yes.

DR. JEFFREY: Okay. Wonderful. Thank you.

I think this is a tough question, but similar

to previous respondents, I, too, focused on adequate evidence. Ultimately, I think the data that demonstrated that AR19 was able to be manipulated for intranasal use using common household tools and much time needed for manipulation, specifically I was focusing on Tools 4 and 6, which yielded a 42 percent and 47 percent yield, I'm thinking with a 30-milligram dose, somebody would get up to 12 milligrams of usable product for intranasal use, which I do think would be reinforcing for the individual, so my vote was no.

DR. NARENDRAN: Thank you.

Dr. Habel?

DR. HABEL: This is Laurel Habel. I also voted no. While I think the product probably is harder to manipulate into a powder for snorting, I didn't think the likeability data was adequately convincing that is going to be a meaningful deterrent for intranasal use.

DR. NARENDRAN: Dr. McGough?

DR. McGOUGH: I voted no. I think reliance on a marginal outcome from selected post hoc tests from a study, that shell validation is just not compelling.

DR. NARENDRAN: Dr. Krishna?

DR. KRISHNA: This is Sonia Krishna from Dell Medical School at UT Austin. I voted no for reasons listed above and described by others. I'm surprised, still, that the rates of snorting are still so high. I'm a practicing child adolescent and adult psychiatrist, but I think the data shows that there is still likeability, and I do think people can be motivated to modify, as the FDA has shown.

DR. NARENDRAN: Thank you.

This is Raj Narendran. I'm next. I was not convinced. The fact that the validity test failed was a big thing for me. If these people couldn't even tell, with reliable -- distinguish amphetamine from placebo, to me that in itself is a problem to really tie that much more weight and try to interpret the AR data, so that was a big thing. The pharmacokinetics also suggests -- it's 30 percent less, but there's still a significant amount there for people to get reinforced. So those two things were pretty clenching for me, and I was not satisfied.

Next is Dr. Jain.

DR. JAIN: Hello. This is Dr. Felipe Jain, Massachusetts General Hospital. In this question, I focused on whether the AR19 formulation would deter intranasal use relative to amphetamine sulfate, not relative to everything else on the market and not in general. I think that the FDA has a very hard job to set a threshold for a primary endpoint that does not have validation in the clinical research literature. I fear that's not meaningful and impedes innovation, to design a trial for approval around such an endpoint.

In this situation, I consider it more meaningful to consider the pharmacodynamic data along with the aggregate primary and secondary outcomes, in which the 95 confidence intervals of all of them were greater than zero. Although the ease of manipulation may be greater than what the company expects, the FDA's results still provide optimism relative to amphetamine sulfate. The most parsimonious interpretation of the trial results, in my view, is that AR19 would deter intranasal use relative to amphetamine sulfate. Thank you.

DR. NARENDRAN: Thank you.

Dr. Thomas?

DR. THOMAS: Hi. Patrick Thomas from Baylor College of Medicine. I voted no for two sets of reasons: one for the issues around validation that were not compelling for reasons previously stated; and two, if you're looking at it specifically for deterrence of intranasal use, period, I question the deterrence approach. While I appreciate that there is a need for something, I think there are nonmedical ways to help.

I think what happened with the FDA providing evidence after the fact -- I'll even argue how fair it was that the company didn't get a chance to rebut that -- what that is, is really a real-world example of what would happen with people who are motivated to abuse substance and something comes out. You think that it goes one way and another group tries another thing, and suddenly it's a abusable. So those are the reasons I voted no.

DR. NARENDRAN: Thank you, Dr. Thomas.

I do want to remind -- I was guilty of this -- to please state your vote, whether it's yes or

no, and then go forward.

DR. THOMAS: Okay. I voted no.

DR. NARENDRAN: Thank you.

Dr. Marshall?

DR. MARSHALL: Brandon Marshall, Brown School of Public Health. I voted no for the previously stated reasons. Thank you.

DR. NARENDRAN: Thank you, Dr. Marshall.

Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted yes, and like Dr. Jain and Dr. Posner, I was taking it in comparison with other amphetamine formulations. I thought that at least in some populations, because of the increased efforts needed, although it is not impossible for intranasal preparations to be used this way, the reduction in the benefits and the rewards, this formulation will deter the use, at least in some patient populations, compared to these other existing amphetamine formulations. Thank you.

DR. NARENDRAN: Thank you.

Dr. Kulldorff?

DR. KULLDORFF: Martin Kulldorff. No. I will first commend the sponsor for trying to reduce the negative effects from the medication; I think that's very important. I think there may be some reduction, making it more difficult and have some reduction in intranasal use compared to other medications, but I interpret it was stronger than that, so I think it's still possible, so I voted no.

DR. NARENDRAN: Thank you, Dr. Kulldorff.

Dr. McCurdy?

DR. McCURDY: This is Chris McCurdy at the University of Florida. I voted no for many of the reasons that were already discussed. But I also think that this is a different product in that it's an immediate-release product orally, so somebody could orally take it and then insufflate the boost a little bit and get that good feeling. So if they really wanted to go after it and go at the effort, it could be done.

I think that something is desperately needed in this area that is manipulation resistant or abuse deterrent, but I just didn't see the evidence in this

case.

DR. NARENDRAN: I guess that concludes our voting for question number 2. We will now move on to question number 3. It's our second voting question.

Question number 3. Based on the information provided, including the syringeability study, has the applicant provided adequate evidence that AR19 would deter intravenous use?

Are there any questions about the question? If there are, please raise your hand.

Dr. Jain, go ahead.

(No response.)

DR. NARENDRAN: Dr. Jain, you can ask your question about the question.

DR. JAIN: Oh, sorry. I was on mute. Dr. Felipe Jain, Massachusetts General.

Could the FDA clarify whether this question is meant to be interpreted relative to amphetamine sulfate and other stimulants on the market; whether it's meant to be interpreted relevant to particular populations; or simply in general, whether we're supposed to take it as it is?

DR. FARCHIONE: This is Tiffany Farchione. The question is intended to be about this product in particular, have they demonstrated abuse-deterrent properties by the intravenous route.

DR. JAIN: So is it deterrent relative to any other products on the market or it's just open?

DR. FARCHIONE: I guess it's an open question.

DR. JAIN: Okay.

DR. FARCHIONE: All of the studies --

DR. JAIN: Thank you.

DR. FARCHIONE: -- were -- yes.

DR. NARENDRAN: Thank you.

Dr. Jeffrey, you can go ahead and ask your question.

DR. JEFFREY: Sorry. That was an error on my part. I'm lowering my hand. Thank you.

DR. NARENDRAN: Okay.

Dr. Posner?

DR. POSNER: This is very similar to the last one, and the question is, deter intravenous use; does it make it more preferable to try to go through all the things they showed, to put in a syringe versus just

taking it orally? That was the problem with the last question, the definition of "deter." Deter to me means make it more difficult, and if it's only for this medication, they can take it three ways. They can snort it, they can inject it, or they can swallow it.

Are they just asking is it easier to swallow than it is to do it as an intravenous drug?

DR. FARCHIONE: Sorry. This is Tiffany Farchione again. I think perhaps you guys may be thinking about this a little bit too much. The main issues here are the product is intended to deter abuse through the intranasal and intravenous routes. The last question was focused on the claims related to the intranasal route. This question is focused on claims related to the intravenous route and the evidence that was presented to support those claims.

DR. NARENDRAN: Thank you.

Dr. Baker? Do you want to ask your question?

DR. BAKER: Yes. Thank you very much. Robert Baker from Eli Lilly, industry rep. I'm just thinking it might be helpful for the agency to get a little more clarity on how they would expect the committee to weigh

the new data that were presented with the FDA's presentation today.

Dr. Farchione already appropriately mentioned that it would be a review issue as they continue to assess it, but I think from a general standpoint, I think sponsor would be concerned if the decision turned too much on data that the committee hasn't been able to see and the sponsor hasn't seen. Because it's going to be a review issue, I thought it might be helpful just to have a little more clarity to the committee as to how they should weigh that.

DR. FARCHIONE: This is Tiffany Farchione again. I think it's really up to each individual committee member to determine how much weight they want to put on that information. Again, we just received it. We're still reviewing it. We thought it was important to at least mention it because it will weigh into our decision, but in what way it's going to weigh in, we're still trying to determine that. So I think knowing that, it's up to the committee members to judge for themselves before casting their vote.

DR. NARENDRAN: Thank you.

It seems like that clarifies our question about the question. So based on how you feel, what you've seen, and based on the information provided, including the syringeability study, has the applicant provided adequate evidence that AR19 would deter intravenous use?

If there are no further questions about the question, I think we can move forward and vote on this question.

DR. BONNER: Hi.

DR. NARENDRAN: Now, can --

DR. BONNER: This is LaToya Bonner, DFO. Sorry, Chair.

Again, we will now move voting members to the voting breakout room to vote only. There will be no discussions in the voting breakout room.

(Voting.)

DR. BONNER: This is LaToya Bonner, the DFO. The voting has closed and is now complete. The vote results are displayed. I will read the vote results into the record: 8 yeses for question 3, 15 nos; zero abstain.

Now, I will turn the meeting back over to the chair.

DR. NARENDRAN: Thank you.

Once again, we'll just go down the list and have everyone who voted state their name and vote into the record. You may provide a justification for your vote if you wish to. We'll start with Dr. Nelson.

DR. NELSON: Thank you. This is Lewis Nelson from Rutgers New Jersey Medical School. I voted no. This is a quantitatively small but clinically huge issue. The limited data provided by the sponsor leave open many questions for both scientific and clinical relevance. This is definitely, in part, due to the limitations of doing premarketing research on this very challenging issue.

But I am concerned that the product manipulation did not fully incorporate the lessons of OxyContin manipulation by street pharmacologists, and I think that it's very unclear to me how to actually utilize the information that's been provided. So I don't really feel that they've been able to show that the drug does or will deter intravenous use. Thank

you.

DR. GRIFFIN: Yes. This is Marie Griffin from Vanderbilt. I voted no. Again, I don't think the information presented was adequate evidence to determine that it would meaningfully deter IV abuse or misuse.

DR. NARENDRAN: Dr. Iyengar?

DR. IYENGAR: This is Satish Iyengar from the University of Pittsburgh. I also voted no, although I have to admit that I was tempted to abstain given the tentative nature of the recent data that the FDA has. But for the reason that Dr. Griffin said, I decided no. Thank you.

DR. NARENDRAN: Dr. Green?

DR. GREEN: Traci Green. I think based on the data that were provided, the syringeability studies were really clear, and in parallel I think from the sponsor and what the FDA provided, indicating that syringeability was quite evident, that wasn't sufficient to deter intravenous use if it were to move forward in this formulation, so I voted no.

DR. NARENDRAN: Ms. Witczak?

MS. WITCZAK: Kim Witczak, Woodymatters, consumer rep. While I appreciated all the efforts that they went through to test the syringeability, I am concerned about both the information that the FDA presented, the new stuff, as well as the company, as well as the unknown material. And I believe, again, there will be some future unintended consequences, potential unintended consequences, of this ability, syringeability, as well as, again, I think we need to establish a higher standard for any products that will be given this type of abuse-deterrent formulation going forward.

DR. NARENDRAN: Dr. Calis?

DR. CALIS: This is Karim Calis from the NIH, and I voted no. I had to think a lot about this, as I'm sure the others have, because I think, in a way, the applicant certainly appears to have made it more challenging to prepare the product for intravenous use. However, I think that there are some questions about the syringeability, and I think, unfortunately, there are very creative individuals, and there could be creative methods of manipulation that could subvert

that, and those can be very quickly and widely disseminated on social media and what have you. And I just don't think that, again, they've met that bar with regards to deterring intravenous use. Thank you.

DR. NARENDRAN: Dr. Dunn?

DR. W. DUNN: This is Walter Dunn. I voted no. I'm going back to my framework of considering effort and reward informing the issue of deterrence I think at no fault of the sponsor because I think they're being put in a difficult position that they cannot demonstrate a direct advantage of AR19 in reducing the reward or reinforcing benefit since human abuse potential studies are not possible. So this led me to conclude that there's not adequate evidence to demonstrate deterrence of IV use.

We're asked to deduce the advantages in regards to reward based on percentage of amphetamine extracted, however, I think this really misses the human element that is difficult to quantify, and that's why HAP studies are needed. For example, the placebo effect of IV administration perhaps as an element of misuse experience, that is interpreted as a high for

the patient, so perhaps not as much absolute amphetamine is required to establish a repeated abuse behavior. So mechanically, yes. I know that the effort components of the deterrence question, it does require more effort to get into an injectable form, but I don't know about the reward portion of that equation.

Finally, I think there's a misguided focus on looking only at or focusing on Extract 8 to demonstrate the difficulty manipulating AR19 into injectable form. Although that was the one that yielded the highest percentage of amphetamine -- and I'll address this the safety issue or safety question -- I think there should have been also some discussion about how difficult or how easy it was to obtain the other injectable extracts. Thank you.

DR. NARENDRAN: Dr. Meisel?

DR. MEISEL: Hi. Steve Meisel with Fairview in Minneapolis. I reluctantly voted yes on this because I looked at the word "deter." I think there is no doubt that this is more difficult than other products to put into a syringe, and find the red diluents, and deal with the gunking of the stuff once

it's in the formulation. So it's going to make it more difficult to do. It's going to take the casual user, the first-time user, and maybe deter them from doing it at all.

But I agree with the others that over the long haul, the meaningfulness of that is probably in doubt because, as I mentioned with the intranasal forms, before a month is out, if this product were to be approved, there will be all sorts of recipes on the internet. So if you're with somebody that has access to that, who's done it before, or whatever, it's going to end up being relatively easy for somebody to go ahead and do it. But there is that mild deterrence for that first-time casual user who doesn't have the motivation to go and look for the way to get this done right. So I look at that word "deterrence" in maybe sort of a narrow frame. Thank you.

DR. NARENDRAN: Thank you.

Dr. Posner?

DR. POSNER: Hello. Philip Posner, and I voted yes and agree with Dr. Meisel. I once again look at pick-resistant versus pick-proof on a lock, or

water-resistant versus waterproof on a watch. Clearly, there's a way around it if you really want to, but it is going to deter the burglar and it's going to deter the diver from losing something. Again, I think the question would have been better phrased than using the word "deter."

DR. NARENDRAN: Thank you.

Dr. Zibbell?

DR. ZIBBELL: Thanks. This is Jon Zibbell, RTI International. I voted no. I thought, based on the info provided, there was really no meaningful evidence to deter IV use. Sure, I agree with Dr. Calis, it is a little more difficult, so there might be the neophyte user who won't want to put in the effort. But my work with injectors, and the literature is pretty clear, that people that do prefer injecting will take inordinate time to prepare an injectable solution. They prefer the rush, and it's worth it. Any effort in this case is worth the reward.

Plus, really, since this is an instant release and not an extended release, if you orally use it, you get a dose dump. They can just eat the pill while

they're preparing it, even if it takes an hour. So get a dose of 30 milligrams orally so they can feel that effect while they're doing it.

I also want to just say that people don't get to choose what prescription stimulants they use. I kind of heard some discussion, "Well, people can choose a different product." But contrary to the supply and demand of neoclassical economics, when it comes to illicit drugs, really, supply creates demand, and people are going to use what's available to them. And my fear is if this is available, they will try to inject it, and the harms associated with that -- that we can talk about in the next question -- and the safety come to the fore. So that's why I voted no. Thank you.

DR. NARENDRAN: Thank you.

Doctor Fiedorowicz?

DR. FIEDOROWICZ: Yes. Jess Fiedorowicz in Ottawa. My vote was yes. Excepting that the ability to say this is really inherently limited, AR19 seems to be substantially harder to extract in injectable form, and that should deter intravenous use as was worded in

the question. I have concerns about the potential for this to be circumvented from the agency's late-breaking, albeit vague, data. I may be somewhat ambivalent about this vote, and I do have safety concerns about injection-related harm, as previously was well articulated by Dr. Jon Zibbell, although those did not weigh into my response to this particular question. Thank you.

DR. NARENDRAN: Thank you.

Dr. Jeffrey?

DR. JEFFREY: Hi there. Jessica Jeffrey here from UCLA. I voted yes, and the reasons I voted yes were actually already previously stated by Drs. Meisel and Posner, and I don't have anything to add to that. Thank you.

DR. NARENDRAN: Thank you.

Dr. Boudreau?

DR. BOUDREAU: Hi. Denise Boudreau, and I also voted yes, and I don't think I have anything to add other than agreeing with what's been said by other folks that voted yes as well.

DR. NARENDRAN: Thank you.

Dr. Habel?

DR. HABEL: This is Laurel Habel. I voted no, basically for the reasons that have been stated by others.

DR. NARENDRAN: Thank you.

Dr. McGough?

DR. McGOUGH: Dr. McGough, UCLA. I voted no as well, and again, the reasons have been stated.

DR. NARENDRAN: Dr. Krishna?

DR. KRISHNA: This is Sonia Krishna from UT Austin. I voted yes for the reasons others have stated. I believe that it will deter. There is a limit to what the sponsor was able to do, and they tried, and people will be able to circumvent it. I don't think it will prevent, but I do think it will deter.

DR. NARENDRAN: This is Raj Narendran. I voted no. I just want to echo the comments of Dr. Zibbell and Dr. Dunn, and I have nothing more to say. They put it elegantly.

Dr. Jain?

DR. JAIN: This is Dr. Felipe Jain, Mass

General. I voted no for the reasons stated by Drs. Nelson and Dunn. However, if the question had been relative to other immediate-release preparations on the market, I would have voted yes.

DR. NARENDRAN: Thank you.

Dr. Thomas?

DR. THOMAS: This is Dr. Patrick Thomas. I voted yes for some of the reasons stated by Meisel and Posner. It's technically harder, but it might not matter. Also, the newer FDA report I think was only relevant to insufflation. If it was syringeability, I might have changed my vote.

DR. NARENDRAN: Thank you.

Dr. Marshall?

DR. MARSHALL: Brandon Marshall. I voted no. For me, this is a question of both the deterrence mechanism but also the proposed dosing, which are very high in this case. So even a 30-milligram pill, it seemed like there were quite a few conditions where you could extract 40 percent of the active amphetamine, which is 12 milligrams, which appears to be sufficient for a rewarding mechanism.

So I think I might have voted yes if the maximum dose were lower, particularly given the rather impressive data that the multidose extractions didn't seem very feasible, but with these high-dose pills, I just think there might actually be an incentive to inject them for that reason. Thank you.

DR. NARENDRAN: Thank you.

Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted yes because although it is not impossible, it is more challenging to prepare the product for intravenous use. I think that maybe in at least some patient populations, not in the usual injectors, it would deter compared to oral use, given the availability and other amphetamine formulations. Thank you.

DR. NARENDRAN: Thank you.

Dr. Kulldorff?

DR. KULLDORFF: Martin Kulldorff. No.

DR. NARENDRAN: Thank you.

Dr. McCurdy?

DR. McCURDY: This is Chris McCurdy at the University of Florida. I also voted no, mainly for

most of the reasons that Dr. Zibbell outlined

DR. NARENDRAN: Thank you. That concludes our voting on question number 3.

I think we could pause for maybe a 10-minute break just for people to use the restroom, maybe grab a cup of coffee, or whatever, and then we can meet back at 3:41. Panel members, please remember there should be no chatting or discussion about the meeting topic with anyone during the break. We'll resume at 3:42 for question number 4. Thank you.

Dr. Bonner, do you have anything else to add?

DR. BONNER: No, sir.

DR. NARENDRAN: Okay. Thank you.

(Whereupon, at 3:32 p.m., a recess was taken.)

DR. NARENDRAN: I hope everyone is back.

We will now move on to question number 4.

Question number 4. Based on the information provided, has the applicant adequately characterized the safety of AR19?

Are there any questions about this question? Please raise your hand.

(No response.)

DR. NARENDRAN: No questions? It sounds pretty clear-cut. I think we could go ahead and vote. I'll pass it over to Dr. Bonner.

DR. BONNER: Hello. This is LaToya Bonner again, DFO. We will now move voting members to the breakout room. There will be no discussions.

(Voting.)

DR. BONNER: The voting has closed and is now complete. The vote results are displayed. I will read the vote results into the record. For question 4, 2 yeses, 19 nos, 2 abstentions.

Stand by. We're still waiting for the vote to post.

(Pause.)

DR. BONNER: This is LaToya Bonner, DFO. I will read the vote into the record again. For question 4, 2 yeses, 19 nos, 2 abstentions. I will turn the meeting back over to the chair.

DR. NARENDRAN: Thank you.

So we'll just do the same thing. We'll go down the list and everybody could state their vote for the record and justification if you feel it's

necessary. We'll start with Dr. Hernandez-Diaz.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted no in the sense of there is still a lot of uncertainty around many safety aspects, and I don't think we can say that we can characterize the safety of AR19 at this point.

DR. NARENDRAN: Dr. Griffin?

DR. GRIFFIN: Yes. This is Marie Griffin. I voted no. I'm concerned that it can be injected intravenously and that it contains high molecular weight PEO and some unknown additives. I just don't think the studies done were reassuring enough that it's safe if this were to happen.

DR. NARENDRAN: Thank you.

Dr. Iyengar?

DR. IYENGAR: This is Satish Iyengar from Pittsburgh. For the same reasons as have been stated, I also voted no.

DR. NARENDRAN: Dr. Green?

DR. GREEN: I voted no for many of the same reasons, including the chemical composition and the high molecular weight PEO. I also have additional

concerns around the use of talc and the amount of talc that would be exposed in a repeated number of injection or insufflation episodes, as might happen with a stimulant using independent lipid [indiscernible] tool, as was used by these routes. So I have additional safety concerns that they weren't adequately addressed, the data that were presented.

DR. NARENDRAN: Thank you.

Ms. Witczak?

MS. WITCZAK: Kim Witczak. I voted no. We already know that there are safety issues in general with stimulants, however not knowing the chemical material makeup in some of the injections, we don't know what the future unintended consequences could be, and I don't think it was really studied enough to know if there were any safety issues that we can claim.

DR. NARENDRAN: Thank you.

Dr. Calis?

DR. CALIS: This is Karim Calais from the NIH, and I voted no as well. I think although the safety data are limited given the nature of the application, given that it's using the 505(b)(2) pathway, I would

have relatively few concerns with safety if it were to be used exclusively orally for the proposed indication, given what we know about stimulants and so forth. Obviously, these are not benign products, but at least we would have adequate safety information.

However, as proposed by the applicant, this product, if it were approved, would have this unique space and unique distinction of being a first product for stimulants with that designation that we talked about. So in light of that, the burden of proof is on the applicant to clearly demonstrate safety if the product were intentionally manipulated and abused, and I don't believe that they've done that. Thank you.

DR. NARENDRAN: Thank you.

Dr. Dunn?

DR. W. DUNN: Walter Dunn from UCLA. I voted no. For me, this was really the key question regarding AR19, specifically the potential toxicity with IV administration to cause complications such as thrombotic microangiopathy. The sponsor stated in their document that the animal toxicity studies, they selected an extract that described, quote/unquote,

"worst-case scenario," based off the extractable amount of amphetamine content. I think Extract 8 recovered 50 percent.

I think, in fact, this was probably the best-case scenario or at least a close second. Extract 1 and 8 were probably the safest out of all the extracts because they contained the lowest amounts of PEO, greater than 1 million in size, and it suggested that toxicity is likely correlated to the higher molecular weight PEOs. So I interpreted Extract 8 as the worst-case scenario in terms of potential reinforcing effect but not toxicity.

But the question really is, is it toxic and is it safe, or is there potential toxicity, is it safe? What they should have done is selected the injectable extract with the greatest potential to harm as the, quote/unquote, "worst-case scenario." For example, Extract 2 and Extract 6 potentially have the highest milligram content of high molecular weight PEOs, so the other aspect they should have considered was the likelihood that these extracts would represent real-world manipulation with the compound.

But patients will not be measuring amphetamine content before they inject the manipulated product. They will inject the first injectable solution they achieve, and that's one that probably requires the least amount of pretreatment of manipulation to produce, see if it achieves the reinforcing high, and then go back to the drawing board.

So by going to the extract of the least amount of effort, and furthermore, by testing the extract of the least amount of effort, this also will give you a clearer picture of how toxic it could be, as it's suggested that the amount of manipulation is correlated to the amount of high-weight PEOs present. The more manipulation seems to break it down to smaller pieces.

Finally, what I'm not confident about is how injecting these toxic, easier to obtain extracts would be, even after a limited amount of administration. In these studies, these poor rabbits didn't even make it past one round of PEO 7 million administration. So even though there's an argument that may be made that IV is not a major route of administration, AR19 would likely be targeted to a high-risk population in risk

for IV use. And I know as a clinician, I would be very nervous to prescribe it to a patient who I think is at high risk for IV misuse, based off of this safety data. Thank you.

DR. NARENDRAN: Thank you.

Dr. Meisel?

(No response.)

DR. NARENDRAN: Dr. Meisel, you may want to unmute yourself.

DR. MEISEL: Is that better?

DR. NARENDRAN: Yes, I can hear you now.

DR. MEISEL: Ok. Somehow I was muted on the computer and on my phone. Anyway, Steve Meisel with Fairview in Minneapolis. I voted no for the reasons that others have already stated.

DR. NARENDRAN: Thank you.

Dr. Nelson?

DR. NELSON: Lewis Nelson, Rutgers New Jersey Medical School. I voted no, and I do think it's very difficult to characterize the, quote/unquote, "safety," based on the three classes of studies performed. The in vitro and preclinical data really do not speak to

the safety of this product. I have concerns of the large volume dilution and injection, and as a medical toxicologist, it's hard to ignore the problems with talc and PEO injections. Really, to find any safety data for that would really require epidemiological evidence, which is a bit of a catch-22 in this case because the product is not marketed. Thank you.

DR. NARENDRAN: Thank you.

Dr. Fiedorowicz?

DR. FIEDOROWICZ: Yes. Jess Fiedorowicz in Ottawa. I voted no, and I have nothing to add. Thank you.

DR. NARENDRAN: Thank you.

Dr. Jeffrey?

DR. JEFFREY: Hi. Dr. Jeffrey from UCLA. I voted no. I don't believe the applicant has adequately characterized the safety of AR19. In terms of the intranasal studies, I don't believe the applicant sufficiently considered higher doses or repeat administration with intranasal use, which is common with intranasal use.

In terms of safety with IV use, the pivotal

toxicity study in rabbits was not interpretable. In addition, multiple conditions were injectable at physiological temperatures and yielded amphetamine, but these were not tested. Some of the injectable extracts yielding higher amounts of higher molecular weight PEO were evaluated.

DR. NARENDRAN: Thank you.

Dr. Boudreau?

DR. BOUDREAU: Denise Boudreau, and I voted no as well for many of the reasons that were stated, concerns over the data that was presented, and also lack of data and lack of studies that I would like to see, as was mentioned by somebody else, around epidemiologic studies, although I know that is somewhat challenging in this case.

DR. NARENDRAN: Thank you.

Dr. Habel?

DR. HABEL: This is Laurel Habel. I voted no. I have nothing to add.

DR. NARENDRAN: Thank you.

Dr. Posner?

DR. POSNER: This is Philip Posner, and I

abstained just because there was insufficient data, and I don't have a sufficient clinical background to have voted no on it.

DR. NARENDRAN: Thank you.

Dr. Zibbell?

DR. ZIBBELL: Hey. This is Jon Zibbell, RTI International, Atlanta, Georgia. I voted no. Others said safety wasn't clearly demonstrated. I totally concur. When I think of safety, I put it in three buckets: addiction, infectious disease, and overdose.

Addiction is something that we can have on the oral route. This is a high-dose medication, but it's not extended release like the high-dose opioids usually are extended release. So when you orally inject it, you get a dose dump, so we're not really preventing addiction.

Infectious disease, I think there's a big concern that wasn't really addressed. We're talking about HIV, hepatitis, endocarditis, osteomyelitis, soft tissue infections, and then we're talking about overdose. With methamphetamine, and amphetamines more generally, the mortality risk is very low. You'd be

hard-pressed to go back a hundred years and find any mortality epidemic with stimulants. And even the current stimulant epidemic that we're seeing as related to fentanyl, there is a small population of people dying from methamphetamine, but when you look at their medical examiner records, there's a ton of other drugs on board, so the OD risk is generally low as well.

Since there is a high dose, people will insufflate. I want to echo what Jessica Jeffrey said about the nasal damage. We don't know, from the higher size particles and people are reproducing, if there is going to be any nasal damage with that. As I said before, I think people will IV this drug, and on the IV aspect, high molecular PEO with TTP and TMA wasn't addressed.

The talc is an issue, but talc is in all drugs. The thing with talc is talc is basically a silica that will cut up your veins, and that's really the biggest problem with the talc, is all the vein damage and the stuff to the heart. But the congealing, I'm really nervous about that. We saw that with Opana, and people used more water and, hence, they used larger

syringes. The applicant mentioned larger syringes were needed, so that raised all of that dead space, and HIV, and the evidence we have with that.

I also know that a lot of these medications are going to be in resource-deprived communities without many other options, like Scott County, Indiana that happened, and people take more risky behaviors when they're in those situations. So for all of the above, I thought the safety wasn't clearly demonstrated, and I voted no.

DR. NARENDRAN: Thank you.

Dr. Kulldorff?

(No response.)

DR. NARENDRAN: Dr. Kulldorff --

DR. KULLDORFF: Yes, I'm here. Martin Kulldorff, yes. I work a lot with postmarket safety surveillance, so obviously no drug is -- we don't have complete information about the safety of any drug when it's approved. But I think the applicant made an adequate [indiscernible] of the safety of this, both in terms of the positive and negative aspects of it, so I voted yes.

DR. NARENDRAN: Thank you.

This is Raj Narendran, and I voted no for all the reasons mentioned by my other colleagues.

Dr. Jain?

DR. JAIN: This is Dr. Felipe Jain, Mass General. I voted yes for the reasons stated by Dr. Kulldorff. If the medication were intended to be labeled for IV use, I may have voted differently, but as an oral medication, as Dr. Calis stated, its safety profile has been characterized. Thank you.

DR. NARENDRAN: Thank you.

Dr. Thomas?

(No response.)

DR. NARENDRAN: Dr. Thomas, you may want to unmute yourself.

(No response.)

DR. NARENDRAN: I think we lost Dr. Thomas.

Dr. Marshall?

DR. MARSHALL: Brandon Marshall. I voted no. I was struck by the fact that the FDA questioned whether rabbits were even an appropriate animal model for that in vivo study, and I agree with Dr. Dunn that

I didn't really know how to interpret the findings when all of the positive control rabbits died in 30 minutes.

So I had concerns about that, and then I share the concerns around the high doses of these medications that Dr. Zibbell raised. I think that does provide an incentive to use these medications nonmedically. So I would encourage sponsors to think about the dose of these medications in addition to some of these supposed deterrent effects to get to the result that we're looking for.

DR. NARENDRAN: Thank you.

Dr. McGough?

DR. McGOUGH: James McGough. I voted no. The reasons have been stated.

DR. NARENDRAN: Thank you.

Dr. Thomas, if you're there, if you want to go ahead and register your vote and reason.

DR. THOMAS: Hello? Can you hear me?

DR. NARENDRAN: I can hear you now.

DR. THOMAS: Hello?

DR. NARENDRAN: Yes, I can hear you, Dr. Thomas.

DR. THOMAS: Dr. Thomas. I abstained.

DR. NARENDRAN: Thank you.

Dr. Krishna?

DR. KRISHNA: This is Sonia Krishna here in Austin, and I voted NO. Thank you.

DR. NARENDRAN: Thank you.

Dr. McCurdy?

DR. McCURDY: Chris McCurdy at the University of Florida. I voted no.

DR. NARENDRAN: Thank you.

This concludes our voting for question number 4. I think we can move on to question number 5.

(Pause.)

DR. NARENDRAN: Give it a second for it to upload.

Question number 5, do the benefits of AR19 outweigh the risks for the proposed indication?

Are there any questions about the question? It's pretty straightforward? If there are, please raise your hand.

(No response.)

DR. NARENDRAN: We see none, so I think we can

go ahead and vote.

DR. BONNER: We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. BONNER: This is LaToya Bonner, DFO. The voting has now closed and is now complete. The vote results are displayed. I will read the vote results into the record.

For question 5, zero yes, 23 nos, zero abstain. I will turn the meeting back over to the chair.

DR. NARENDRAN: Thank you.

The same; if people just want to run through the list from the top and just state for the record their vote.

Dr. Jain, we'll start with you.

DR. JAIN: I voted no.

DR. NARENDRAN: Dr. Thomas?

DR. THOMAS: I voted no.

DR. NARENDRAN: Dr. Griffin?

DR. GRIFFIN: This is Marie Griffin, and I

voted no.

DR. NARENDRAN: Dr. Iyengar?

DR. IYENGAR: This is Satish Iyengar. I also voted no.

DR. NARENDRAN: Dr. Green?

DR. GREEN: I voted no, and that was based on the past three other questions that asked some more things to lead to this overall risk-benefit decision here, which was also consistent with no.

DR. NARENDRAN: Thank you.

Ms. Witczak?

MS. WITCZAK: Kim Witczak. I voted no, and for a lot of the same reasons from the previous three questions, as well as I think we need to be setting a higher standard for something new like this.

DR. NARENDRAN: Thank you.

Dr. Calis?

DR. CALIS: This is Dr. Calis, and I voted no as well.

DR. NARENDRAN: Thank you.

Dr. Dunn?

DR. W. DUNN: This is Walter Dunn. I voted

no, primarily based off a concern that AR19 would introduce safety and toxicity issues that were not adequately addressed in their studies.

DR. NARENDRAN: Thank you.

Dr. Meisel?

DR. MEISEL: This is Steve Meisel. I voted no. I thought the benefits, if any, were slim to non-existent in terms of its ability to deter manipulation and abuse, and the risks of the excipients are way too high and uncharacterized, so I voted no.

DR. NARENDRAN: Thank you.

Dr. Nelson?

DR. NELSON: Lewis Nelson. I voted no for the reasons we've discussed earlier today.

DR. NARENDRAN: Thank you.

Dr. Zibbell?

DR. ZIBBELL: Hi. This is Jon Zibbell, and I voted no for the reasons that I discussed today. Thank you.

DR. NARENDRAN: Thank you.

Dr. Fiedorowicz?

DR. FIEDOROWICZ: This is Jess Fiedorowicz in

Ottawa. I also voted no and, again, I have nothing to add to what hasn't already been discussed. Thank you.

DR. NARENDRAN: Thank you.

Dr. Jeffrey?

DR. JEFFREY: Jessica Jeffrey from UCLA. I voted no.

DR. NARENDRAN: Thank you.

Dr. Boudreau?

DR. BOUDREAU: Denise Boudreau. I voted no, and I have nothing to add.

DR. NARENDRAN: Dr. Habel?

DR. HABEL: This is Laurel Habel. I voted no; nothing to add.

DR. NARENDRAN: Thank you.

Dr. McGough?

DR. McGOUGH: James McGough, voted no, nothing to add.

DR. NARENDRAN: Thank you.

Dr. Kulldorff?

DR. KULLDORFF: Martin Kulldorff. No.

DR. NARENDRAN: This is Raj Narendran. I voted no; nothing to add.

Dr. Hernandez?

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz. I voted no; reasons already stated.

DR. NARENDRAN: Thank you.

Dr. Marshall?

DR. MARSHALL: Brandon Marshall. I voted no for the reasons we've already discussed.

DR. NARENDRAN: Thank you.

Dr. Posner?

DR. POSNER: Philip Posner, and I voted no, agreeing with my colleagues.

DR. NARENDRAN: Thank you.

Dr. Krishna?

DR. KRISHNA: This is Sonia Krishna. I voted no. Thank you.

DR. NARENDRAN: Thank you.

Dr. McCurdy?

DR. McCURDY: This is Chris McCurdy. I voted no.

DR. NARENDRAN: Thank you.

This concludes our voting questions. Now we will proceed to question number 6, which is a

discussion question, if we could get that question up.

Question number 6. What, if any, additional data are needed to address outstanding issues of AR19?

Are there any questions about the question?

(No response.)

DR. NARENDRAN: I don't see any questions about the question, so I think we can open it up for discussion. Is there anybody who wants to go first? Please raise your hand.

Dr. Dunn?

DR. W. DUNN: Thank you. This is Walter Dunn from UCLA. I think I just want to reiterate the issue about safety. The sponsor is in a tough position to demonstrate safety advantages in a context where there is not thrombotic microangiopathy occurring from injection of a manipulated stimulant currently, so any incidence of that that occurs, if the product is approved, it could be a black mark. I think that's a tough bar to clear.

Speaking more for myself, looking at potentially considering future data, I think, really, we should be looking at potential real-world situations

as far as which of the extracts or compounds might be used in IV administration. I think looking at the amphetamine content is one aspect of it, but, again, as I mentioned, it's really about a safety issue, and subjects are not going to be measuring the amount of amphetamine present before they try it. They're going to try the first thing they come up with, and that's going to be probably the least manipulated solution they come to. And the question really is how much toxicity could that cause after a single administration.

So I would have been much more reassured if they had tested at least two or three of the other compounds that they themselves mentioned required less manipulation to see what impact they had on the animal models. So for me, primarily, it was a safety question. Even though I voted no for most of the benefits side of it, if you can show that your compound is safe, I think I would be a little more lenient about how definitive the benefits have to be established. But if there's really a question about safety, I think that overrides any kind of marginal benefit that the

compound could provide. Thank you.

DR. NARENDRAN: Thank you.

Dr. Hernandez-Diaz?

DR. HERNANDEZ-DIAZ: Hi. Sonia Hernandez-Diaz. This is kind of a discussion or a question that is a follow-up to an initial question from Dr. Meisel regarding the standards, because I'm a little concerned that we are raising the standards. I'm not arguing against doing so, but it's kind of unfair maybe to raise them at the time we are seeing the results presented, both in the need to present proof of public health impact -- and maybe we have to discuss whether we've seen any abuse-deterrence or system [indiscernible] formulation that is going to meet that standard. And then within the deterrent formulations, if we want to raise the bar for the first product, trying to do so to get to higher levels of deterrence of use for the intranasal and injected use routes.

So I don't know if it's a good time to discuss it, but I wanted to raise that same question that Dr. Meisel asked. Thank you.

DR. NARENDRAN: Thank you.

Are there any other comments; what other data is necessary?

Dr. Meisel?

DR. MEISEL: Hi. Steve Meisel. I don't think it's a point of data necessarily, although certainly the data that was presented here needs a whole lot more flushing out with a much larger sample size and so forth. I've said this before to the agency when we were talking about abuse deterrence for opioids; we need some clear definitions and some clear thresholds for any product to have these kinds of labels associated with them.

I think Arbor did a nice job of using a different term, "manipulation resistant," and I think that probably is a superior term, but without definition, that term is also meaningless, sort of like "all natural" at the grocery store. What does that really mean?

So I think before a drug like this were to be resubmitted, or Arbor or somebody else, whether it's for a stimulant or another drug of abuse, I would

suggest that the agency come up with much clearer, cleaner definitions and thresholds to meet because without those, I think we put the applicants in a very difficult position where they don't really know what does and what doesn't meet the expectations of either the agency or these advisory committees. Thank you.

DR. NARENDRAN: Thank you.

Dr. Zibbell?

DR. ZIBBELL: Thanks. Jon Zibbell, RTI International. I kind of want to echo Dr. Meisel a bit. I feel like the applicants are in a tough spot, and not just these applicants, but other applicants we've heard that are wrestling with the abuse-deterrent formulations. FDA has embraced a logic of ADFs, but I think, as Dr. Meisel just said, there aren't really clear standards. And I've sat on multiple of these committees, and I'm not sure that abuse deterrence is even possible in terms of creating new harms. It's kind of a chemical response to a chemical problem.

I don't know. I've been saying this several times. FDA and us as a country, we might just want to think that maybe a chemical response to a chemical

problem isn't the way to go; that maybe the opioid epidemic can teach us something about responsible prescribing. We're talking about overprescribing prescription stimulants for sure, there's no question about that, and this one is a high-dose one just like we had the overprescribing of high-dose opioids.

So responsible prescribing I think would go a really long way, primary prevention and education with young people at school, people with ADD, low-threshold treatment; universal needle exchange access; I think there are other ways where we can reduce these harms. But it just seems like the ADFs are creating more harms, and I think that's a hard place for the applicant to be. They don't know clear standards. They sometimes don't know the population that we're dealing with, and a lot of us do.

So I just wanted to make that point, that I think this is a larger question about we should rethink abuse-deterrent formulations more generally. Thank you.

DR. NARENDRAN: Thank you.

Dr. Green?

DR. GREEN: Thank you. I wanted to just add to things that haven't been said because I think the meeting has provided some good suggestions here for additional data that are needed to address those outstanding concerns around AR19.

I was taken by some of the questions around the age of the population, the study populations, especially for the HAP study, and the age range was quite large. So maybe consider data that focus more exclusively on a younger population, 18 to 85 perhaps, where we're more concerned with potential misuse and where the prevalence of misuse is much higher rather than a much larger range; just one particular thought.

I think also, even the company or future other companies maybe could address issues around manipulation methods, and toxicity, and what is meaningful clinical reduction, and even consider lower dose ranges for potential ADFs to reduce the interest or drive and demand to potentially misuse these medications.

Any future such product really needs to focus on the plan for postmarketing surveillance that aligns

with what we have learned from the postmarketing surveillance problems and the prescription opioid epidemic, and our prior ADF guidance challenges. Specifically, we missed and did not follow unintended consequences, especially with illicit use and potential transitions to other drugs.

We are focusing a lot on snorting and inhalation, and intranasal routes, and on injections, but we really should also encourage and insist that postmarketing surveillance plans also include tracking of things like methamphetamine and counterfeit medications because Adderall and other medications that are already used for prescription stimulants are being crossed with methamphetamine.

We need to track and make sure that these decisions or these approvals of new medications are not linked to and creating larger problems that were unintended. We haven't really talked about that much today, the hallmark of what's been missing in that larger conversation about ADFs, and when these committees have reviewed data, missing heroin from those reviews. I don't want to miss methamphetamine or

other illicit stimulants that we really should be considering in that larger public health impact of any new medication. Thank you.

DR. NARENDRAN: Thank you.

Dr. Nelson?

DR. NELSON: Thank you. Lewis Nelson from Rutgers. I actually lowered my hand. But I do want to just say that I'm a little concerned that we think we're going to be able to predict real-world effects from this preclinical data. I think if we go back -- and I'll say it again -- and look at the history of what's happened with the ADF opioids -- and I know everybody's already said a lot of great things already, and I'm not going to repeat it -- we will learn a lot on how to inform what we should be doing going forward. I'm just not sure this three-stage process really gives us the information we're going to need to adequately predict what we want to know. Thank you.

DR. NARENDRAN: Thank you.

Dr. Griffin?

DR. GRIFFIN: Marie Griffin. I just want to

say briefly that although I think most of us would say "manipulation resistant" is a better term than "abuse deterrent," I'm not sure we want -- I think FDA would have to think long and hard about whether they want to go down that rabbit hole and whether manipulation resistance gives us anything if there's always the chance that we're going to be getting unintended consequences.

DR. NARENDRAN: Thank you. This is Raj Narendran. I'm just going to put in my discussion thoughts, but I think it would have been helpful to see all those extracts probably characterized in a more robust model like the Hunt study had done, in guinea pig as opposed to rabbits. That was probably already available in the literature.

It would have also been helpful, really, for Arbor to maybe determine what is a reinforcing dose of racemic amphetamine. I think that question was sort of inferred from the literature. My biggest concern, and probably to the agency, is just reading through these human abuse potential studies that -- we've done this for some of the buprenorphine formulations and some of

the other formulations in the past and advisory committees.

Looking through these human abuse potential studies and measuring drug liking, this is research done by Marian Fischman and Herb Kleber in the 1980s. We're still in sort of the 20th century. We know so much about reward, and drug wanting, and drug craving, and incentive salience, as opposed to not everybody who uses a drug and likes a drug is going to use it again and become a drug addict, for example, or abuse it.

I think it will be nice to have some panel where we could really usher these human abuse potential studies into the 21st century. Just looking through this, we can even measure how much dopamine they release after a compound in the ventral striatum and see if this is less and is it more. So you can have a pharmacokinetic readout, a pharmacodynamic readout, and also a behavioral read out.

So I think that's probably something to demonstrate and give some guidance, based on the current status of literature, as opposed to going back to these old paradigms of liking and could be very

helpful for industry and also in evaluating it in a more current research model. That's all I have to say.

Are there any other questions or any other thoughts that people want to chime in? I'm going to look through this list.

I don't see any other raised hands. Does anybody else have any other closing thoughts? Does the agency want to provide some thoughts?

DR. FIEDOROWICZ: I have my hand up I believe.

DR. NARENDRAN: Is this Dr. --

DR. FIEDOROWICZ: Fiedorowicz.

DR. NARENDRAN: Dr. Fiedorowicz. Go ahead.

DR. FIEDOROWICZ: Yes. I just want to make a brief comment. I do have some concerns about some of the statements that were made about the idea of having medication intervention to treat alcohol and substance-use disorders being problematic. I think that that idea has been somewhat pervasive and has actually impeded some people from getting the help and treatment that they need.

I do have some concerns that the result of this meeting -- I think we all made thoughtful and

prudent decisions here in these votes, but I have some concerns that the results of this meeting may stifle innovation in this area, and I would not want to see that happen. That's all. Thank you.

DR. NARENDRAN: Thank you.

Dr. Zibbell, your hand is raised still.

DR. ZIBBELL: Yes. Jon Zibbell, RTI International. I just wanted to speak to Jess' comment. I think he was talking to me. But when I said a chemical response to a chemical problem, I was talking about ADTs, abuse-deterrent formulations, not medical-assisted treatment. I just want to be clear on that. There's evidence that that works. Thanks.

DR. FIEDOROWICZ: Thanks for clarifying.

DR. NARENDRAN: Dr. Griffin?

DR. GRIFFIN: Oh, sorry. I forgot to put my hand down.

DR. NARENDRAN: Okay.

Anybody else? I'm looking through.

Dr. Calis?

DR. CALIS: Yes, just very briefly. Thank you very much. I think, overall, the intent of the

applicant was to highlight a unique feature that would help distinguish their product from other stimulants. I think they've actually succeeded in making it somewhat more difficult, but as we've seen today and from our discussion, it's certainly not impossible to manipulate and abuse such a product, and I think that's where most of the concern rests.

There are a number of limitations with the application as have been noted previously by FDA staff and others, but I do want to circle back to I think had we had more ideas about -- and this is very challenging because it would be difficult to do regardless, but I think with regards to the safety, particularly with the excipients and what would happen in a worst-case scenario, I think if there was more reassurance in that regard, I think we'd probably all feel maybe quite differently about this. Thank you.

DR. NARENDRAN: Thank you.

We don't see any other hands raised. Before we adjourn, are there any last comments from the agency? I want to hand it to you guys.

(No response.)

DR. NARENDRAN: No comments from the agency?

DR. FARCHIONE: Sorry. We're conferring on our Skype.

DR. NARENDRAN: Oh, I have to summarize, too.

In terms of question number 6, the discussion, I heard that people were very concerned about the safety, and the excipients, and the TMA issues were unresolved, although they felt that some of these things could have been potentially addressed and could have alleviated some of the questions that remain.

I also heard that it would benefit sponsors if the agency could provide clear definitions, and clear thresholds, and clear standards of what is an abuse-deterrent formulation and how it should unravel so they can have a clear roadmap if they were to develop this. I also heard some thoughts about maybe abuse deterrence, a chemical response to a chemical problem may not be the way to go, and it might be too complicated because it's very hard to predict what real-world use could look. There was also some thoughts about maybe the human abuse potential studies could be more clarified or use more advanced models

that might be available in the literature.

With that, I will turn it over to Dr. Farchione for the agency's closing comments if any.

DR. FARCHIONE: Yes. This is Tiffany Farchione. I think this has been a very interesting discussion to say the least. There has been a lot of comments made, some of which were unexpected. You guys have given us a lot to think about and a lot to try to incorporate into the remainder of our review prior to the goal date coming up.

So it's certainly very helpful and informative, and, again, with this being the first stimulant to try to pursue an abuse-deterrent claim, it really is unprecedented. I know that we gave you a lot to wrestle with, so we certainly appreciate your thoughtful contributions and your patience with the virtual environment, and, again, it's been very helpful. Thank you.

Adjournment

DR. NARENDRAN: Thank you.

I do want to thank Dr. Bonner, the DFO, as well as the FDA technical staff who put together such a

great platform. I didn't even feel like I was missing the in-person meeting. So thank you very much, and with that we can adjourn the meeting. Thank you.

DR. BONNER: Thank you.

(Whereupon, at 4:38 p.m., the meeting was adjourned.)