FOOD AND DRUG ADMINISTRATION (FDA)

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

PRE-MARKET EVALUATION OF ABUSE-DETERRENT PROPERTIES OF OPIOID DRUG PRODUCTS PUBLIC MEETING

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College Park Marriott Hotel and Conference Center

3501 University Boulevard East

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Reported by: Samuel Honig,

Capital Reporting Company

A P P E A R A N C E S

Lucinda Buhse, PhD
Director, Office of Testing and Research (OTR),
Office of Pharmaceutical Quality (OPQ)
CDER

Anshu Choudhri, MHS
Managing Director, Value-Based Policy
Office of Policy and Representation
Blue Cross and Blue Shield Association

Daniel Cohen, MALS
Executive VP, Government and Public Relations
Kem Pharm, Inc.

John Coster, PhD, RPh
Director, Division of Pharmacy
Center for Medicare and Medicaid Services

Jeffrey M. Dayno, MD
Chief Medical Officer
Egalet Corporation

Gregg DeRosa
Vice President, Global Clinical Research & Development
Teva Pharmaceuticals

A P P E A R A N C E S (Continued)

Ellen Fields
Deputy Director, Division of Anesthesia, Analgesia and Addiction Products, Office of New Drugs
CDER

Chester (Bernie) Good, MD, MPH
Chair, Medical Advisory Panel for Pharmacy Benefits Management, Department of Veterans Affairs;
Professor of Medicine and Pharmacy
University of Pittsburgh

Stephen W. Hoag, PhD
Professor, Department of Pharmaceutical Sciences
University of Maryland School of Pharmacy

Jeffrey Kelman, MD
Chief Medical Officer
Center for Medicare and Medicaid Services

Penny Levin, MS
Director, Global Regulatory Intelligence & Policy
Teva Pharmaceuticals

A P P E A R A N C E S (Continued)

Robert Lionberger, PhD
Director, Office of Research and Standards (ORS)
Office of Generic Drugs (OGD)
CDER

Richard (Rik) Lostritto, PhD
Acting Associate Director for Science, Office of Policy for Pharmaceutical Quality, OPQ
CDER

Patrick Raulerson
Regulatory Counsel, Office of Regulatory Policy
CDER

Douglas C. Throckmorton, MD
Deputy Director, Regulatory Programs
CDER

James Tolliver, PhD
Pharmacologist, Controlled Substance Staff
CDER

Xiaoming Xu, PhD
Senior Staff Fellow, Division of Product Quality Research, OTR, OPQ
CDER

A P P E A R A N C E S (Continued)

Liang Zhao, PhD

Director, Division of Quantitative Methods and Modeling, ORS, OGD

CDER

C O N T E N T S

C O N T E N T S (Continued)

C O N T E N T S (Continued)

P R O C E E D I N G S

WELCOME AND LOGISTICS

DR. LIONBERGER: Good morning, everyone. Let's get started. I'm Rob Lionberger. I'll be the moderator of today's session. I'm from FDA's Office of Generic Drugs, where I'm the director of our Office of Research and Standards.

Welcome to FDA's public meeting on premarket evaluations of abuse-deterrent opioid products. During this meeting, we will discuss scientific and technical issues related to formulation, development and premarket evaluation of opioid drug products with abuse-deterrent properties.

Today, we will discuss the approach to testing generics recommended in FDA's draft guidance, general principles for evaluating the abuse deterrence of generic solid oral opioid drug products. We will also discuss comments and proposed revisions to the draft guidance. These discussions are intended to encourage comment and discussion and FDA will consider comments at this meeting before finalizing and revising the draft guidance.

Tomorrow, we will discuss FDA's efforts to develop standardized in vitro testing methodologies for evaluating the abuse deterrence of opioid drug products more generally. And we are pleased that you have joined us for this important discussion.

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.

During the meeting, we will provide an opportunity for public comment and FDA has established a docket to which comments may also be submitted after the meeting. First, I would like to identify the FDA press contact, Sarah Peddicord. Sarah, can you please stand up? So she's over there in the back. So if there's any media present, she'll be your contact to provide any information that you would need.

A few housekeeping meetings for -- items for the meeting. Restrooms are located down the hall to

the right of the meeting room across from the common restaurant. Lunch will be available in the Patuxent Room at noon. If you'd like information on other offsite eateries, please check with the hotel concierge.

Parking in the Marriott parking garage next to the building is free. If you do need shuttle service to the Metro, please see staff at the registration table and they can link you up with the hotel staff. And finally, if you have an emergency, please see the staff at the registration desk.

I'd like to quickly go over some ground rules for the meetings. Please take this time to silence your cellphones, smartphones and any other devices which you have not done so. Complimentary Wi-Fi is available. Please get the passcode at the meeting registration desk.

Please do not interrupt the speakers. Public comment will be only taken during the open public comment period, as identified on the agenda. You were asked to request to speak at the time you registered and FDA has notified you if you will be

talking during one of the public comment periods. There are still a few public speaking slots available. If you would like to speak today in the public comment segment, please see Michelle Eby. Is Michelle here? Or she'll be out at the -- she's also out at the registration desk as well.

So this meeting is being webcast and it also is being audio-taped and we will provide transcripts of the meeting on FDA's public website within a certain amount of time after the meeting.

We ask that speakers provide any financial conflicts of interest that you may have before you begin your speech, and we also ask this of people talking in the public comment period as well. Please note that we are not aware of any conflicts of interest for the FDA speakers. So they won't be repeating that.

You have been provided an agenda. I'll be moderating and I'll try to stick very strictly to the agenda. And so, please come back from the breaks on time.

So now, let's get started. It's my pleasure

to announce our first speaker, Dr. Douglas Throckmorton, the deputy director for regulatory programs at FDA. So, welcome, Doug.

PRE-MARKET EVALUATION OF ABUSE-DETERRENT PROPERTIES OF OPIOID DRUG PRODUCTS: FRAMING THE MEETING

DR. THROCKMORTON: Thank you, Rob. Good morning, everybody. I tried to think of a Halloween joke, but couldn't. First, this isn't a funny topic, so -- and it's not a scary topic either. But I am glad that you've all been able to make time to share your Halloween day and tomorrow talking about this really important topic. Thanks to Rob for inviting me to participate and give some opening comments.

The intent of my talk today is to frame what you guys are going to be doing in the next couple of days, to give some high level remarks about the framework for the larger discussion around opioids abuse because that is what we're here to discuss, preventing opioids abuse, and then, talk about both the Health and Human Services response to that and then some of the things that the FDA is doing with a particular focus on abuse-deterrent formulations.

We had a terrific meeting in 2014 on this same topic related to brand name development of abuse-deterrent formulations. I'm really looking forward to hearing the discussion these next couple of days focused especially on the generics developments.

So overall messages are pretty straightforward, and ones that we talk about a great deal. Abuse-deterrent formulations fit into the broader context of what FDA is doing. We understand this is an important area for us to focus on and we're doing it and we need to figure out a way to include all things related to abuse-deterrent formulations as a part of that work. Today's meeting -- today's and tomorrow's meeting will give us important information that will help us accomplish that goal.

So I selected just a couple of trends in prescription drugs focused on the numbers of prescriptions. I'm not avoiding other epidemiology we could focus on, but I'm given a limited amount of time, and I wanted to put the talks that we're going to be having the rest of the day into some context. The numbers of prescriptions that are made -- written

in the U.S. every year for extended-release and long-acting opioids. And they are the small bar at the bottom of this graph and the larger number of overall and immediate-release opioids that are written every year and the general trends. There's a trend upwards and there may be a slight decline here in more recent years.

One thing I'm going to return to is the small number of products that have abuse-deterrent claims that are currently being marketed. And again, they show up at the bottom of this graph. This slide shows some of those numbers. It shows the selected oxycodone extended-release products, Hysingla and Embeda, three of the products with abuse-deterrent claims through 2015, again showing the very small overall market share that the three of them occupied when this slide was created.

So where does FDA fit into the larger context of focus on abuse -- on prescription drug abuse and the need to address it? First, we're part of the larger White House plan, driven by the Office of National Drug Control Policy. We are also part of

the work going on through Health and Human Services. So in 2011, the Office of National Drug Control Policy issued its epidemic responding to America's prescription drug abuse crisis that we participated in. It has four pillars. I'm not going to go into them in great detail, except to say that the educational pillar is one of the things that obviously we've spent a lot of time working on, along with the proper medication disposal.

We also participated in and are contributing to the Health and Human Services secretary's initiative to combat opioid abuse. Here again, there are three pillars: improving opioid prescribing practice, expanding access to medication-assisted treatment and treatment of opioid drug overdoses. These three pillars are driving Health and Human Services agencies in the activities that we have going on since the issuance of that plan.

There are at least three other activities that I can think of off the top of my head that are critical for us to remember also as far as Health and Human Services activities. National pain strategy has

been released. It's focused on making certain that appropriate pain management is available to patients who need it; pain management, not necessarily opioids, but making certain that the nation appropriately identify and make available treatment for pain.

The national pain resource strategy is paired to that document and is intended to drive a better understanding -- a better scientific understanding of how to treat pain effectively. And then, finally, the CDC treatment guidelines issued at the beginning of this year identified -- made prescriber recommendations about appropriate approaches to the treatment of pain when opioids were necessary. And you can see the hyperlink below where you can go to look at that.

So where does the FDA fit into all of those things and what are the FDA-specific activities that we're going to be doing, including abuse-deterrent formulations work? In February, we issued our action plan. I won't issue -- I won't read through this quote, except to say that it came from the commissioner, Dr. Califf, who basically said we needed

to place in one place the things that we were going to do, the highest important things that the agency, the FDA could take on to address opioids abuse and misuse.

This is a list that comes from the webpage you can go to, to see the details that we announced in February. I highlighted the fifth bullet, expand access to abuse-deterrent formulations of opioids to discourage abuse, to highlight that this is one of the highest priorities for the agency, one of the things that we're focusing on day to day in our work.

Other things that we have here you can see include expanded use of public comment, focused work on extended-release, long-acting risk evaluation and mitigation strategies, review of how we conduct our benefit and risk analyses when we regulate these products, and a number of other things.

And finally then, within the FDA Center for Drug Evaluation and Research, response to each one of these plans obviously incorporates them into our planning and we're focused on those -- on two things, providing patients in pain access to effective relief and reducing the misuse and abuse of prescription

opioids through those same pillars that the Health and Human Services plan identified. We do this through all of the available tools that the agency has.

So we can do a great many things when we're given the available data and when they're the right things for us to do. We can take regulatory activities, rulemaking and the like. We can make policy to help shape the development of products to make them safer and more effective. We can work to support the science necessary to address and inform those policy decisions and we can work with communications experts, both internal to the agency and through collaboration outside the agency, to extend our reach and make our plan more effective.

And now, I get to abuse-deterrent formulations, one of the things -- one of the focuses of this Center for Drug Evaluation and Research in our response to opioids abuse, one of the focuses of the FDA, obviously an important part of the HHS plan as well.

We had two goals that the FDA stated. We identified these in 2014. They remain the same two

goals that we have today. I don't know if you can even read the second one. Okay, you can read it better on the screen than you can here. I'm going to talk about that first one now.

Incentivize the development of opioid medications with progressively better abuse-deterrent properties and support their widespread use. I'll return to the second in a little bit. So we have been successful in developing products to address the opioids abuse crisis. Among those products are the approval of seven opioids with labeling for -- as being abuse-deterrent. We also have numerous INDs under development.

In addition to those products, we have approved products for medication-assisted treatment and products to treat opioid overdose. And I won't go into those any further except to say that they're part of a whole. Our totality of our medical products development include products both for the prevention of abuse as well as for its treatment.

Those seven products are important for us to pay attention to today because they represent at least

two major kinds of technologies, technologies related to preventing the crush and extraction of the active opioid and technologies intended to make the products less attractive for abuse by including an antagonist, a product that could either precipitate withdrawal or at least blunt the effect of the opioid if they were used together inappropriately. As you can see, those products have been approved over several years, most recently in August.

What's the future hold then? So we said that we intend to continue to support the development of these products. Where's the future going? I would say you can break this field, like many fields, up into three areas: early, middle and late. We are in the early phases here. We still have a relatively few numbers of products using what I would say is 1.0 technologies, extraction and crush resistance and antagonist properties.

We believe there are other technologies on the horizon. Because of this, we're focusing our attention on the data that are presented to us for each individual product. As we gain more experience,

as we get more products, we expect to be able to understand better the broader principles underlying the abuse-deterrent formulation, what works, what doesn't work and make some larger policy decisions, potentially shifting to class-wide scope.

And then late, late in terms of the developmental, obviously we would have abuse-deterrent formulations available for all major opioids. And then, the focus is going to shift to making iterative improvement, making it possible to have continued improvement in the abuse-deterrent formulations as they come along.

How will we get there? We're going to get to it through a series of regulatory steps based on the data we have, based on a fuller understanding of the real impact of these products in the marketplace. So we began by giving individual claims for specific products. That's the first bullet, data sufficient to support a claim of the specific product. That's where we are now, giving claims to products that support -- that provide us data that predict a likely effect to reduce abuse.

Once we -- once we're able to have that greater assurance about the true impact of those data, we can then move to make approval -- we can potentially move to block approval for other drugs that lack the same or better abuse-deterrent properties and then obviously as we continue to gain an understanding and confidence in terms of the impact of these products, we can potentially take action against existing products and then ultimately consider class-wide activities even against products -- against opioids different -- that are different than the one that we have data on.

Implementing this framework is going to first require clear standards. You all are going to help with that today. You're to help be giving us information about the guidances that we've released. You're going to help us talk through the in vitro assessments that we've proposed to understand whether the framework that we could be using going forward.

We have other work going on around abuse liability assessments -- abuse liability testing, work that we think is going to be important in

understanding the clinical consequences, the preclinical -- the premarket testing using clinical tests. And then, finally, assessment of real-world performance, as I'll return to in a moment, is absolutely essential.

We've got to figure out which ones of these products work and under what circumstances. We're going to have to have a framework -- a policy framework that's more detailed than the one that I've laid out to date to discuss what level of performance is necessary for us to move from stage one to stage two to stage three to stage four in the proposed outline that I mentioned earlier.

And in all things, we need to maintain a careful awareness of the overall marketplace. We are talking about a marketplace of almost 200 million prescriptions. So whatever actions we need -- we take have to be taken in the context of that broad, large marketplace so that it's not -- so that we're not disruptive.

We understand -- we have to -- we need to support both brand name and generics development,

generics obviously associated close to 90 percent of our prescriptions in the U.S. today. We have to make sure that both kinds of developments are supported. We have to support encouraging iterative development, first generation, second generation, third generation, et cetera.

We can't stop with the first technologies. We understand that there are better things out there potentially. We need to explore those. And then, we need to be able to manage expectation. Many of us in the room over and over and over remind people that this is not a silver bullet.

Opioids are going to remain abusable. We will not -- at least not in the time that I'm working in the agency, get to a place, I believe, where we can prevent abuse. But we can significantly reduce it with these products, I believe, and it's important for us to work to get there.

And then, one particular challenge I'm going to focus just a little bit on, which is this real-world assessment. I mentioned earlier one of the things we have to do is understand what works and what

doesn't. to date, we've not yet concluded that any of these products have a real-world impact based on post-marketing data.

Our current actions are based on premarket data, in vitro data and clinical data predicting that the formulation would reduce abuse. We stand by those predictions. We're confident in the science. We're confident in the assessments that we've conducted. But we understand the importance of having real-world information to buttress that, to give us a better understanding, to give us the strength to go take other actions.

A challenge here is the size of the market that I alluded to earlier. Opioids are dominated by the non-abuse-deterrent formulations, with a market share for abuse-deterrent formulations being small as a fraction of the overall market. That presents challenges for us as far as looking at the impact of the approval of a specific abuse-deterrent formulation on real-world abuse. Those are challenges we're working on. But it's a challenge that's important for us to confront.

The data that we have available often gives us limited information about individual products and how they're being abused, generic versus brand name, for instance, formulations, liquid, solid, solid oral, patch.

We also know that there are social factors that underlie the choices that abusers make, whether to choose oxymorphone or whether to choose hydrocodone is not simply a matter of the molecule. There are also social patterns that we need to understand in order to assess this impact. And then, finally, there are many other activities going on in this area, many agencies, lots of state and local activities. Teasing out the effect of a single activity like the approval of abuse-deterrent formulation proves challenging.

And now, let's talk a little bit more about the second goal and the things that we're going to be doing today. The second goal for the agency related to abuse-deterrent formulations is to assure the appropriate development and availability of generics -- generic abuse-deterrent formulations in this case -- reflecting their importance in the U.S. healthcare.

To do that, we start with policy, and that's the focus of this first day today. You have the draft guidance before you. We're soliciting comments, actually eager to hear them, to make certain that we understand if we're on the right path towards the support of generic abuse-deterrent formulations.

CDER is also conducting research. You'll hear about that research the next couple of days, to underlie the policy decisions that we're proposing, research on formulations, research on other kinds of aspects of manufacturing to help us understand the best ways to set that policy.

And then, finally, underneath all of that, we have to remember that the generic drugs user fee -- generic drugs program is a very large, very important part of the U.S. healthcare system. And whatever else we do around generic drugs needs to be done in the context of that program.

There is product-specific information that's available, supporting the development of generic abuse-deterrent formulations. The generics program meets with sponsors, talks to them about the best ways

forward. We'll use this policy to help inform those conversations.

Obviously, we understand that these products, these actions on abuse-deterrent formulations play a role not just for generics, but also for brand name. So I've got a good example here. We took an action two or three months ago to require labeling of opioids and benzodiazepines to expand the warnings around their concomitant use.

That resulted in 250 changes to abbreviated new drug applications, a large activity, obviously a lot of resources that need to go into that. So as we do things in this space, we need to understand the impact on the generic manufacturers and the generic market and the generics program.

GDUFA II recognized that challenge, identified abuse-deterrent formulations as complex products, products that required special attention from us, special focus in terms of the generic drugs support. So we believe that's going to help provide additional help as these products are developed.

So for today, we're looking forward to

hearing what you have to say, genuinely hoping to hear the kinds of discussions we heard last time.

2014 is really one of my favorite meetings. As I think back on 25 years, it was one of the most useful meetings I can remember participating in, in terms of the kinds of information we got, the kinds of feedback that we were able to use as we finalized that guidance.

I'm looking forward to hearing more of the same today and tomorrow. It's critically important for us. We need to make certain that the generics program, the generic products are supported in the same extent that we've been able to support the brand name. Important for us to hear comments not just simply from the scientists and academics but also from public -- from other interested parties.

Tomorrow, we're going to be talking about standardizing in vitro testing methodologies and you're going to be hearing a lot about the science that we've been conducting. Here again, we need to hear your feedback to make certain we're on the right path because that science undergirds the policies that

we're going to be putting forward, hopefully policies that are going to help encourage the development of products in this space.

So I'm going to end by thanking all of you -- genuinely thanking all of you for making time to come today. This is a very important topic, very important for the agency, very important for Health and Human Services and I'm looking forward to all of the comments we have.

Ongoing and planned activities at the FDA reflect all of the other activities going on in the U.S. government to address the opioids abuse crisis. This meeting focused on one particular aspect of that work, is one important step in that direction. And with that, I will thank you very much.

(Applause)

INTRODUCTION TO FDA'S DRAFT GUIDANCE ON THE GENERAL PRINCIPLES FOR EVALUATION OF ABUSE DETERRENCE OF GENERIC SOLID ORAL OPIOID DRUG PRODUCTS (HEREINAFTER, GENERICS ADF GUIDANCE)

DR. LIONBERGER: Thank you very much, Doug. So I am the next speaker in today's program and I'll

be giving an introduction -- an introduction to the technical content of the meeting, walking through some of the -- some of the aspects of the draft guidance to make sure everyone's aware of where we are in this and talk a little bit about some of the comments we received to the docket that's been opened after the guidance has been published and hope this will help spur the discussion of this guidance as we move through the rest of today's meeting.

So I want to put up a disclaimer. This is, you know, a different kind of disclaimer than you sometimes see from the FDA staff. But this is talking about how we're going to talk about potential changes to the draft guidance at this meeting. So this meeting is not where we're going to finalize the changes. Those will happen through the process of posting another either revision or final version of the guidance.

But we are going to talk I think very openly and clearly about places where, based on some of the comments we've received so far and where we are, where FDA is, considering changes to the current draft

guidance and we want to point those out to make sure that people on the panel and people who want to comment to the docket have the opportunity to -- you know, to continue to provide their input on those particular aspects of that.

So we will be talking a little bit speculatively at this meeting. But none of these are final decisions until there is a next formal revision or guidance. But this is, again, in the spirt of an open discussion of some of the issues in this complex area.

As Doug mentioned, the generic drugs are, you know, an essential part of the U.S. healthcare system. Eighty-six percent of the prescriptions are generic products. And in the specific case of abuse-deterrent opioids, the goal is that as new abuse-deterrent technologies appear in the brand products, there's a clear pathway for which they can then show up in generic products as well and generic products that are equivalent and substitutable for those particular brand products.

And, you know, as from the Office of Generic

Drugs perspective, we recognize that this 86 percent of prescriptions is a significant responsibility for us. We don't think that generic products should be available unless they match the performance of the RLDs.

So we take that responsibility very seriously as we set the standards and as we review generic applications that reference these products. So there's, you know, a balance of two FDA -- really two concerns here -- providing access to generic drugs for all RLDs and making sure that the standards for generics meet public expectations for products that are substitutable.

I want to talk a little bit about the context for the generic guidance, and this -- by context, I mean -- and sometimes the division of labor between what happens in the review of new drug products and what happens in the review of generic drug products.

They are different processes because they take place at different points in an overall product life cycle. You know, for an NDA submission, you

know, the studies in the NDA are really intended to map the performance of the RLD and set label -- what FDA -- and set what FDA thinks meets the criteria for getting abuse-deterrent claims in the label.

So there's a broad investigation. There's a wide set of data. There's new both preclinical and clinical data, a wide range of bioavailability studies under various different conditions -- human abuse liability studies. There's clinical studies that support, you know, the normal patient use of the product. There's, you know, bioavailability studies in there. There's extensive product characterization. But the goal of these is to map out the performance of the product.

But in this life cycle, this product ecosystem, in the NDA review process, there's a little bit of a different focus. For the abuse-deterrent attributes, it's, as I said, to ensure the performance is no worse than the RLD.

But overall, as we look across, you know, the entire generic drug program, the reason for its success is this division of labor. New safety and

efficacy data is evaluated through the NDA process.

In the generic drug process, the focus is on demonstrating product equivalence, comparative studies that efficiently and effectively identify and match the critical attributes of the products that ensure substitutability. And so, I think this is a critically important distinction to keep in mind as we go through today, right?

So you can't just say, well, the brand products did this in their NDA. Therefore, the generic products should do this in their ANDA. It's a very different context and that has to, you know, factor into our discussion here. And so, I think that's -- you know, as I looked through the comments, I think this is an important aspect to understand some of FDA's responses to those comments.

And so, I encourage all of you to keep in mind this context as today we're really focusing on the sort of equivalent side, right? I have a reference product that's already been approved and also already has abuse-deterrent labeling. How do I show that a generic product can be successfully

substituted for that?

And so, in my talk today, what I'll do is go through some of the key aspects of the guidance. So these are areas where we've received comments. But I think it will also serve to walk through some of the important points that are in the generic drug guidance. And overall, today we've received 78 public comments to the docket, and I'll try to -- you know, some of the more significant ones will be covered in these points here.

But again, these are all intended to really give you some context about the generic drug guidance and encourage the discussion throughout the rest of the meeting and our panel discussion. And you know, if you then -- as you leave this meeting, and you reflect on what you've heard, we encourage people also to submit the comments to the docket as well.

So just to talk through the key aspects of the guidance, the first and most important part -- and I think this needs to be made absolutely clear -- is the scope of the generic guidance. When does it apply? What products to apply? So what the guidance

says, I hope very clearly -- if it doesn't say it clearly, then this is something we might revise to make sure that the message gets through. It says when the RLD for the opioid product has any abuse-deterrent labelling, that triggers -- that's the scope of this guidance. So that's what triggers what's in this guidance. The RLD has abuse-deterrent labelling for any route of administration.

Once you're in the guidance, we ask that the ANDA provide data for all the routes of abuse in the guidance. This is -- this is because the evaluation of the abuse-deterrent labeling and substitutability requires us to look across the whole scope of the way abusers might manipulate this product, even for things that didn't get in the label of the RLD product. So we ask for data across all of those routes.

When the RLDs do not have any abuse-deterrent labeling, then this guidance doesn't apply to those. Those are out of the scope of this guidance. They're handled through the normal ANDA review process focused on bioequivalence and pharmaceutical equivalence of the products.

But once the RLD has the abuse-deterrent labeling, then you're in the scope of this guidance and we ask -- and the guidance asks -- recommends that ANDA sponsors cover the whole scope of activities. This provides data for a holistic evaluation, as we'll talk about, a weight of the evidence to ensure substitutability of the product.

And the key routes of administration that are covered in the guidance are the parenteral routes. This can be extraction from intact or manipulated products in preparation for injection. It talks about or a potential oral abuse. This can be extraction from an intact or manipulated tablets for direct ingestion or it can be chewing the tablets to release the drug faster than, you know, normal swallowing would be.

It talks about nasal route of abuse. All the seven products actually have claims about nasal abuse. So that's the one that covers all of the approved products have nasal abuse claims. And this talks about insufflation of manipulated product, but also can touch on some of the presence of aversive

agents. And then, the final route in the guidance is respiratory route, sublimation just in terms of heating the product and preparing a vapor that can be -- that can be inhaled.

And one of the key questions that we got under the scope area was that the guidance as a statement called FDA considers the totality of the evidence in evaluating abuse-deterrent properties. And there were, you know, several comments that pointed to please clarify what this -- what this means and the claim that, you know, without clarity, this can disincentivizes generic drug development.

And you know, we're sort of happy to have further discussion at the panel discussion. But to trigger that discussion, really the way to think about totality of the evidence or, in other contexts, weight of the evidence is to look very specifically at what FDA has done for other complex generic products.

So we have guidances on drug devices for inhalation. We've approved very complex products such as glatiramer acetate using what we've called a weight of evidence approach.

So for these complex products, in order to evaluate the ability of a generic product to be substitutable, you have to look over a wide range of in vitro and in vivo data sets to make that decision and that's really what we mean when we say we have to consider the totality of the evidence.

So it means that it's not limited -- that gets back to the scope as well. It's not just limited to the specific route of administration that's in the label. But we have to identify that there's no concerns with any of the other routes that aren't in the label, that the generic product isn't so much more vulnerable to one of those other routes that it poses a public health concern, even though the RLD is not labeled in that area. That's part of this decision process.

And you know, I think there's been perhaps some concern -- maybe we'll hear this in the panel from the generic industry, this what is -- you know, what does this actually mean. But the other way to think about the weight of evidence is that the guidance says here's the data set that we need. The

totality of the evidence looks at let's look at that data set and make a decision.

So the decision point in the guidance is should the generic be approved or not. And that comes from looking at the data on all the different in vitro and in vivo studies that go into this. And it allows for decision-making based on, you know, we've identified a difference.

Is this difference going to be potentially significant as part of the overall decision process? And this really recognizes I think linking into Doug's talk where we are in the evaluation process, still at a product-specific -- you know, a very product-specific stage. But the guidance really identifies I think clearly the data package that FDA would need.

So the second section of comments that were significant were what's called the stepwise approach. And so, if you look at the draft guidance for generics, one of its very significant features is for each of the routes of abuse, it breaks up the in vitro testing into different tiers of complexity. And these include stepwise testing that goes from simple to

complex manipulations.

And I'll talk -- you know, I'll talk a little bit more about that. But that seems to be a point of confusion. It's a very unique approach. It's a little different than what's done in the new drug submission. But the intention of this is that the comparisons between the brand and generic product stop when the RLD product fails.

So there's been I think a lot of comments about the need for testing to failure. So the generic guidance actually does talk about testing to failure, but in a little bit different way. All right. The stepwise testing says that you test until the RLD product fails, right?

Once the RLD product has failed, you don't have to show you're equivalent to the RLD product in other ways that it fails that are of higher, more complex ways to manipulate the product. It's really those initial points of failure which sort of provide the -- limit the scope for the generic products.

And so, before the RLD fails, that's where the comparisons are critical to show that the generic

product is going to be equivalent to the RLD in the space where the RLD is effective. Once the RLD is not effective, there's not a requirement to be as not effective as the RLD in the areas where it's not effective. So that's one of the key underlying aspects of the stepwise approach.

And the current guidance is not particularly prescriptive about test conditions. This is indicated by the fact that we're having a day two of this meeting to talk about moving toward standardizing these conditions even more. Because we're not able to be prescriptive at this time, you know, the guidance is outlining a framework.

And it sort of has things like a negative control, all right, to say if we can't provide specific testing conditions, can we have a framework for the data that you look at that would help you make decisions? Am I testing these products in an appropriate way?

And so, instead of having prescriptive conditions that are well-defined and well-established, which I think would be a benefit to have that, to say

here's how you do the comparison. Everyone does the comparison the same way. But in the case when we're not at that point, the guidances provide a process rather than specifics to help a generic company justify their particular testing conditions that they're comparing their product at.

And this involves both looking at what we call in the guidance a negative control and the results from testing both the RLD and the proposed generic under a range of conditions. So again, there's a set of data that says I'm proposing that my product is equivalent to the brand product under these conditions.

This is the pivotal comparison. And here's the data that justifies that this is the right place to compare it, because I can look at a negative control. I can say, look, here's the performance of the reference product. Here's the performance of my product across a range of conditions, and this is the appropriate point for a pivotal comparison.

And so, I want to illustrate the stepwise comparison and, you know, this is not a real example

form the guidance. It's a very simplified situation. But I want to illustrate sort of the idea of different scenarios, how a stepwise approach works. So, you know, the guidance is actually much more complicated than this. There's much more things going on. But this is trying to distill it down to sort of a simple model that can explain in a few minutes.

So if we start with the idea in the stepwise approach that you break the type of manipulations into different levels of complexity. So if you don't agree with these levels of complexity, you think they're on the wrong order, that's certainly something that we're open to comments on.

But here I've proposed one where you start with a simple solvent at room temperature. You go to a simple solvent at higher temperatures. You go to a more complex solvent at room temperature and then a more complex solvent at elevated temperatures. And then, you could even go to more complex manipulation.

So it basically breaks up the space into similar levels of complexity in terms of time and energy, things that we think would be important to the

ability of a product to deter abuse, the amount of time and energy that it would take to defeat a product, you know, to have to go to a chemical supply house to get certain solvents or I think these things I would find at home. Do I have to get industrial equipment or can I use things that I might find at home or at a store in my neighborhood? So level of time and energy needed is what governs the division of the testing into the levels of complexity.

And so, I'm going to step through a very simple example and say, well, part of the guidance talks about, you know, preparing intact tablets. So in this example, might you say, well, I'm going to start with my intact tablet in the first tier.

So it looks -- there's water at room temperature. So I have a control product. A control product is an immediate-release product, right? Every immediate-release product is going to release all of its drug in 30 minutes. So we already know that.

But we find that both the test and the reference products, they're extended-release products. So obviously you'd expect them in -- you

know, when exposure to water, to maintain release-controlling mechanisms. So this would indicate that the reference product, it doesn't dose dump. It doesn't release drug immediately. So this is a tier where you have to provide comparison of the test-to-reference product to support substitutability.

If you go to the next level of the tier, all right, say, well, if you just raise the temperature of the water, perhaps in this example you find that the reference product fully releases in 10 minutes, the reference product in -- so in this case, what the identification of the testing would do is say, well, here's where the -- here's the level of complexity that you need to defeat the reference product. This is where I need to stop my comparative testing. So the comparative testing would then stay at the first level.

If we look at another example, all right, a similar type of comparison, the first point stays the same. You need to compare the test and the reference products under the first tier condition. You go to the second condition, but you find that, no, the

reference product actually is resistant to release under this condition. That means that you also have to then compare the test and the reference product under those conditions.

So the advantage of the tier-based approach is as the reference products get better, that they resist more manipulations, there's more comparisons that the generic products have to do to support equivalence. So it rewards advances in abuse-deterrent technologies but it has, you know, a reasonable set of testing that allows generic products -- it doesn't require generic products to show equivalence in areas where the brand product is not supporting abuse deterrence.

If we look at just a third variation in this example, you move then from intact tablets to cut, grated or milled tablets. So you would say in that case, I would manipulate the product. I would look at, you know, the control product. The immediate-release products might release even faster.

But in this case, both the test and reference products hypothetically when they're

crushed, they have release controlling excipients and formulations that maintain their release control over that.

But then, if you go to a second level of manipulation beyond grating, milling or crushing the tablets, then you find that at elevated temperatures, the reference product releases faster. Then, there's no further comparison of the test product. But in this case, then, you have to take the test and reference product and compare them after taking both the cut, ground and milled products show that they both are substitutable in the simpler extraction after that manipulation.

So the tier-based testing and the role of the control is really identifying where do I stop testing, right? How many tests do I have to do for a -- to support approval of a particular generic product? And so, the tier-based approach is one way to organize the type of manipulations by time and energy to provide a limitation -- you know, a focused area on where the points we really have to compare the brand and generic products and show their equivalence

to support an ANDA approval.

Now, we received some other comments on this. We've talked about I think one that will hopefully have some discussion around here, cases where the test and the reference product might have slightly different technologies. So how should we try to manipulate them when they might have slightly different vulnerabilities?

And I think one point that, when we looked at this comment, on these points where we're comparing test and reference products -- so the reference product has maintained its resistance across that tier.

We should make sure that we include the worst case for the test product in that level of complexity of manipulations to clarify that that's the intention, where they intended to be compared, so that you're basically on a -- in a similar level of complexity, the idea is that in a sense you'd be saying what's the worst that happens to the test product in these types of manipulations and what's the worst that happens to the reference product and ensure

that those are similar.

Again, remember that this is a case where the reference product is resistant so that there is space for the generic product to be equivalent or to be worse and/or to fail, so succeed or fail.

And then, certainly we received a lot of other comments about asking for more specificity, about what should be involved. We'll be doing, you know, revisions for clarity when needed. But we also encourage some discussion on the day two about the different testing conditions and moving them to more standardized conditions.

Next category of questions -- where we've seen a lot of questions and comments into the guidance is in the use of control. So people look at this and ask, well, why do I -- why does FDA even need a control when you know the characteristics of the reference product. So sometimes, you know, we may know the characteristics of the reference product. But that data may not be publicly accessible. You may not have the right of reference to it.

I think a common example in generic drug

development is when we use BCS classification. We ask each company -- even though FDA has determined that the reference product was eligible for BCS class one bio waiver, generic companies have to provide their own data on solubility and permeability to show that their product is also eligible for that. So there's some aspect of access to data that's not publicly available.

There are a lot of questions about, you know, identifying the comparator and can we use all sorts of -- you know, almost crazy comparators from other countries. Can we make our own? And so, if you go and you look at the list of the -- you're within the scope of the guidance. It's products with approved abuse-deterrent labeling.

So that's seven -- you know, as Doug mentioned, seven products. And if you look at those seven products, there's, you know, a smaller number of APIs and some antagonist combinations, right? But for all of those, really if you're looking at the opioid aspect, you know, there's available immediate-release products for almost all of those. There's options of

tablets or capsules.

There's some of these -- there's non-abuse-deterrent extended-release products available. I think, you know, maybe -- I think there's maybe some confusion of hydrocodone. There's no single-entity hydrocodone product available. But there's certainly many immediate-release hydrocodone combination products available for use as potential control.

So we see that there's lots of approved products. Almost all of them are available in generic form as well for the non-abuse-deterrent properties. So we don't see that for -- in the space for generic products and the products that -- and the brand products that currently have abuse-deterrent labeling, we see that there are multiple choices for controls available for all of those products.

So we don't really see the need for non-U.S. or manufactured formulations as being a significant limitation in this case, that there are available products that you can find.

An important area we think for clarification of the guidance has to do with the evaluation of

agonist/antagonist combinations. So three of the products include either naloxone or naltrexone in the product as an active ingredient. And you know, the guidance isn't -- maybe isn't as -- you know, based on some of the comments, isn't as clear as to how the testing should apply to those types of products.

But there are some things that we can certainly say clearly, that all active ingredients are measured in the normal BE PK studies. So these are the normal bioequivalence studies that support any approval. They have to look at, you know, is that other ingredient -- is it support to be absorbed.

If it's not supposed to be absorbed, is it also not absorbed from the generic product when it's given normally to patients? So that's a part of the baseline when something's an active ingredient and these antagonists are all specifically listed as active ingredients.

So they have specific equivalence criteria on those active ingredients -- pharmaceutical equivalence, bioequivalence on both of those active ingredients for all of the generics. Now, the draft

guidance does recommend measuring all active ingredients in all the in vitro tests. So that was specifically intended to apply to these agonist/antagonist combination products.

But the area for revision where I think we need to provide clarity is how you evaluate that data more specifically. And I think the things that we're looking at for revision is to make sure that you're looking at the differential separation.

Do any of these manipulations separate the antagonist from the active ingredient -- from the active opioid ingredient? And do they maintain -- you know, they expect it to maintain the ratio that was linked to abuse deterrence in the original NDA application and the data that we have.

And so, this might include PK studies to look at if you have a product that's intended to release the antagonist only after the product is crushed, right? So that might be something that there might be new PK data that's needed to support that particular aspect. And we see some of those things as maybe coming in product-specific guidances for, the

specific PK programs that are needed for those products but mentioning, you know, a revision to the guidance indicating, you know, specifically how to apply these testings to the antagonist/agonist combinations.

You know, some of the other comments on in vitro testing are, you know, select -- how do you select specific solvents, questions about the statistical acceptance criteria and particle characterization. I think most of these are intended to be in the area of clarification.

So there'll be some revisions to make these specific things more -- you know, more clear. But we're happy, you know, to discuss more larger conceptual issues in the comment period. But I think these were -- these seemed to us to be mostly things where more clarity was needed in the guidance.

In the -- you know, the final role of in vitro testing, there's a group of comments that, you know, really challenge the overall aspects of the guidance in terms of saying that the in vitro and PK studies recommended in the guidance sort of

traditional bioequivalence, pharmaceutical equivalence type of approach to generics isn't sufficient.

You know, we generally see this -- from FDA's point of view, this is something that's made not just in this category but in many categories where there's complex products saying that there needs to be also clinical data or pharmacodynamics data in these cases.

And as for other generics, our approach, you know, really is to use in vitro methodologies and the Pharmaceutical equivalence, bioequivalence studies whenever possible to evaluate equivalence of generics. So again, this gets back to the appropriate context for new clinical data is really things that are evaluated in the NDA, they demonstrate the potential of these products to be abuse-deterrent.

The equivalence studies focus on the product performance and identifying substitutability. But certainly we're open to comments that identify mechanisms of abuse deterrence that aren't captured by either the in vitro or PK approaches in the current draft guidance. I mean, these abuse-deterrent

properties of the products, they happen by either physical properties or drug exposure properties, right? So we think that all of those, with the proper understanding, can be captured through the approach for generic products.

Another set of comments comes from aversive agents. And you know, this is an area where the draft guidance, you know, talks about really if something's identified as an aversive agent, really recommending that the generic product also have the same amounts of the aversive agents.

There are a lot of comments to say, well, maybe we don't -- maybe there's other things that lead to aversive agents other than the aversive agents, that it's a function of the formulation, of their combination, that it's really due to the overall complexity of the product.

And again, this is another place where it's important to recognize the division of labor between the new drug reviews and the generic drug reviews. I think the expectation -- the expectation is that during the new drug review, the contribution of each

ingredient to the aversive effect should be identified, right? You shouldn't have label claims about having an aversive agent without sufficient data in the NDA application to understand the origin of that aversive effect.

So a lot of these comments about, well, you know, we've got -- it seemed to imply a situation where you get the label claims but yet have no idea of why you're getting them. And so, the generics have to repeat the full set of clinical data to show that. So we think that we have a better understanding of the origin of these effects.

But I mean, we do consider revisions to this point, especially, you know, if there's questions about, you know, ensuring that a generic product, the aversive agent is available, right?

If you have a generic formulation and the aversive agent is sequestered in some way and is not available to contact the biological membrane where it has its effect, you know, that's obviously something that's going to impact the substitutability and effectiveness of the product.

So we want to make that clear, that that's part of the evaluation. And, you know, we also want to make sure that manipulation -- if manipulation could -- if a manipulation would destroy or separate an aversive agent, right, that could be something that could potentially have an effect. So we'll be looking at revisions, whether revisions are necessary to ensure that that's a significant effect, to clarify that.

So we'll be having a -- Liang Zhao will be giving a talk that will be focused on -- specifically on the PK studies. But we want to just indicate that there are several areas in the PK section of the draft guidance that will be considering revision; probably most significantly, the populations for PK comparisons, ensuring that especially for nasal abuse, that experienced nasal abusers would be a more appropriate patient population.

Some revisions to the statistical criteria for PK comparisons to make them -- harmonize them more with the more general approaches that are used for bioequivalence. And this covers also the PK metrics

and the use of partial AUC, which is the common way that we look for comparing whether there are specific aspects of the PK profile that need similarity.

We received some other comments on what I call more general policy questions about the applicability of the generic drug review process. And so, you know, one of the key questions -- you know, some of the -- there are multiple questions about that the ANDA pathway should be permitted for generics with novel abuse-deterrent technologies. And you know, so sometimes the answer to this depends on what's a novel abuse-deterrent technology, right?

So the generic guidance really provides pathways for comparing. You have to be -- if you're a crush-resistant product, the generic has to be a crush-resistant. It doesn't provide any pathway to say, well, I have an aversive agent that's equivalent to a crush-resistance approach. So the draft guidance only provides pathways that follow that same broad -- those same broad mechanisms.

But within those mechanisms, so say I come up with a new crush- and extraction-resistant

technology, that's something that's acceptable in the ANDA as long as it meets all of the other ANDA requirements, right?

So it's often difficult to get very new excipients approved through the ANDA pathway because they might need new clinical data specifically for excipient safety.

But if you can meet the other requirements for the ANDA and the requirements for performance showing equivalence in the abuse-deterrent aspects, then, you know, a technology in terms of, let's say, a mechanism for imparting crush- and extraction-resistance could be permitted in the generic product.

However, you know, you wouldn't be able to say that you're better than the brand product. If you want to have new claims about that, then that's something that you really have to follow through the NDA process to say I have a mechanism that's better than other products. You know, generic is an equivalent mechanism, not a better mechanism.

And we've received another set of comments on how the proposed guidance would apply to -- would

potentially apply to immediate-release abuse-deterrent generic products. And you know, currently there really aren't any, you know, immediate-release products with abuse-deterrent claims. I think those are more -- those are challenging because immediate-release products do need to release the drug quickly in normal use. So, you know, there's challenges there.

But we think that, you know, if a product -- if an immediate-release product did go through the NDA process, provide sufficient data to say that they are going to have a significant effect on abuse deterrence and they got the labeling, then the general framework, you know, I think in this guidance would apply in terms of how you would compare the products.

But you know, you'd see that immediate-release products, you know, they have to release the drug in a short period of time to have their normal effectiveness. So there may be -- you know, there may be challenges to getting that and getting those claims. But if they did appear, then you'd see -- I think we'd see a similar approach. But there are none

in the space at this time.

So just to -- you know, just to conclude, to talk a little bit about where we're going in the future. As I think it's very clear, the ANDA guidance comments are under review and under deep consideration from FDA. And we're bringing some of these issues out to the public here to get broad sets of input and comments into that.

So the docket for this meeting remains open until December 1st. So you can -- if you hear things, you want to reflect -- go back, reflect on them, put those comments in, get them in by December 1st. They'll be considered -- they'll be considered in the revision process to the guidance.

There's regulatory science in this area that continues under our -- you know, this is supported by the GDUFA regulatory science activities as well. And you'll hear a lot more about these from both our external -- some of our external collaborators today and our FDA scientists -- FDA internal scientists from the FDA's laboratories who are doing significant amounts of work on abuse-deterrent formulations

internally, both today and tomorrow. So this is -- you know, this is an evolving area. We constantly learn from both the science that we're doing and also the reviews that we're undertaking.

But we do have mechanisms to communicate with ANDA sponsors around this in addition to this guidance. So we have product-specific recommendations. So we've recently posted some product-specific recommendations that have the first step of pointing to this general guidance. But as we learn more and, you know, identify specific information for those reference products that we think needs to be broadly communicated, we'll do that through the product-specific -- revisions to the product-specific recommendations.

And there are also -- in the generic drug review process, there are mechanisms for pre-ANDA input. You can -- you know, if you have very specific questions about this guidance and how it applies to the development of a specific product, you can use the control correspondence process.

Again, I want to emphasize don't send us

control correspondence on sort of general questions about the whole system and statistical acceptance criteria. Control correspondence is really for specific development questions about specific RLD and your specific generic product. And so, you know, they're very -- they're intended -- they're a very fast turnaround question.

So they have to be very specific. So don't send us general questions to control correspondence, but specific development questions through there. And then, as we move -- as Doug mentioned, as we move into GDUFA II, we have a more formal process under GDUFA II for pre-ANDA meeting requests for alternative approaches to the guidance.

So if you're planning something completely different, there are opportunities to discuss that approach with FDA if there's a -- you know, if you're proposing alternatives to the guidance. But you know, the control correspondence is a faster response, but has to be very specific.

The meeting requests are really for broader alternative approaches. And to get a meeting request

granted with the Office of Generic Drugs, we really expect that you have significant data packets, so that you've done some characterization of the reference product, characterization of your own product to support that meeting and the scientific discussion around potential alternatives. So this isn't a hypothetical meeting. This isn't a "I'm not sure about the guidance." It's really a "I have data and I want to talk about an alternative approach."

And so, finally, just to conclude, the review standards for generic opioids support the FDA policy goals: access to generics, but ensuring high standards for generic substitutability. They encourage progressive development of improvements in abuse-deterrent properties.

As you see from the tier-based approach, right, as the reference products get better, the generic products have to do more testing to show equivalence. If the reference products are, you know, easily defeated but still have some benefit, then it's easier for a generic to show equivalence. As the reference products get better, the bar for generics

rises and that's captured in the guidance.

But we think it's also important that, you know, any of these approved technologies, for any of them to be widely used, they have to be -- make it into the generic product pipeline eventually. And I think this is, you know, essential for widespread use of abuse-deterrent generic products is that they become available eventually through the generic route. So it's not going to happen until that point.

So I'd like to -- that concludes my talk. I'd like to thank you all for your attention. Thank you all for coming here today. So we'll reconvene the meeting precisely at 10 a.m. for the -- to continue our scientific discussions. But thank you very much for joining us here today.

(Applause)

(WHEREUPON, the foregoing went off the record at 9:36 a.m., and went back on the record at 9:59 a.m.)

DR. LIONBERGER: All right. Welcome back, everyone. So before we go into the speakers for this session, I want to have two logistical announcements.

So one, just a little bit more details on lunch. So the lunch will be -- there is a lunch buffet in the Patuxent Room. So this is as you go out of the room, go to the right. There'll be a $15 charge for this lunch, but it will be a lunch buffet, not a boxed lunch and there's a room available there. So that's a little bit of logistics for lunch.

And then, the second logistics item is in the afternoon, there's a public comment period. There are still slots available in the public comment period. So you should see Michelle if you want to speak during those periods. If the public comment period is not filled, we will go directly into the panel discussion when the public comments are completed.

So, you know, so just be prepared. If you're interested in the public comment period, we may begin -- if you're interested in the panel discussion, we may begin the panel discussion immediately after the public comment period. So this will just allow more time for the panel discussion.

So with that, I'd like to introduce our

first speaker for this session is Xiaoming Xu. He's a senior staff fellow in our Division of Product Quality Research in CDER's Office of Testing and Research. So he's been doing significant laboratory work on the abuse-deterrent formulations. So, welcome, Xiaoming.

FOUNDATIONS OF IN VITRO COMPARISONS OF GENERIC OPIOIDS TO REFERENCE LISTED DRUGS (RLDS) WITH LABELING DESCRIBING ABUSE-DETERRENT PROPERTIES

DR. XU: Good morning. My name is Xiaoming Xu, and I work in the Office of Testing and Research, which is a laboratory-based office within the FDA. So within the last few years, together with many of my colleagues, we have been working very hard in the area of abuse-deterrent formulations for opioids to understand the formulation design, manufacturing science and, most importantly, the evaluation method.

So today, I'm going to share with you some of our learnings and throughout the talk, I'll try to give examples to illustrate what are the considerations you should consider during the development of the in vitro method and also some of our past and current research projects in the area of

product and process understanding. So I will cover two things. First is that this talk -- today's talk will be focused entirely on the in vitro methodologies. And second is that due to the nature of this topic, I will not be able to go into specific details of some of the methods. So let's get started.

In the last public meeting, probably you have seen similar slides, just to show the commitment of the FDA in the area of understanding the manufacturing science with regard to the abuse-deterrent formulations. And in the last few years, we have made significant progress in terms of the infrastructure.

So we have completed a lot of manufacturing science equipment, analytical equipment installation and training and also hiring of the staff with proper background to study this area. And also, most importantly, we have a dedicated research program looking to the materials, a lot of them excipients used in the formulations and also processes to understand their impact on the ADF properties.

And this research is now done in isolation.

So a lot of research staff also involved with the review and also we closely work with the other offices in the agency to both review and policies.

So today's topic is the generic abuse-deterrent guidance. So I want to highlight a few things. As Rob mentioned earlier, the expectations for the generic product is when the reference product has the abuse-deterrent properties described in its labeling, the generic version of it is expected to be no less abuse-deterrent. And this applies to all potential routes of abuse. And importantly, the evaluation strategy is comparative in vitro methodologies.

So additionally, as we understand -- trying to -- we have been understanding the science behind these formulation designs and manufacturing technologies, we recognize the importance of understanding the product and the process and this is particularly important for the companies who are developing the product. It really needs to be -- you really need to understand your product and your processes.

And this is important for a few reasons. One, it helps to identify the strength and failure modes of the reference product. And because of that, it can guide the design of the in vitro development -- in vitro evaluation methodologies.

And also, importantly, a lot of the abuse-deterrent formulations utilize new materials and new processes which we need to really understand their potential impact, not just on the product quality but also abuse-deterrent performance.

So some of the general considerations when you are developing abuse-deterrent formulations, we recognize the biggest challenge associated with evaluation is the complexity of the design. And this applies to not only the formulation design, the process design, but also just design how to evaluate the formulations.

So a possible scenario example provided here -- I won't read through it. But the idea is that if we're not fully aware or careful of the experiment needed to evaluate the formulation goes into tens of thousands. So we really need to avoid situation like

a data dumping because this creates burden both for the industry as well as for the agency.

So one way to do that -- to eliminate the potential data dumping is, as mentioned earlier, stepwise approach and testing to failure. So that potentially can eliminate some of the unnecessary testings. And the other way, or the other potential is to understand the design and then to choose or develop methodology wisely.

So a lot of you who are in the business of doing the testings should be very familiar with some of the standardized approaches, standardized equipment methodologies. But what we have learned is that some of those standardized equipment, standardized methodologies cannot be assumed to be appropriate directly for the evaluation of abuse-deterrent formulations.

And one of those examples is dissolution testing. As we know, we have the compendia apparatus, USP 1 and 2, which are commonly used for the dissolution testing of the intact tablets and capsules. But when we are talking about abuse-

deterrent formulations, talk about the manipulations, many times the formulations are compromised in terms of their dosage form.

So you may see situations like shown in the picture on the right. There at the beginning, we have in that basket the powders, which are manipulated tablet, and the end of the dissolution we see still powders but they are floating on top of the basket and then they completely gel. The end result is that they prevent further dissolution, showing on the left graph there is that after 60 minutes, we only see half amount of drug being released.

So the reason for that is because of the polymer. It stopped further dissolution. So this is an analytical problem in terms of methodology. And so, the message here is that standardized equipment methodology should not be assumed to be appropriate.

As mentioned earlier, the in vitro method should be discriminatory in order for compare of reference and a generic product. And it's also equally important that the method is discriminatory and also the variations usually expressed as relative

standard deviations should also be properly controlled. And there's a perception that evaluation of ADF associated with large variations.

So what we have done is we're looking to the data that we have generated internally where we prepared formulations that are mimicking some of the commercial ADF formulations. And then, we evaluate manipulations, extractions, et cetera. What we found is that in certain situations, for example, the early time points, it's true that there might be a slightly elevated variation.

But as the time progresses, for example, in this case, 30 minutes after the starting of the experiment, the variations tend to be very similar to what we still found with any other analytical method. So it's possible to develop a method -- an in vitro evaluation method that is discriminatory and also with reasonable variations.

And perhaps the most important aspect of looking at in vitro evaluation method is the details. And this has been highlighted in both the 2015, the labeling guidance as well as the current draft generic

guidance. A lot of the expectation for details are mentioned there. So I will highlight a few of them here.

The first thing is about the time point. Looking onto the graph, if you look onto the right, that represents two extraction or dissolution profiles from two different products. And then, if we just take a single time point from that profile, we show on the left these two may look identical. But when we consider entire profile, we may generate a different conclusion.

So that just highlights the importance of a profile comparison rather than a single time point comparison. And with regard to the temperature, what's important is to understand this is the material driven. A lot of polymer excipients used, they have special behavior on a different temperature.

So when we do the evaluation, we need to consider what's relevance of that material property to the selection of the temperature. And same thing here is applied to the -- also applied to the solvent. So understanding what is solubility of the drug in

particular solvent and also maybe the excipient will help with the development of the method.

In terms of the sample repetitions, a general rule is that we need to have sufficient statistical significance. So greater than three, that's a very common rule. Last, but not least, the volume of the extraction studies. There is a tendency trying to mimic what the abusers' practice would be to do during the extraction.

So one of those conditions is using low volume, such as 1 to 2 mL. We need to be really careful about doing in vitro evaluation in that regard because, as we know, when we reduce the sample volume, there may be a violation of the same condition, which may prevent further release or dissolution.

So we need to strive for a balance between, on the one hand, we're trying to be as relevant as possible but, on the other hand, we need to make sure the method is appropriate. So that is the method details.

So these slides highlight or capture the complexity of the abuse-deterrent formulation

evaluation. Don't be intimidated by the lines drawn between the boxes. Those are there to help to draw the connections between the boxes. So I will walk you through a case here.

So let's say a company is developing a product to prevent parenteral abuse and starting from the left side. And then, you may choose the different designs, such as making it create a physical barrier or a chemical barrier in order to achieve that parenteral -- preventing of parenteral abuse.

And in terms of -- let's just pick the physical barrier -- what are the potential characteristics of that design? It may be that this design would impart a physical strength that resists a physical manipulation or it can directly prevent parenteral administration.

So those characteristics are the ones that we can develop an analytical method and then we can evaluate and we can assess. And of course, some of them can be grouped together into different categories. That's what's showing on the right-hand side.

So imagine for the company what potentially the evaluation or the idea is you go from the left to the right. You identify the target, the goal and then start developing product and start proving that those are effective. And as we are evaluating them, we will go from right to the left. We see whether those evaluations provide justification for the claim.

So the next few slides, I will give some examples, research examples to further explain that complexity. So this one is about physical manipulation. Shown here are two formulations. On the top, material A, you see that after some time in the coffee grinder, it became fine powder. And again, this powder can pass through a typical sieve that we use to fraction the materials. But the bottom formulation, material B, even after a certain time in the grinding, still remained its integrity.

So if we look at in terms of comparing these two products, we have two potential ways to compare. One is look at the effort. We may conclude that material B withstands the grinding better than material A. And the other way is to look at the

outcome. In this case, the particle size. So clearly, the material A generates finer powder so that -- so that it's not as good as material B.

So this is a typical way we've found doing the comparison to show this physical -- strength to physical manipulation. So we ask ourselves "is there any better ways, more fundamental methodologies to understand the physical strength," for example.

So shown here, on the left side, is an instrument called a texture analyzer. So what it can do is the arm is going to move down and then press against a subject -- in this case, a tablet -- and apply force. And then, we will plot the force against the distance it travels so we can get a profile of this material.

So shown here in the middle on the graph is a comparison of these two materials, the A and B shown in the earlier slides. You can see that material A, the blue one, it fractures at an early -- at a lower force and material B does not fracture, but it deforms. In material science, we call this plastic material. So what this shows is that there are more

fundamental methodologies that we have as tools to evaluate the physical manipulation or physical strength of the tablet.

I mentioned earlier that a lot of the abuse-deterrent formulations use new material and new process. One thing that's really important to understand is the formulation and process impact on the abuse-deterrent properties. So shown here is two types of formulations prepared using two different processes, process A versus process B. They're very similar in terms of the formulation composition. But the only difference is the process.

What we found is that for the process A, this material, even though in water, it released very little drug. But in 95 percent ethanol, it shows almost 90 percent of the drug, and this is in 30 minutes. After manipulation, the material from the formulation from process A shows large amount of drug release in both the 95 percent ethanol and in water where the formulations through process B, still it retained its property to deter the extraction.

So shown here is the impact of the process

on the abuse-deterrent properties. And not only the abuse-deterrent properties, but what we found here is actually it may have some safety concerns too because showing on the left-hand side, that is a dose dumping in 95 percent ethanol. This is the through internal -- with prepared formulation to look at the process and the material variation and their impact.

And we can certainly go one step further to understand what is really happening with regard to the phenomenon we saw earlier. And without going into much detail, I can simply explain that this is due to -- these two formulations due to the process using different process.

They generate a different internal structure of the tablet and one has higher porosity and the other one has less porosity. And because of the material, in combination with this structure, it gave rise to the phenomenon we saw earlier.

So as you may be aware of, that within FDA, we have a method verification program that is routinely being used during the review processes to look at the analytical method, to verify the method is

suitable for its intended purpose. And because of the experience we have accumulated in the last few years on the abuse-deterrent formulations, we are now fully capable also to conduct some of the studies on the abuse-deterrent properties.

And to summarize, to date, the abuse-deterrent evaluation has been non-standard, making the comparison relatively difficult. And to support the development of new products with abuse-deterrent properties, we have investigated significantly in the research to understand the manufacturing science and also throughout the external work with the academic institutions, trying to enhance advancing our understanding in this area.

And as we recognize that current generation of abuse-deterrent products can still be defeated with a certain degree of difficulty, and there are more/other different technologies that may be used to improve upon this. And certainly, we need better methodologies to look at these categories of products and there will be a whole lot of discussion tomorrow on that topic.

And with that, I would like to acknowledge many of my colleagues, some of them are here today, who really spent a lot of time and effort to understand the science behind this technology; and also Office of Generic Drugs, Office of Pharmaceutical Quality and controlled substance staff. And with that, I'd like to thank you for your time and attention. Thank you.

(Applause)

DR. LIONBERGER: Thanks, Xiaoming. So our next speaker is Professor Stephen Hoag, from the University of Maryland School of Pharmacy. And he's been a collaborator with FDA on some research activities related to abuse-deterrent opioids.

DR. HOAG: Thank you for giving me the opportunity to speak to you today, and as Rob just mentioned, we've collaborated with the FDA and they've provided some funding for this work. The outline, I'm going to do a little bit of an introduction about this. We took an approach of looking at material science, applying some of the things that are known in material science to the abuse-deterrent formulation,

show you some data that we collected on manipulation and then summarize our findings.

This is just from the patient package insert of Avinza. That was one of the early controlled-release formulations and just showing you that it was one of the early once-a-day dosing for the chronic management of pain. And so, this is -- I think some of this has led to the abuse because if you take that and take the Avinza, which is a combination of immediate-release and controlled-release beads, that if you just crush those between spoons and snort them or swallow them, you can get euphoria.

And so, this kind of -- when we did our studies, we kind of took the perspective of what would the abuser do and then try to look at test methods that at least capture some of these elements. And so, the abuser -- the goal of the abuser is to acquire the drug and the rapid uptake, you know, as indicated by like C_{max} and t_{max}, you know, if you take your medications as prescribed, then, you know, you don't get the euphoric high.

But if you abuse these, if you misuse these,

you can get euphoria and that leads the reward and drug-seeking behavior. So the goal of the abuse-deterrent formulations are to develop barriers to prevent this or at least -- maybe I shouldn't say prevent, but deter this and create a situation where it's undesirable, perhaps the inclusion of an antagonist or an aversive agent.

And what are the modes of abuse? So from the abusers' perspective, they can snort the drug. And one of the key things is there are -- like pharmaceutical sciences, they have to get that drug into a form that can be administered. And so, for example, with snorting, a key thing is reducing the particle size. And then, that is absorbed through the nasal cavity by snorting.

And so, and also, the nasal cavity, there's the physiology of the nasal cavity, and some of the drug, if it's not absorbed readily, is also absorbed orally. Another possibility is smoking. Again, you have to reduce the particle size and here, you're heating up the drug until it's vaporized and it's absorbed by the lung. Also, things such as IV

extraction -- IV administration. One can extract the drug after they reduce the particle size and then orally, if you break down the barrier or take more than prescribed, you can also acquire something.

And here, this has already been mentioned today, but this is from a summary of the guidance with some added information. The different types of things that they can do -- you can do the physical barrier, the agonist/antagonist combinations, aversive agents, prodrugs, combinations and then there's a lot of new things on the horizon.

So here's just an example. As mentioned, there's -- and I think this was shown previously -- that, you know, there's certain products are actually approved and there's a lot of things where people are working on but haven't received approval yet. And also, something to keep in mind when developing formulations or test methods for the evaluation of these formulations is a spectrum of abuse.

And they go -- you know, can go anywhere from, you know, one-minute effort all the way up to a PhD thesis. And so, you -- you know, the range of

what abusers are willing to do to acquire or misuse the drug can vary quite a bit. And it's fair to say that no drug is abuse-proof. But as shown here, there's a level of deterrence. And if you can prevent someone from getting into this process, that can really help or at least prevent abuse of the drugs.

And so, now looking at what are some of the methods, and you know, looking at valid test methods for the in vitro test methods, you know, you have all the same things, the accuracy, the precision, the robustness, are they stable, are there inter-lab variability, intra-lab variability. All these types of things are very important in developing test methods.

Some of this is mitigated by the fact that you're doing comparisons. But still, you know, you want to have reliable results and things. And so, the ideal test method should correlate what the abuser does with real-world product performance. So coming -- and we'll talk about that. And you know, we're not doing in vitro/in vivo correlation. But kind of along those ideas, that they should be representative.

So actually, this is kind of a similar table -- we developed it -- to what was shown on the previous talk. But here, the modes of abuse -- so when we were working on this, you know, the modes of abuse are the mechanical, the grinding, the crushing, the thermal treatment, the extraction and separation for aversive agents and then what are the routes. And in this slide, I don't have the arrows drawn, but you can see that, you know, you have to consider all of these and then come up with the right test method.

So on the right side, we have the test method selection. So that test method selection is a combination of what is the abuser doing, what type of claim are you going to do, what route of administration are they going to do and then you would pick a test method that would work accordingly.

So here, getting onto the next level, here are some of the things that are available when doing this. So things like mechanical -- you know, you can cut that. You can crush it. You can grate it. These are the types of things that are available to the abuser for cutting, crushing, grinding, all of these

types of things. I'll talk about this a little bit more, along with thermal extraction, microwave ovens, heating, all those types of things.

So these, when you're looking at trying to simulate these things, these are some of the things that are readily available. Our thought was that abusers aren't going to call up scientific houses and order, you know, complicated equipment or something, but some of them might.

So when we did our study, we tried to mimic household tools and so here are some common things that can be used. And one of the problems when working with these household tools is if you're using, for example, a coffee grinder, they're not set up for grinding for long periods of time. So you'd better go out and buy like 10 of them because if you want them to last the whole study. So these types of things, the Dremel tool, the cutting and all of that.

In terms of the cutting, there's a lot of different ways of cutting this, and we were thinking about what is the reproducibility of this method. And you know, for example, using a razor blade or a grater

or something and we decided to use the cutting shears. This kind of eliminates the size of the lab tech and hand strength and all that. And so, you know, but there are multiple ways of doing this.

And so, how do we use these? How do we set up the test methods? How do we evaluate these? This slide here on the right kind of shows -- this is a summary of about three weeks of a graduate course on evaluation of tablets, where if you have a material, you can apply a force to that material. That material will respond, depending on how the force is applied. So for example, applying a cutting force is going to be different than applying a milling force. And the materials behave differently, depending on how the forces are applied.

So if you go into the engineering literature and you look at the application of force, you may hear things like materials can fail in shear. So if you look at the lower example there where you're applying a force, if that force creates like cutting, creates a lot of shear, that material will fail and shear if you're crushing it, that can actually cause other

types of forces, volume changes. And the material properties of these are very different, depending on how the force is applied.

So you have to be careful of this because the polymers and materials that we're working with are viscoelastic. And so, like what is the rate of the material? How fast do you apply it and things? So when we're designing this, you have to consider all these types of things and I'll give you some examples of that in just a second.

So the first way of applying a force, for example, if we look on the right side there, crushing. For example, I gave you the example of Avinza, which is multi-particulate beads. Those materials are very readily -- there was -- that was an early product that never had any abuse-deterrent labeling.

But those materials are readily susceptible to crushing, if you can break that coating on the outside and extract the drug. With the newer formulations like OxyContin and things, as part of this study, we did monitor some of the websites and YouTube, where abusers -- that's one downside of

social media, is that they can share information for good and bad. And it seems like with these newer formulations, crushing is less popular. Not zero, but is less popular.

So we focused in on cutting. And when you apply a force, if you look at the left side there, when you apply that force, you can break that force down into its components and then calculate things like the shear and really kind of understand how that material will do that.

So if you're trying to produce reproducible results, you know, what kind of blade, all of that. And if you remember those cutters that I showed you previously, you know, that -- if you go to an engineering handbook, you know, the leverage and the length of the blade and all of that, you can reproducibly determine the cutting and how much testing. So this is one set of forces that are applied, well-known, well-understood and can be analyzed.

Another way of abusing materials -- we just saw a previous one in the coffee grinder -- and here,

the key aspect is that the material is put in there and there's momentum. So it's a mill. As you can imagine, most pharmaceutical products are milled. So there's a lot of information on this. Things like what is the tip speed, what is the shape of the tip, the area.

If you look at, you know, showing kind of on the lower side here, two examples, you know, is that tip a blunt one? Is that a sharp one? I just noticed on the previous slide, noticed that this has kind of -- if you look on the right side here, on the right side of that impellor, this is a close-up of the impellor in the coffee grinder.

You can see that that has different shape to it than the previous one. And you can see that there's a curve on the right side. And then, on the left side, it's flat. And I think this is designed to get kind of that roping motion to move the material throughout the coffee grinder. And so, you know, this is the important thing. You know, what is the shape? What is the speed? That determines the momentum or the energy that the particle or the tablet will

experience.

And then, the final look -- way we looked at these are with grinding. So cutting, crushing had one set of forces, one set of parameters that are very important. Then, also people like can do grinding of the materials. And here, it's a frictional effect. So looking at like sandpaper. If you look at the right side, that's kind of a close-up view of that.

And you know, the key factors that dictate that are how hard you put -- how fast you move it, the sliding velocity and then the textures of the materials that are done. If you look at the upper right, there's an insert showing a tribology unit that can be used to assess this. So you can put that on there. That's kind of a rigorous test.

When we did some of our tests, we used a Dremel tool. But you can see that you could better standardize that. You know, because of controlling the normal force, how much the velocity and the distance traveled and things. So these are all things that need to be controlled.

And so, each of these failure modes, as

pointed out previously too, is that each type of abuse deterrent will have failure modes specific to that. And so, when you're developing a test, you have to look at how is this thing working and what should we be testing.

So also, I'll show you in the next slide here, here is the example of the abuse process for the nasal route of administration. So if you look at the top, you know, you can do these three modes that we just talked about of cutting, milling and grinding.

But also, when that system interacts with the biology, for example, the nasal cavity, the properties of that abuse-deterrent formulation still carry through. When you think about nasal clearance, the -- you know, the nasal clearance -- the mucus, the mucociliary clearance is a relatively rapid process.

So even if you put something in the nasal cavity, if it takes, you know, eight hours to dissolve, then that is probably not relevant because it will be cleared from the nasal cavity. So that's what I tried to show on the lower curve here. It's an attempt of a nose here. You know, if particles are --

one thing is -- if -- for it to land in the nasal mucosa, typically it has to be less than 100 µm.

And then, once it lands there, you know, because these polymers also have things to prevent extraction of the drug, there's swelling and those types of things that can happen. And so, that can affect the process also. So the PK factors are very important. So we found that, you know, you have to look at the destruction and then how is that done.

And when you think about the nasal cavity, what is the process -- that does the particle land on? It lands on a moist surface. So doing something like a USP apparatus 1 with a basket or something may not be reflective of this. But you know, that method of nasal disposition, but it may be reflective of oral absorption and things. So you have to consider the route.

Here is just -- so if we look at the first part up here, how did we abuse it, here's just showing you the manipulations. So just to orient you, we had two products, Opana and OxyContin. And so, this is the cumulative frequency distribution of the

particles. So if you look along the x-axis, that's the particle size. And if you look at the y-axis, that's the cumulative percent. And I have that red dotted line drawn there. That's the average.

So most of these curves, the particles were fairly normally distributed. And so, those -- if you look at that dotted line, that can tell you the average. So for example, if you look at the top one there, and the green is the ground -- it may be hard to read the legend here -- the yellow squares are the milled and then the diamond -- the triangles are the cut.

So you can see that the grinding produced the smallest particle size, as shown by the red. And if you look at -- you know, drop down from that red line, it's about 100 µm. The milling produced about 500 µm-sized particles and then the cutting produced the largest average particle size. And you can see that we did exactly the same manipulations on two different products. And you can see that on the lower one, the grinding had the smallest particle size and it was similar to that above.

But also, if you look at the milling and the cutting, that had very similar particle sizes. And the difference in these materials, in our opinion, is a little bit based on their plasticity and things. And it's kind of interesting because some -- you saw in a previous slide where they did similar studies where they ground it and the tablets rolled up into a ball.

But I don't know. You know, they had a different blade. So if you -- and I don't know if we're testing the same products. But if you look at this blade difference, if they had used a different blade, would those particles -- the tablets ground up, you know. So there's kind of some interesting questions there.

With everything we did, we were able to mill those down into particles. You can see some of these are a little bit large particles. The other thing that we found that was important to characterize was the yield. These different methods had different yields. If things get all over, it can be harder to control. That can affect abusers' liking.

So after we milled it, we then put it in a diffusion cell. Now, this diffusion cell -- it might be hard to see from where you are -- but if you have a nice monitor, you can see that what we did is we wet the membrane. So we -- and if you look at the picture on the right, that's filled up with liquid.

At the top of that thing is a membrane and then if you look at the picture on the left, you have that membrane and then you put a cap on that so it's a moist environment. So we put the particles and you can see on the top here, these are the top views. And so, you can see those particles and they swell in there. And then, they release the drug.

And so, that was one way of looking at the release rate. And because that absorption process, they have to absorb moisture to release the drug. And here, you can see some of the results that we got. So if you look at the black diamonds, that is the API by itself. So these are the same products that we just manipulated. And you can see that they have different release rates. So the different particle size produced different release rates and at least in this

vertical diffusion cell. So you know, the different manipulations produced different particle sizes. And at least in this test, they produced different release rates.

Here's just another example. We tested commercial products. But we also wanted to look at some of the factors that affect that in terms of evaluation of excipients. and our environment is not practical to start up a tablet press and make large quantities of tablets of things, of opioids.

So we used metoprolol tartrate, which has similar solubilities. And you can see on the bottom here, there's just these pictures showing the different materials, so the different rights. And so, you can see that what I would like to point out is that purple line. We formed gels of these materials and then put those in there. And so, you can see that that hydration process is important in your evaluation.

So just in summary, you know, this is a really rapidly evolving, you know, field that is changing by the minute almost. And so, I think using

material science properties for evaluation, considering this, is very important in developing good test methods. So, and finally, here are some of the collaborators that helped us with this project. It was a multi-university project.

(Applause)

DR. LIONBERGER: Thanks very much, Stephen. So our next speaker is Liang Zhao. He's the director of the Division of Quantitative Methods and Modeling in my office, the Office of Research and Standards, in the Office of Generic Drugs. So he'll be talking about some of the aspects of the PK studies in the in vivo parts of the guidance.

FOUNDATIONS OF PHARMACOKINETIC COMPARISONS OF GENERIC OPIOIDS TO RLDs WITH LABELING DESCRIBING ABUSE-DETERRENT PROPERTIES

DR. ZHAO: I was introduced by Rob earlier in the opening, so I'm going to cover the PK part of the generic guidance, followed by the nice presentations from Dr. Xu and Dr. Hoag for the in vitro comparison.

The general principles for evaluating the

abuse deterrence of generic solid oral opioid drug products include the following. First, if the RLD's labeling describes properties that are expected to deter misuse or abuse, the potential ANDA applicant should evaluate its proposed generic drug product in comparative in vitro studies and, in some cases, in relevant PK or other studies to show that it is no less abuse-deterrent than the RLD with respect to all potential routes of abuse.

Second, FDA intends to consider the totality of evidence when evaluating the abuse deterrence of generic solid oral opioid product. As mentioned in the guidance that PK studies should be conducted to ensure the absence of significant difference in the rate and extent of absorption. Comparative abuse-potential studies are generally not necessary, except in certain circumstances.

This slide shows a list of products with abuse deterrence claims by insufflation. The active ingredients are hydrocodone, oxycodone, morphine. Given their abuse-deterrent claim, the ANDA applicant should conduct study to confirm that the generic

product is not -- no less abuse-deterrent than the RLDs. Abuse by insufflation generally involves snorting of the milled oral solid product. Approaches to deterring the abuse include reduced availability and reduced -- reduced availability and reduced ability.

A PK program is usually expected for products with abuse deterrence by insufflation. In this regard, a decision tree was provided in the current draft guidance. First, use reference product to identify milling method. Mill the test product using this milling method.

After milling, then we will decide whether the percent mass of the fine particles of less than 500 µm of the test product is less than 10 percent. If yes, we stop further testing. If no, then we conduct a nasal PK study on milled reference and test products. Of note, the threshold of the 500 µm for particle size evaluation is considered for revision. This decision tree exemplified a case that a PK study is needed where in vitro characterizations of physiochemical properties cannot predict in vivo PK

profile of nasal powder.

There are not much details about a PK program in the current guidance. However, there are some K features regarding the PK study, which include study in healthy volunteers incorporating naltrexone to block the PD effects of opioids. The data analysis should include PK variables in terms of C_{max}, t_{max}, AUC and a pAUC for both opioid API and any active metabolites. The decision should be made based on the presence of statistically significant difference in PK profiles.

The revisions to be discussed today in the panel discussion -- I hope also in the open session for comments -- that the revisions needed in the -- further needed in the draft guidance. Currently, we are thinking to revise the study population to be experienced nasal abusers.

Confidence interval criteria will be applied in the data analysis. When comparing reference and test, the same level of mechanical or chemical manipulation to maximize the availability of reference and test should be applied prior to administration

through the proposed route. Further questions regarding the study protocol can be sent to FDA via the controlled correspondence pathway or via the pre-ANDA meeting platform, as Rob mentioned earlier.

The points to be discussed in the panel discussion should include when a PK study should be required for a product with oral abuse deterrence claims. The current thinking that PK studies should be conducted for single API product with oral abuse deterrence claims when in vitro testing is not sufficient. For example, an in vitro release testing method has not been established to waive the PK study for abuse deterrence claims by chewing.

For agonist/antagonist combinations, all active ingredients should be measured in the BE PK studies on intact products. PK studies to confirm oral absorption of sequestered actives after manipulation should be recommended in product-specific guidance if needed.

The second important topic regarding the PK program is data analysis. Before we progress to this important topic, let's have a quick review on the

standard BE assessment for generic products. The study design involved for a solid oral dosage form usually is single-dose, two-way crossover under fasting and fed conditions. The confidence -- the 90 percent confidence interval for the test reference ratio of the PK variables in terms of C_{max} and AUC must fall within the acceptance region of 80 to 125 percent.

In comparison, evaluations of C_{max} and AUC only may not be sufficient for abuse-deterrent products. Although conventional BE assessments typically based on C_{max} and AUC following single dose. To establish sufficient set of PK metrics, we are exploring relationships between PK metrics and abuse deterrence in terms of VAS and the PK metrics include the rate of rise of initial PK profile.

To allow clinical significance of the PK metrics, the focus investigation is on relationship between PK metrics and VAS. The current thinking that abuse deterrence can be correlated to the rate of drug onset and an equivalence in AUC and C_{max} do not ensure a similar rate of rise in the initial part of the PK

profile.

Partial AUC in this regard has been evaluated at the clinically relevant PK metric. Partial AUC is the metric OGD uses when the drug exposure within certain time period is clinically meaningful. For abuse deterrence, the initial drug exposure is important and a partial AUC can be used as a measure of rate of drug onset.

In addition, it also reflects the drug onboard at the interest of time interval. Appropriate partial AUC can be identified by closely examining the degree of correlation between partial AUCs of different time intervals to the PD endpoints of clinical significance. Recommendations of partial AUC can be API and product-specific. Intent to identify partial AUC as a PK metric to support the abuse-deterrent claims has motivated further research on the PK/PD relationships based on data currently available.

To assess the PK/PD relationship, several endpoints that have been used in clinical abuse-potential studies are under investigation. Visual analogue score assesses subjects liking or disliking a

drug either at the 13 time points or over a time period. Addiction Research Center Inventory Questionnaire Scales assess patients' stated mood and feelings about a product. Pupil dimeter size is also objective endpoint measured very often.

In the 2015 guidance for abuse-deterrent opioids evaluation and labeling, it is mentioned that the VAS should be the primary measure for drug liking because it appears to correlate most directly with potential for abuse. Take drug again VAS assesses patient perception to take the drug again at least eight hours post the dose.

Drug liking VAS assesses the patients' liking of the product at the moment the question is asked. It is useful in understanding the time course of drug effect. We consider VAS to be the most important endpoint in assessing the clinical relevance of abuse-deterrent effects of products.

In the next several slides, I will go through a case, Hysingla ER tablet regarding its PK study design and PK/PD profiles. Hysingla ER has been determined for it to have abuse-deterrent properties

for intranasal abuse, oral abuse when chewed and intravenous abuse.

Purdue Pharma has conducted two clinical studies for its oral and intranasal route of administration. The study assumed randomized, double-blinded, placebo-controlled crossover study design. The treatment includes positive control, placebo and Hysingla ER product, intact or manipulated. The take drug again VAS was measured at 12 and 24 hours post dose and drug liking VAS was densely measured from as early as 15 minutes to 36 hours.

I'm going to show a comparison of PK profiles for its oral route and intranasal route. The plot on the left panel is for the oral route and the plot on the right panel is for the intranasal route. In both plots, the blue curve on the top is for the positive control, as expected.

For the oral route, the flattest red line is for the Hysingla product -- the intact Hysingla product. And the two curves in the middle, with increasing C_{max}, are for the chewed and milled manipulated product respectively.

For the intranasal route, the two curves at the bottom are for the manipulated product with a slightly higher C_{max} observed for the fine particle than the coarse particles. Overall, in comparison to the positive controls, abuse-deterrent formulation has lower C_{max} and longer t_{max}. Manipulated tablet has higher C_{max} and shorter t_{max} than the intact tablet. Changes in the AUC_{0-last} are less prominent following oral route of administration.

Then, we put the PK/PD curves together for the oral route to have a preliminary understanding of the PK/PD relationship. Now, the plot in the left-hand panel is for PK and the plot in the right panel is for drug liking. You can appreciate that the drug liking curves usually follow a similar pattern as observed for the PK curves.

Of note, the area under the drug liking for the Hysingla intact product is comparable to that of the placebo and is disproportionately lower than the ones associated with other treatment when compared to the difference in PK. The maximum take drug again VAS (E_{max}) from oral route is shown in the table. The E_{max}

for Hysingla intact or chewed, but not milled, showed lower value significantly than the API solution, which is the positive control. This supports labeling language regarding abuse deterrence for chewing, but not for milling.

Similar analyses were performed for the intranasal route. Again, the plot in the left panel shows the PK and the plot in the right panel shows the drug liking curves. The bottom line in the drug liking curve in the right is for the placebo treatment. Again, the PD curves follow a similar pattern as observed for the PK curves.

For the maximum take drug again VAS, the E_{max} of the manipulated product, either for fine particles or for coarse particles, are significantly less than the value of the API powder. This again supports the labeling claim for abuse deterrence following intranasal route.

Conclusions with this case: for the hydrocodone abuse-deterrent product, drug liking VAS curves follow a similar pattern as observed in PK curves. Based on take drug again VAS, the manipulated

products show less abuse potential than control for the routes of abuse-deterrent property as described in its labeling, which is intranasal route or oral route when chewed. Things you also have appreciated a higher variability for the PD endpoint in terms of take drug again or drug liking VAS. The higher variability in the PD endpoints makes it challenging to assess BE based on the PD endpoints.

There are ongoing internal assessments to quantitatively explore the relationship between PK metrics and PD endpoints, including take drug again VAS, for other opioid APIs with abuse-deterrent formulations. It's quite an exciting research.

Summary of guidance regarding use of PK data. PK studies are important for products with abuse-deterrent claims. For agonist/antagonist combinations, PK studies to confirm oral absorption of sequestered actives after manipulation will be recommended in product-specific guidance. PK studies are generally expected for abuse-deterrent claims by insufflation and by ingestion when in vitro testing is not sufficient. I hope this can be a focal point in

the panel discussion later.

Finally, I want to thank all the contributors from within CDER, across different offices, including OGD, OCP/OTS, OND, the Workshop Planning Team and the CDER Opioids Taskforce. With that, I conclude my presentation. Thank you again for your attention and time. Looking forward for further discussions in the afternoon.

(Applause)

DR. LIONBERGER: So, thanks very much, Liang. So now, we'll be moving to presentations from first the generic industry and then the brand industry. So a little bit of background on the origin of these presentations, that FDA requested, that both the brand and generic industry formed working groups and developed presentations that represent a broad industry perspective.

So these people are not -- again, I think they'll tell you this. But I'll tell you again, that they're not speaking on behalf of their specific company. But they're representing the working group which both represent a range of companies in that

industry. So our first speaker will be Penny Levin from Teva on behalf of the generic industry working group. So, thanks Penny for participating and organizing this working group.

GENERIC INDUSTRY PERSPECTIVE ON THE GENERICS ADF GUIDANCE

MS. LEVIN: Thank you. I want to thank the FDA for everything. They've addressed a lot of our questions actually. So this has been really fruitful already for everyone. Okay, our disclaimer.

Okay. So what I'd like to discuss with you today is a short background about the situation for the generic industry, address the FDA questions that were identified in the Federal Register, give you a brief case study and summary.

So the background, I guess my statistics were a little off or we had different citations. But we understand that generic products now account for I guess roughly between 86 to 89 percent of the U.S. prescriptions today. As new abuse-deterrent formulations are approved for brand products, we believe there should be appropriate FDA guidance

available timely for the development of the generic products.

Going back to 2014, FDA held a very fruitful two-day meeting like this one where we discussed the then draft guidance entitled "Abuse-deterrent Opioids - Evaluation and Labeling" and asked input from the generic industry and brand industry. 2015, the FDA issued final guidance in that.

So you know, it was really very fruitful to see all of the input from everyone here today working to address and help advance that in such an expedient manner. And then, this past March, as we know, the FDA issued the draft guidance we're discussing today.

However, currently there are no FDA, approved ADF opioid generics. The current draft guidance requires further clarity on FDA's requirements for a generic to develop the data for submission of an ANDA. The draft guidance we feel must be revised, reissued for public comment and then finalized expeditiously. And the FDA issuance of product-specific guidance should be in close proximity to that of the RLD.

Question one, FDA has asked based on any testing you have attempted to perform or performed in accordance with the March, 2016 draft guidance, are there any aspects of the guidance that need clarification or improvement. So we broke this into basically three buckets. We looked at it from a regulatory perspective, a studies and analysis perspective and a legal/policy, if you will. So I'm going to run through the regulatory and then move along into those other categories.

So from a regulatory perspective, we feel it's really important that there's a provision of consistent guidance across all ANDAs and this is to ensure that there is homogeneity of all generic ADFs to keep in step with the confidence that we've raised with the American public over 30 years to develop safe generic products.

We need a regulatory pathway for those pending ANDAs. We know when GDUFA reauthorization comes next year, we believe it now will be classified as complex and we're very happy to hear that. But there are ones under review and in this year period

where we submit.

We need some clarity with regard to that. That includes additional communication venues. If we could have more open dialogue analogous to that, that will come with complex products, that would be really helpful, especially since this is such a dynamic space. And if we don't have the opportunity for those venues, the technologies will have advanced and we may not have the opportunity to offer the American public the generic.

We do feel as long as the ANDA contains the appropriate studies for abuse-deterrent formulations, it should be accepted for filing and recognizing that there may be some back-and-forth questions and so forth. But it should be considered accepted for filing. And similarly, priority review would be great if that could be an option for generic ADF sponsors to apply for.

We know that is an option in GDUFA II. But if we could have this in the interim period as well to apply for that, that would be great. We also feel that the nomenclature between the innovator guidance

and the proposed draft generic one right now are very different. And we feel it would help both the innovator and the generic in ultimately getting these products developed and approved if we order the topics similarly as well as used analogues nomenclature. I'll talk about that a bit more later.

From a legal policy perspective, you know, I was excited to hear from Dr. Throckmorton about that we will continue to advance these products and see -- and continue to want to evolve and make the better products. But this does leave a policy question and both on the branded and the generic side regarding clarity on the conditions of approval.

What is incremental improvement? We need to ensure that ever greening doesn't occur, as that will prevent approval of generic ADF products. From a study technology and analysis perspective, I know you said this, so I feel bad.

But I couldn't change my slides up after Rob addressed some of these points. But we do need guidance on the newer technologies coming, beyond the immediate-release, the ones that are beyond resistant

to crush. We need to address the number of test units for testing and statistical power to detect specified difference should be performed on. And ideally this should be standardized at some point.

Need statistical principles, and I was glad to hear more about that that's coming, for us to understand and ensure that the inherent analytical variability within a method is properly accounted for.

We need dedicated sections on the required in vitro studies included in product-specific guidance. And my colleague, Elisabeth Kovacs, tomorrow when she speaks with in vitro is going to take that a step further and also talk about technology/platform guidance. But from our perspective at the moment, I'm going to stick with the product-specific. But, stay tuned.

We need clarity on when a PK or PD study may be required. And when that is the case, there should be more clarity around the basic requirements of such studies in the general guidance and then details of each of those studies in product-specific guidance. When possible, we believe the controls should be the

same as that of the RLD and, when not, details should be in product-specific guidance.

We would like the FDA to help develop the acceptance criteria for the in vitro and PK studies. And we believe that should be one-sided; for example, no worse than. And we would love to comment on that. But we believe the FDA has the plethora of the data with probably -- in 2014, it was 26 INDs. So I imagine it's more open INDs. We have seven approved products. So if you can help put a proposal together on that, industry would help react and give comment.

Demonstration of the AD properties should only be performed against the RLD. In vitro methods are used to verify the suitability of non-dosing strengths. Additionally, evaluation of the drug product's AD performance would not be part of routine QC testing.

In other words, we would continue with our regular drug development and anything that would come up would come up in part of the development process and such testing would catch it there.

Some assumptions that the generic industry

working group made. We believe category one in vitro testing is mandatory and category two PK and three would be based on the science of the RLD.

So some examples, I mean, there are obviously more but here are some ones we believe would help illustrate. When category one and category two are predictive, meaning a correlation exists or can be established to that of category three, then only category one and two would be needed.

If category one and two however are not predictive, meaning a correlation does not exist or cannot be established to that of category three, then category three would be required. And this would be explained in the product-specific guidance.

Other areas that this may go beyond the in vitro study are the platform approach, which leverages multiple drug products over a range of strengths. Other assumptions include that the generic ADFs would not be subject to post-marketing or post-market commitments or requirements and that the section nine labeling would be comparable to the brand -- no carve-outs. We believe that's very important from a safety

perspective, and that generic ADF opioids will be recognized as therapeutically equivalent in the Orange Book.

Question two, are there any characteristics of currently approved ADF RLDs for which issuance of product-specific guidance beyond what is in the March, 2016 draft guidance can facilitate development of abuse-deterrent opioid products?

So in this one, we feel that FDA -- and again, I'm just glad it was clarified, we were recommending that they categorize the ADF generics as complex with the provisions that come with that in GDUFA II. We believe that will be very helpful and any help in this in-between period would be most appreciated.

We also recognize that with advances in technology, a product might not be comparable in size or shape or some other attributes. But we do commit that we will test to ensure that it is no less abuse-deterrent than that of the RLD.

In going back to GDUFA II with the complex products and pre-submission meetings, we believe this

is a really important vehicle, not just when you have guidance, but even to have that discussion with the agency on your proposed plan.

So not just when you want to deviate from guidance, but rather confirm that there's a meeting of the minds going forward. So we believe that that should be something, assuming that you put your plan together and proper meeting package materials and it's well thought out, that you should be granted such a meeting.

Furthermore, we're asking that product-specific guidance should be issued within 30 days of the approval of the innovator. And you know, we recognize that there are concerns about the product-specific guidance particularly being published on the FDA website because we don't want -- the people would try to deter defeating these formulations to have access to such information.

So we were thinking maybe FDA could have a closed-door meeting with generic manufacturers or some private mechanism to ensure that they can give the guidance but also not share publicly what could

actually wind up defeating and impact safety of the American public.

We believe it should be consistent with abuse-deterrent attributes described for the RLD in the label. And referring to studies in both general and product-specific guidance in an analogous manner to that of the brand, which I said before I'd expand on.

In other words, in the one guidance, in the branded guidance, they very nicely refer to the category one and explain in vitro and get in great detail. Category two, PK and so forth. In the high level generic, which we want to commend the agency with, because it's a really great start, it didn't do that in the same way.

And we feel that if you break it into those categories and use much of what's in the brand as it was explained, that would be most helpful. And of course, where differences are, it's different because of the science needed and the legislation.

Are there any approaches or technologies for FDA evaluating the abuse deterrence of generic opioid

drug products that were not included in the March, 2016 draft guidance? I was really happy to hear Rob expanded about totality of evidence. I think most of us, you know, you know it or can feel it or look at it, those of us that have worked on small molecules.

But it's a little different. This is new to a lot of us. So the more clarity we have in understanding that would be most helpful. And there was very little information about the PK or PD studies. No details as to when they would be required or the conduct of how to do them and what the combination, as well as the statistical acceptance criteria. After you got into the in vitro, it was very light. So we believe that would be most helpful.

What additional actions could FDA take to encourage the submission of an ANDA -- ANDAs, excuse me, that reference an opioid drug product whose labeling describes abuse-deterrent products? We really believe, not to be redundant, but timely product-specific guidance is going to be key in this area.

Again, it's a fast-moving space, and to

ensure that our patients here can have an opportunity to benefit from these products, that that guidance needs to come out timely.

The generic ADF product must have the same label as the innovator to mitigate potential safety events. And then, you know, similar to pediatric or orphan development, we're thinking perhaps incentives for the generic manufacturer to address this public health crisis. One might be priority review.

And again, I know that there's an opportunity with complex products with GDUFA II to apply to that. But if we can have some interim opportunity and maybe a reduced fee structure for the submission of ANDAs or at least those that maybe have a battery of tests beyond the in vitro, recognize that this is a very different model for generic manufacturers.

Depending on the route of abuse, we really would love to see FDA establish specific standard tests and then give confidence to the manufacturers that products meet the acceptable level of rigor. And that would be -- we look at that as the collaborative

endeavor between FDA and the industry. And again, you know, being that it's new, certain areas we don't feel are ready to standardize. But other areas where you've had a lot of insight into the data that's been submitted, perhaps we can, you know, put a stake in the ground as a start.

We also feel there's an opportunity to design a more effective human abuse liability study or of a surrogate that is more reliable than the current design. We've watched the innovators have their challenges with that study for many years and feel maybe it's time to look at some other solutions and roll up our sleeves and think innovatively about how to capture that.

Are there potential consequences of the development and instruction of abuse-deterrent opioid drug products that warrant further consideration? Well, the generic industry is committed to testing and developing ADF products in accordance with the requirements associated with the RLD; hence, any approve generic will demonstrate it is no less abuse-deterrent than the RLD. However, if incremental

improvement is not clarified from a policy perspective and evergreening is not prevented, the American public may not be able to benefit from a generic ADF product.

This is just a quick case study and it is no means intended to point out pain therapeutics or the FDA. The product's not approved. But it is to illustrate how challenging a space it is for everyone in the room. And this is an example of a company that -- and it's recent, if you note -- has gone to FDA three times. And they're still struggling, both sides of this, on how to address it.

So our concerns came of that is the effectiveness of our pre-ANDA discussions, that we really have to ensure we go in with a very clear strategy and that we come out with either clarity on that, ideally agreement, but if not, what do we need to do to get that so that perhaps only a second meeting would be required.

This seems to be maybe subjective interpretation of study designs, conditions and corresponding data that can result in additional studies. So any clarity we could help each other

within that regard I think would benefit all of us. And additional studies can be resource-intensive and time-consuming.

So again, that goes back to really making your ANDA meetings most effective. And when you're asked for one, make sure your packages are thorough and you know the questions you want to ask.

So in summary, the generic industry working group is recommending that generic ADFs be considered complex products and included in the pre-ANDA program. The category one testing be mandatory and category two and three be required as needed for generic ADF opioids.

FDA develop a policy to ensure that no ever greening will occur blocking the approval of a generic ADF and FDA revise the draft guidance reflecting recommendations identified by the groups here today and issue product-specific guidance timely. Thank you.

(Applause)

DR. LIONBERGER: Thank you very much, Penny. So our next presentation is from the brand industry

working group and the speaker will be Jeffrey Dayno, the chief medical officer from Egalet Corporation. So welcome, Jeffrey.

DR. DAYNO: Okay. Thank you, Dr. Lionberger. And on behalf of the branded industry working group, I would also like to thank the FDA for convening this public meeting on, you know, a very important topic. It gives us the chance to come together to address, you know, the issue of the opioid crisis, opioid abuse and misuse happening in our communities. And I think, you know, it's a very good opportunity to build on some of the learnings that we've been hearing this morning.

I also attended this similar meeting in October, 2014 and, as Dr. Throckmorton said, it was a really excellent discussion. And there were learnings in this space that went, you know, from the draft branded guidance and brought that forward to a final guidance and we continued to build off of that, an opportunity today to look at the draft generic guidance.

I think that you'll also understand that on

behalf of the branded industry working group, I'm going to provide a perspective on the generics ADF guidance. The members of the branded industry working group are listed on this slide, 10 companies. All of them actively participated in the preparation of this presentation and, just as a disclaimer, the remarks in the presentation don't necessarily represent my own individual perspectives or those of the individual companies, but represent sort of the best available consensus of the group as a whole.

My financial disclosure, I am an employee and officer of Egalet Corporation. And the topics I will be covering, I think, first, the public health imperative to respond to the opioid crisis.

Dr. Throckmorton sort of laid out of the framework for this meeting and from the branded guidance that was issued in April, 2015 to the important area of looking at the generic space and bringing abuse-deterrent opioid development guidance forward there. Looking at progress to date, the branded industry working group perspective on the generics ADF guidance at a high level and also our

rationale for our position. And I'll offer some concluding remarks.

I'd also like to add that as the last speaker this morning, I think you're going to see and hear some common themes that you've been hearing all morning, some that Penny offered from the generics group as well as areas where the FDA has already identified some, you know, potential things to look at for revisions in the current draft guidance and will be part of the discussion this afternoon and again tomorrow.

The public health imperative to respond to this crisis involves multiple stakeholders, as we're all aware. I think the FDA has taken a proactive approach and, in February of this year, stepped forward with the opioid action plan. Again, Dr. Throckmorton outlined some of that.

It focuses on both patients and the community at large. And this is a very interesting sort of different way to look at risk-benefit profile. Compared to looking at it individual patient, individual sort of therapeutic decision-making, it

looks at both aspects of that and it calls for the balance of access to effective pain medications for patients that need them while reducing the societal burden of opioid abuse and misuse.

So what are we doing today? Well, we can treat the problem on the back end, in the acute setting, sort of when we're in crisis mode. Moving quickly with naloxone for treatment of overdose or offer medication-assisted therapy for those who become addicted and have opioid use disorder.

Another very important approach, and it's the design of abuse-deterrent formulations, is to try to prevent this problem upfront. And abuse-deterrent opioids are one component of that multifaceted approach to address the significant challenge of opioid abuse, addiction, overdose and death that we are facing.

Progress to date, that's been noted thus far. And notably, the final guidance for the branded industry issued last April. This is a roadmap for the development and labeling of branded abuse-deterrent opioids and it supports the goal of creating safer

opioid analgesics. But it recognizes, and I think the theme that you've heard this morning, the science of abuse deterrence is relatively new and continues to evolve. And some of the case examples that we've seen and have been presented demonstrate that concept.

So the FDA takes a flexible, adaptive approach to the evaluation and labeling of these potentially abuse-deterrent products. It is based on the totality of the evidence and that evidence continues to grow in the FDA's database, you know, looking at that as how can we advance the field.

But that being said, beginning this year, advisory committee meetings are now convened for all opioid product candidates with potential abuse-deterrent properties to evaluate the nuances and these data sets to see whether they've met the burden and the level of proof to get abuse-deterrent labeling.

So at a high level, let me share with you the perspective from the branded industry working group on the draft generics ADF guidance. We clearly recognize the importance of this guidance to ensure widespread access to safe and effective analgesics for

appropriate patients who need them.

This could help to accelerate the transition to abuse-deterrent opioids and eventual replacement of opioid products without abuse-deterrent properties. The different stages and levels of what is part of the overall FDA's plan of where we want to get to over time, and we very much support that.

At the same time, we also recognize the imperative to ensure that a product is no less abuse-deterrent than its reference-listed drug with respect to all potential routes of abuse. So this is so abusers will not sort of preferentially seek out and abuse such easier to abuse generics as cited in the draft guidance.

So the field is complex. The science is complex. And the range of existing and emerging abuse-deterrent technologies, the current draft guidance we don't feel adequately addresses what is needed to fully demonstrate comparable abuse-deterrent properties on a product-specific basis relative to all potential routes of abuse.

So one could consider a broader approach

that's more flexible and inclusive to the generic ADF guidance for the full range of approved abuse-deterrent products as well as the emerging technologies or a theme that you've heard all morning, take a product-specific guidance approach for generic ADF opioids.

What about the state of the science? 505(j) ANDA pathways to demonstrate therapeutic equivalence are fundamentally based on, you know, the demonstration of bioequivalence, which forms the scientific bridge to safety and efficacy.

This has been developed based on years of data generation, evidence and confirmation of these scientific principles around the primary fundamental elements of safety and efficacy. It allows for the generic products to be substitutable for the branded agent.

However, the scientific bridge to demonstrate abuse-deterrent properties has not yet been established. There are ongoing efforts to standardize category one testing. But with that, even if there is a core set of studies, further product and

technology-specific testing is usually required to take a product to defeat, to hit failure mode. And in the experience of the branded industry, we've seen that time and time again and that's been the pattern.

Because of the unknown and inconsistent correlations across different categories of abuse-deterrent testing, additional research needs are identified in the FDA's final guidance for branded abuse-deterrent opioids. Notably, the correlation between category two PK data and category three pharmacodynamic PD outcomes data from the clinical abuse-deterrent studies.

We saw some data, some information. This continues to evolve. There's a lot of good work going on in this field. I think all of the branded companies as well are looking into those potential relationships. But it is still unproven and a very important part of the development path.

If we take a step back and look at the development path to demonstrate abuse-deterrent properties, beginning with category one studies, the branded products have required an iterative approach

based on these proprietary technologies.

A standardized approach may not demonstrate the full extent of abuse-deterrent properties of the RLD. The iterative approach required to test a product to failure involves much more extensive laboratory testing.

So rather than start sort of in a broad way and narrow down to find sort of the failure mode, you'll hear tomorrow from the branded group and my colleague Alison Fleming that we start on the branded side from a base of studies and then build out in this iterative approach to fully test the product and the technology and find sort of to-failure mode which is the basis of the in vitro testing prior to going into the clinic.

So a formulaic tier-based approach doesn't cover the full range required based on the experience of the branded group. Also, the current guidance as we've heard I think focuses on physiochemical barrier approach to abuse-deterrent products that are hard to crush with gelling properties. For agonist/antagonist products, the impact of the antagonist on induction of

withdrawal in the user can't be demonstrated based on just category one data alone. And I think some of the comments from the FDA today have recognized some of the further testing that does need to be considered for that mechanism of abuse deterrence with regards to agonist/antagonist products.

Currently, the guidance is fairly unidimensional and doesn't address this complexity of the different approaches or mechanisms of abuse deterrence. And there are many other factors that have been alluded to and I'll mention as well. The identification of the discriminatory study conditions is a critical step, but needs to be more tightly defined in terms of what -- you know, what those are.

We also heard a concept earlier about what is the result in abuse-deterrent properties. And I think this is a very important concept, that it's a combination of both formulation and process in terms of these innovative technologies that has resulted in those products that have gained abuse-deterrent labeling. It's not simply the formulation that needs to be replicated. There are very important

contributions from proprietary technologies and these novel manufacturing processes.

It results in organoleptic properties of these products, the total product experience. And that becomes very critical when you are assessing alternate routes of abuse and especially the non-oral route, so not just intact product, but manipulated product taken not as intended, not just evaluating safety and efficacy. And that sort of continuum of learnings and understandings in terms of the experience to date in the abuse-deterrent development is a very important one.

So similar to the concept of the totality of the evidence to assess a product for abuse-deterrent labeling, you have the totality of the product experience, which is why the full range of abuse-deterrent testing is important.

IVIVC models are fundamental to generic product approvals and they're based on multiple bioavailability and bioequivalence clinical studies to support this approach. But an IVIVC correlation for abuse-deterrent properties has not yet been

established. And in addition, we heard about time and effort -- the amount of time and level of effort that goes in, in the beginning, to get a product into an abusable form in the first place. So you have the important aspect of the input as well as what is the output of those efforts.

So just a high level example, this is from a crush-resistant formulation of oxymorphone. And you see on the left, category one in vitro dissolution data, time on the x-axis and percent dissolution on the y-axis, showing that in this assay, in vitro, with an increase in concentration of alcohol, you see a slowing of release with the 40 percent ethanol curve, that bottom one, where you see the arrow.

However, you put this product in the clinic, in category two and in healthy volunteers in this PK study and it is a different pattern. And you see the 40 percent alcohol interaction with an increased maximal plasma concentration and a shortened t_{max}, time to that exposure. So one cannot correlate from this example the in vitro category one findings to the clinical category two PK findings.

Moving to category two studies, the demonstration of bioequivalence of an intact product serves as a bridge to safety and efficacy. Now, we move to the important aspect of generating PK profiles of the manipulated product, comparing the generic product candidate to the RLD in this manipulated state and PK analyses that are very important that go beyond traditional assessment of bioequivalence.

And we heard reference to that, the partial AUCs and other components of that -- the rate of rise, if you will. C_{max}, maximum plasma exposure divided by t_{max}, or the time to achieve that. A concept that's also been referred to is the abuse quotient in assessing the important aspects of PK profile of the manipulated product.

The abuse-deterrent properties represent a unique additional feature of these products beyond a bioequivalent formulation. The development programs run in parallel, whether you're demonstrating bioequivalence or you're doing a clinical program in pursuit of a 505(b)(2) application and then you are also conducting a full battery of category one, two

and three abuse-deterrent studies. This has greater relevance moving from the bench and when you're assessing the clinical impact of all potential routes of abuse.

And it's been mentioned earlier, again, the agonist/antagonist mechanism of abuse deterrence in those products, the correlative data between an antagonist blood concentration, an impact on positive subjective measures, you don't -- that correlation is not known and that's a very important one to assess, as well as the risk of withdrawal. So therefore, category three data, through all important routes of abuse, would be needed to assess that.

There was mention of the oral route and impact of chewing. And then, especially the intranasal route, non-intended route of abuse, non-intended as the product to be taken to begin with. Many factors, both physical and chemical attributes of these technologies, come into play. We saw some basic work being done in terms of a membrane assessment to get at that. But again, the organoleptic properties of the product in the nasal cavity -- particle size,

density, weight, the rate of gelling properties, all of that contributes to the overall drug experience in terms of whether someone would like it or decided to take it again.

The correlation between category two PK data and category three drug liking data is complex and inconsistent based on the experience of the branded group. We've seen some examples showing, you know, potential relationships. But there are also others that refute that and the quantitative assessments are not always predictive of qualitative outcomes.

This is an example from reformulated OxyContin. This was presented at CPDD in 2014, where you've got C_{max} along the x-axis and E_{max}, drug liking, along the y-axis. And as you can see from these analyses, that there's a modest correlation at best from the PK data to the response on drug liking.

Another interesting example, compliments from Collegium, and their DETERx platform, in terms of category two/three correlation. This is using the oral route. And you see on the left panel that although the maximum plasma exposure occurred

following chewing in the fed state, on the right, you see chewing in the fasted state produced greater drug liking. So many aspects, when you go into the clinic through various routes of abuse, where some of the correlations don't carry through as this field continues to evolve and we learn more.

This is summarized in a concept two years ago at this meeting Richard Mannion from Purdue termed the cumulative criticality of abuse-deterrent attributes. And each abuse-deterrent product and technology has multiple attributes that likely contribute to deterring abuse. And you can't really separate them out. You see several of them listed on this slide. And you can't separate the contribution of each of the particular attributes. And they all contribute to the cumulative effect with regards to deterring abuse.

So because of that, if we go back to some of the fundamental level of evidence that the FDA looks at of approving products with regards to safety and efficacy, we propose that the scientific bridge to abuse deterrence has not been established yet. And

especially with regards to category one in vitro data, it'd be very hard to extrapolate on that alone in terms of a product gaining abuse-deterrent labeling.

Because of that, it is very important to conduct all categories of abuse-deterrent studies, category one, two and three, to prove the level of evidence in what's needed to get abuse-deterrent labeling.

The importance of that is small differences in category one, either physical or chemical properties, could result in significant differences of a manipulated product from various routes of abuse in category two PK studies.

And likewise, we've seen from some of these development programs small differences in category two outcomes can translate to significant differences in drug liking. So as we build the evidence base, based on the current state of the science, we feel that all three categories of premarketing testing are very important.

Turning to the generics ADF guidance, and this theme has come through, a product-specific

approach would be very helpful. Additional clarity is needed. Provides recommendations based on unique features of these products, routes of administration, et cetera. And it requires clinical data to demonstrate therapeutic equivalence if the demonstration of bioequivalence is inadequate or not possible or, in this case, not the only feature for these products to be substitutable.

There are many examples that the FDA has put forward in terms of product-specific guidances. One to note is Fentanyl patch and the generic products. The requirement of conducting bioequivalence studies as well as other very important in vivo testing to assess the critical performance attributes of those products and make sure that they are comparable to the branded products.

It's interesting to note, going back to this meeting in 2014, the generic industry working group proposed that the FDA should develop the ADF requirements within each product-specific bioequivalence guidance. And in addition, the guidance should clarify whether the generics should

submit an ANDA or a 505(b)(2) application because of the complexity of the testing.

One construct, one approach to this, because of the range of technologies and the complexity of this space, is to take a mechanism-based approach to the starting point of testing these products. Products with physical/chemical barriers behave very differently, especially at the bench -- in vitro testing -- compared to agonist/antagonist products and as we continue to learn more about prodrugs in development and other NMEs.

So we could look at one standard package of category one testing or possibly consider another starting point would be based on the mechanism of abuse deterrence. And that could help to guide generics companies in terms of doing the category one testing.

But from there, it's very important to understand that within each of those mechanisms of abuse deterrence, be it a physical/chemical barrier or agonist/antagonist, the technologies of each of those products and those individual innovator technologies

are very different and there are a lot of complexities. And that is where a product-specific guidance would be very important to help guide the generics manufacturers in terms of what would need to be done.

So with that, I'll offer some concluding remarks. The branded industry working group agrees with the goal of the generics ADF guidance and recognizes its importance in addressing the opioid crisis.

This is a common goal, to advance the field in order to transition the market so that all opioids are in abuse-deterrent formulations. And the FDA has mapped out a proposed pathway to get there and this is part of it.

We are committed to working with the FDA, academia and the Generics Industry Working Group to advance the science of abuse-deterrent opioid development and identify this path forward. Based on the current state of the science, the following is the position of the branded group on the current state of the generics draft guidance.

In its current form, it doesn't adequately address what's required to demonstrate a full complement of abuse-deterrent properties, especially through all relevant non-intended routes of abuse.

I mentioned the category one testing and covering the full extent of that and addressing the complexity of the different abuse-deterrent mechanisms, with current products as well as being aware of the emerging novel technologies.

Therefore, it's our position that category one, two and three abuse-deterrent data are still necessary to demonstrate that a generic product is no less abuse-deterrent than its RLD with respect to all potential routes of abuse.

And in terms of labeling section 9.2, if the generic products in development have to, you know, generate that data to demonstrate that, then those data should also be included in the label. This is supportive of the totality of the evidence, which is important without an established scientific bridge to link either in vitro data or PK data, especially of an un-manipulated product, to a reduction in drug liking

and other very important pharmacodynamic outcomes.

As I mentioned, two potential paths forward, either a broader approach to the overall generics guidance or evolution of an abuse-deterrent mechanism-based approach to development of product-specific guidances that identify the testing required for each product and each technology based on its mechanism of abuse deterrence. Thank you for your attention.

(Applause)

DR. LIONBERGER: Thanks very much. So that concludes the morning session. So we will reconvene at 1 p.m. for the afternoon session. And as I mentioned before, there's a buffet lunch available in the Patuxent Room down the hall to the right and there will be a $15 cost for that. So, thank you very much and I'll see you all back here at 1 p.m.

(WHEREUPON, the foregoing went off the record at 11:50 a.m., and went back on the record at 1:00 p.m.)

DR. LIONBERGER: So, welcome back, everyone, to our afternoon session. So, this afternoon we'll be having, first, a series of speakers talking about

different perspectives on generic drugs, not from the scientific review or development perspective, but from the patients' and the providers' perspective on the impact of generic drugs on the U.S. healthcare system.

So, and then following that, we'll have an open public -- following that, we'll have a break. Then we'll have the open public hearing and then immediately following the open public hearing, we'll go into the panel discussion.

So without further ado, I'd like to introduce our first speaker. It's John Coster, from the Division of Pharmacy at the Center for Medicare and Medicaid Services. So, welcome, John.

PAYER PERSPECTIVE: PRESCRIPTION OF AND PAYMENT FOR ADF OPIOIDS

DR. COSTER: Good afternoon, everybody. Thank you very much for having me. I was going to defer to my more distinguished colleague, Dr. Kelman, but I guess I got called up first. So it's always really hard to be the first speaker after lunch, especially when you're talking about Medicaid issues. So I don't know what I can do to jazz it up and I

don't have slides either. So other than the candy up here to keep your sugar level up, I'll see what I can do to make this real exciting.

So I am the director of the Division of Pharmacy at the Center for Medicaid and CHIP Services. We're the second half of CMS. So you'll hear from Dr. Kelman next to talk about Medicare. And I just want to spend a few minutes talking with you about our views on the importance of what you're discussing here today at this meeting, the importance of making available to the market a generic formulation of an abuse-deterrent formulation.

So unlike Medicare, which you'll hear about next, Medicaid is a very different program. There are generally 56 Medicaid programs. And if you've seen one Medicaid program, you've really seen one Medicaid program. Every Medicaid program is really different. And also, Medicaid is going through a huge transformation now because most Medicaid healthcare services are delivered not through traditional fee-for-service, which I guess is still the case with Medicare, but most of Medicaid is delivered through

managed care plans.

So in my role as director of the Division of Pharmacy, we're responsible for helping to provide oversight to states in the delivery of their pharmacy benefits. There's another division in the group where pharmacy is, the Division of Managed Care Plans, which is responsible for oversight of what the managed care plans do with respect to drug coverage.

But Medicaid is one of the largest payers for prescription drugs in the United States. We pay for over $57 billion a year in prescription drugs. And if you look at what we pay for, what Medicaid pays for, we pay for a lot of pain medications.

In fact, a recent Kaiser Family Foundation report that came out this past July looked at what Medicaid pays for with respect to prescription drugs and found that our number one product that we pay for, not in terms of dollars but in terms of prescriptions, is basically Vicodin, generic Vicodin. Hydrocodone/acetaminophen is the number one medication that we pay for. It wasn't the most costly. But it is expensive and it is widely used in Medicaid.

Research also shows that the opioid epidemic, which we're all facing around the country, in certain parts worse than others, does have a disproportionate impact on Medicaid beneficiaries. Medicaid patients are prescribed painkillers at twice the rate of non-Medicaid patients and at three to six times the risk of prescription drug overdose.

So as I go around the country and talk to Medicaid pharmacy directors, one of the major topics they want to talk about is what we can do to help reduce the risk of opioid abuse, misuse and overdose. So again, very appropriate that we're discussing this at this meeting.

Let me tell you what states do right now, because as I said before, every state runs their own Medicaid pharmacy program within federal guidelines. So for those of you familiar with the Medicaid pharmacy program, manufacturers have to sign rebate agreements with the secretary of HHS to have their drugs covered under Medicaid. This was a law passed back in 1990, the Medicaid Drug Rebate Program, which specifies that in order for a manufacturer to have

their drugs covered under Medicaid, they have to provide rebates to the Medicaid program. So that program has been operating since 1990. It brings in about $24 billion a year in rebates to the states and we share in those savings at the federal level.

So first, you should know that manufacturers sign rebate agreements and in return, the states would cover the drugs of the manufacturer unless there's some specific statutory exclusion. So in the case of an opioid -- an abuse-deterrent formulation of an opioid, the states would have to generally cover that. Of course, they can subject it to various utilization management mechanisms like prior approval or step therapy, things like that.

So what most states do is they have their own pharmacy and therapeutics committees. The state Medicaid programs form pharmacy and therapeutics committees and that helps them formulate their pharmacy benefit programs. So they will develop, for example, a preferred drug list. And if you look at a state's individual preferred drug list, you will find that within each therapeutic category, a state will

prefer certain drugs over another. And some of that is driven in large part by supplemental rebates that they might negotiate with manufacturers for those particular drugs.

So a state will develop a PDL. It will prefer certain drugs on that PDL and then other drugs will still be covered by the state because they have to cover that under the rebate program. But those drugs won't be preferred. So physicians and other prescribers would have to go through some sort of utilization approval process, like a prior approval process to get those drugs covered.

With respect to utilization management of opioid-type products, a majority of states employ patient review and restriction programs, commonly known as lock-ins. So they'll place a quantity restriction on certain types of opioid prescriptions or they'll put morphine-equivalent daily dosing of narcotic prescriptions.

So there's various controls that states put in place on the prescribing and use of opioid drugs. And again, that's in order to help better manage and

control those. And each state also has a drug utilization review program. So at the point of prescribing, what a state generally does -- I'm a pharmacist. I don't practice. So don't be concerned about me dispensing your prescriptions.

But a state will put in place a prior approval process -- I'm sorry, a prospective drug utilization review program so that at the point of dispensing, the state will provide information to a pharmacist about the drug being prescribed in a real-time electronic manner so that the pharmacist has better information about what the patient is taking before the pharmacist actually dispenses it.

Unfortunately, in many cases, that does not include information from various prescription drug monitoring programs. That would be ideal because then the pharmacist or the prescriber in real-time could see other things that the patient might be taking. But with respect to currently what happens, states do have DUR programs.

Those programs help them to see at the point of prescribing, before the pharmacist dispenses the

prescription, what the patient is taking. And then, also, there's a retrospective utilization review program. So the state will go through various types of reports that are provided to it from the claims that pharmacists submit.

And they'll look, for example, at particular prescribers that might be over-utilizing or overprescribing opioids or pharmacies that might be dispensing them. So the states are really focused on the issue of how to better manage opioid abuse and misuse. And they do it, as I said, through various mechanisms, DUR programs, quantity limitations, MEDD restrictions and things of that nature.

So Medicaid, given the number of opioids we pay for, we have an obvious interest in being able to promote cost savings for prescription drugs in order to maximize resources. And we have an interest in implementing policies within our scope of authority to mitigate the opioid abuse epidemic.

One particular case I'll bring to your attention is we've had over the last couple of years and increased emphasis on trying to reduce the use of

methadone as a first-line agent that's been -- first-line agent that's been prescribed for Medicaid beneficiaries with respect to treatment of pain. Methadone is probably not the best first-line agent for the treatment of chronic pain.

So we at CMS, CMCS have increased our focus on trying to help states focus on that should methadone be on their PDLs. More and more states have taken that off. So we work in partnership with them and they do their own analysis and we help -- you know, help them look at contemporary issues that are affecting the delivery of healthcare to Medicaid patients.

So just as an example, if a new drug like this were to come onto the market, an abuse-deterrent formulation, we'd certainly promote it to the states. And through the utilization review mechanisms, they would be able to see prescribers who are overprescribing branding type of abuse-deterrent formulations so that there would be an ability to switch to the generic formulations.

Now, with respect to this particular product

that might be abuse-deterrent, what we would say to the agency is that for Medicaid programs to be able to comprehensively adopt and promote the use of generic ADFs, it's important that they be rated as therapeutically equivalent in the Orange Book.

In the absence of a generic version being rated as therapeutically equivalent, a prescription written for a brand name ADF is likely to be filled with a brand name drug. So I guess the bottom line is for this to be a success, we have to follow current practices that are used in pharmacies.

That is, the pharmacist would dispense, if the prescriber did not say brand medically necessary, a therapeutically equivalent drug as found in the Orange Book. Anything else will reduce the effectiveness or the savings that would be potentially generated by a generic ADF.

So adoption of lower cost generic ADFs is much more likely if fewer barriers exist for the state and the provider. If a pharmacist must track down a prescriber in order to make a substitution, it's less likely to occur. I don't think that's a big surprise.

And some of what we're seeing and the reasons why we got concerned is because we see this now with bio-similars.

You know, there are many states that are enacting laws that prohibit a pharmacist from interchanging a bio-similar with the reference product biologic because the states are enacting laws that, you know, require prescribers to be contacted or state laws are not keeping up with the changes in what FDA is doing with respect to the Purple Book.

Now, most state laws only recognize the Orange Book. Our federal law only recognizes, Medicaid at least, the Orange Book.

So if we're going to be successful in moving an abuse-deterrent ADF into the market at a, you know, relatively good clip to help reduce cost as well as save lives, then I think it would be important that it be done in the current rubric that we know and that is the pharmacist would be able to dispense an ADF generic as long as the prescriber did not block substitution.

At present, Medicaid utilizations of ADFs is

low. The most recent one-year data that we have available from the second quarter of 2015 to the first quarter of 2016 shows that of the approximately 30 million prescriptions filled for Medicaid beneficiaries for opioids, only about 400,000 were for approved ADFs.

ADFs are expensive. The brand name drugs are expensive. That represents only 1.3 percent of total opioid prescriptions while the Medicaid expenditures for ADFs during that time was approximately 1.8 of the total dollars spent on opioids. So less than 2 percent of prescriptions, less than 2 percent of spending in Medicaid are for abuse-deterrent formulations because, even though a small percent, they still remain individually expensive drugs.

We think that there would be a pretty rapid uptake of these drugs if they were on the market. One example we have from our own data show that when a generic version of OxyContin was available in the market during the years 2011 to 2014, generics comprised 63 percent of the number of extended-release

oxycodone prescriptions filled for Medicaid beneficiaries. In contrast to 63 percent of prescriptions accounted for only 3 percent of total Medicaid reimbursement for extended-release oxycodone prescriptions.

So I think for us in Medicaid, bottom line is we're fully supportive of the efforts of the FDA to bring a generic ADF to market. We think that will help reduce abuse and misuse of drugs among Medicaid patients. As I said, Medicaid is a primary payer for these medications.

The states do have mechanisms in place through various prospective and retrospective mechanisms to encourage higher utilization of drugs like these and I think it's important if a product is approved that it follows the model that we have now for generic substitution and that is unless it's blocked by the prescriber for some reason, the pharmacist could substitute a therapeutically equivalent generic ADF if it's listed in the Orange Book.

So again, I thank you for the chance to come

and speak and I'll turn it back over to the moderator.

(Applause)

DR. LIONBERGER: So I'd like to welcome our next speaker, Dr. Jeffrey Kelman, chief medical officer from Center for Medicaid and Medicare Services, giving a perspective from Medicare.

DR. KELMAN: Well, thank you. I'd like to thank the FDA for inviting us, and I'd like to point out that I agree with everything John said. Medicare always agrees with Medicaid. I'm going to actually go from the specific to the general and give you a brief conversation on what we're doing to reduce opioid overuse and misuse in Medicare.

I mean, Medicare at this point covers Part D at any rate, 1.4 billion prescriptions a year. It's about 30 percent of all prescriptions written in the U.S. And about 30 percent of those beneficiaries take at least one opioid a year. So this is a big area.

We of course -- to cut to the chase, we agree with the FDA's effort to increase the use of abuse-deterrent formulation and we agree with the FDA's effort to move it into the generic world. I

think it will save us money and save us lives and it's the right thing to do.

In general, this is a very big problem and nobody has to be told about the opioid epidemic. We divide, or we think of three cohorts of opioid misuse in Medicare. We think of the mal-coordination, non-coordination use, which is subject to overlapping prescriptions being written by multiple physicians who may need more education on opioid use in any event.

That's the first group. And by the way, I became aware of that first group many years ago when we first launched Part D. I got a phone call from a patient's son who reached me and told me his father couldn't get an antipsychotic drug. Well, what was happening was the father was getting four different antipsychotic drugs from four different physicians and four different pharmacies.

As I recall, it was olanzapine, risperidone, Zyprexa and haloperidol. The reason the son called me was that the father was unconscious, taking all four drugs. This was very easy to repair. But the problem with non-coordination of care is a huge one. The

second group are the high use opioids in the setting of a pain clinic, a hospice or a palliative care service. These may be perfectly normal high use cases. But they have to be looked on completely differently than non-coordinated care.

And the last group are the pill mills, where combinations of unique physicians with unique pharmacies and unique patients are subjecting to diversion and abuse of opioids. That has to do with -- it's a law enforcement issue as much as anything and it should be discussed differently.

We decided to focus in 2011 our Opioid Management System, OMS, on the first group, the non-coordinated care. And we looked at outliers in that group, and by outliers, I really mean outliers. These are people who were taking more than 120 MEDs for more than 90 days in a given calendar year with more than four doctors -- or actually, four or more doctors and three or more pharmacies. This is an extreme group.

This is a retrospective effort and it's going on now, as you'll hear, where the plans were told who these people were and our expectations of

case management. And case management includes direct outreach to the beneficiary, direct outreach to the doctor and direct outreach to the pharmacy. And then, we collected data on an ongoing basis and we had actually greater success than I'd feared at the beginning.

I have to read these, because I don't like to put them up in slides. In 2011, we had 31 million beneficiaries in Part D. There were 32 percent taking opioids. We found 29,404 people met the criteria I just described, 120 MEDs for 90-plus days with more than three pharmacies and more than three providers.

In 2013, the first year that we could measure an effect, we now had 38 million beneficiaries, 31.2 percent were taking opioids, but the number who met our criteria had fallen 25,347. 2014, we're up to 39 million -- actually, 40 million total Part D enrollees, 30.8 percent taking opioids and only 21,838 met the high -- met the trigger.

And by 2015, there were 42 million Part D enrollees, 29.9 percent took opioids and the number who hit the high intensity enrollers were down to

15,651. So this was a real success. It's not enough. So we moved on, going forward. In 2017, excuse me, we're trying real-time concurrent step edits.

We're asking plans to set an MED threshold, say 90 MED to match with the CDC, at which there is a step edit when they're filled at the pharmacy if the overlapping dose exceeds that.

This can be a soft or semisoft edit but it means somebody will look at those prescriptions and will get back to the doctor and to the pharmacy and to the beneficiary so they know that they're exceeding or they're coming close to a dangerous level. We obviously don't know how this is going to work going forward. But we have great expectations.

There's clearly a great deal of use, probably abuse and misuse of these drugs. And the advantage of an abuse-deterrent formulation is that it can take out the changing formulation and the artificial high of using these drugs going down the pike.

And from our point of view, cost relates to access. And access relates to quality. If somebody

can't afford a drug, they can't take it and they can't be adherent on it and it's not going to work. And so, assuming all else being equal and ADF formulations are actually safe.

When I have no reason to doubt it, I always refer to my friends at the FDA -- then we encourage the progression of the ADF into the generic world sooner rather than later because this will expand formularies and will expand access and decrease our costs. Thank you.

(Applause)

DR. LIONBERGER: All right. Thank you very much. Our next speaker is Bernie Good, representing the Department of Veterans Affairs. Welcome.

DR. GOOD: Thanks for inviting me. I brought my stopwatch along. So last night, I was setting my out-of-office notifications and I put abuse-deterrent opioid meds and the auto-corrector changed it to opioid deterrent mess. So I have no conflict of interest. I do chair the medical advisory panel for pharmacy benefits management for VA. I co-direct our VA Center for Medication Safety and I'm a

member of FDA's Drug Safety Board.

So a little background about the VA, we have 8.8 million enrollees. As of 2016, 6.3 million treated. Last year, 4.9 million pharmacy users. We had 7 million outpatient opioid prescriptions in 2016, mostly generic, reflecting a lot of short-acting medications, 1.2 million unique VA veterans received an opioid in fiscal year 2016 and we spend $99 million on those opioids.

Speaking of the opioid crisis, let me emphatically say that we're a hundred percent committed and supportive of efforts to improve the safe and effective use of opioids. And I think we've demonstrated our ongoing commitment to improving the safe use of opioids with a multifaceted approach. And I'm just going to tell you about a few of these. This is not all-encompassing, and the reason I tell you this is so that you can use this within the context of the rest of my comments.

So in August, of 2013, we started our Opioid Safety Initiative. That's a dashboard that every physician or prescriber in the VA has and you can -- I

can click on mine and I get all the patients that I have listed that are on an opioid, whether or not I've gotten a urinary drug screen, whether they're on concomitant benzodiazepine, whether they're greater than a hundred morphine equivalents a day. And it's at patient level.

We have an overdose education and naloxone distribution where we identify high risk patients and provide naloxone rescue kits. And that was started in October of 2013. Since then, we have 5,280 prescribers that have written for these and we've dispensed over 40,000 kits at every VA and we have 172 documented reversals as of August, 2016.

We have a medication takeback program which provides safe and responsible options for veterans to dispose. And we've destroyed quite a bit. We have a stratification tool for opioid risk since June, of 2015 and this is a clinical decision support tool with predictive modeling to assign individual patient risk and mitigation strategies. Again, it's at the patient level and I as a provider get that information.

We have academic detailing since May, of

2014. We have 285 pharmacists who are trained as academic detailers and they've met with over 10,000 staff. And the impetus for this was opioids. We also have them addressing some behavioral health issues, not in the providers.

We also have a buprenorphine initiative and this is a national, consultative service to improve office space treatment of opioid-dependence. And we have -- in 2016, we had nearly 15,000 patients being treated with buprenorphine.

So this is the number of unique patients dispensed an opioid over time, and this is by quarter. And earlier this morning, I think it was Doug that showed some stats and this sort of peaks at about the same time. I do think that our decrease is much steeper than what you saw on the table -- on the figure this morning.

This is veterans dispensed an opioid and a benzodiazepine over time since fourth quarter of 2012. And you can see that it's dropped by more than a half. This is veterans on opioid therapy long-term over time, and again, you can see that it's dropped over

the last couple of years from 438,000 to 292,000. And this is veterans dispensed greater or equal to 100 morphine equivalents a day. And again, you see that we've had a substantial decrease over that time period.

So again, VA Pharmacy supports the development of abuse-deterrent opioid formulations for opioid products and especially, what we're here for today, those generic formulations. And based on what I just said, I believe that we probably lead the nation in our integrated approach to addressing the opioid crisis. I'd be happy to hear of others that are doing more, if they're out there, and learn from them.

I think it's important to say that the great majority of veterans receiving opioids are not at risk for diversion or misuse by crushing, snorting, smoking or IV use of their prescription opioids. We have plenty of veterans that misuse by taking too many or losing them, et cetera. But most are not crushing or snorting and smoking. And therefore, converting all opioids to abuse-deterrent formulations would be quite

costly. We're not afraid to spend money for clinically effective interventions. And the poster child for that, we spent $1.2 billion last year alone on hepatitis C treatments.

So what if VA were to convert all long-acting morphine and OxyContin to Xtampza, one of the recent ones? And there's an obvious mistake in this slide. And I almost changed it, and I said, no, just leave it in because it makes a point. And that is that I had forgotten that all of our oxycodone SR is abuse-deterrent.

So you can see that for fiscal year 2016, we spent $18 million on an abuse-deterrent product. And that represents 18 percent of our overall opioid budget. So you heard that CMS is spending about 2 percent. We're spending about 18 percent. But you can see that even -- so we wouldn't switch that product to Xtampza just for cost savings, because it'd be -- we have an abuse-deterrent product.

However, you can see that it's about twice as expensive. So that sort of gives an idea of what a generic product would be to a branded product. If we

compare OxyContin brand to oxycodone abuse-deterrent product, it's about 40 percent as expensive. Morphine SR, quite cheap with us, and you can see that if we were to convert to an abuse-deterrent product, it would be more than a 60-time increase in the cost.

So this is one of these silly little back-of-the-envelope calculations where we look at -- so what would the budget impact be. And again, we're not -- we wouldn't be switching the oxycodone. But the point is, depending on whether it be a 10 percent chance, -- 10-time increase or 16.2 or whatever, it would be basically another hepatitis C scenario for us where we're spending more than a billion a year.

So I said, well, what about -- this isn't about the VA. This is about patients in general. So what about non-VA patients on opioids? And if you -- I took the -- several of the products that are available now in abuse-potential and I went to GoodRx to get the best price, and this is as of October 25th. So for Embeda, the best price for 60-day supply of the 30/1.2 mg b.i.d. dose was $543 at Kroger. And if you just gave the equivalent of morphine SR, the best

price is $42. So more than 10 times the cost at best price. And it's the same thing for Zohydro, Hysingla and Xtampza. You can see there. I won't spend more time.

So likely outcomes for mandating universal abuse-deterrent opioid formulations, we've heard several times today that that is the direction that some of us think we're going and maybe that is. If we were to do that, we would see a dramatic increase in cost for opioid patients, including healthcare systems.

I don't know if it's a tenfold increase. Hopefully generics would be less expensive obviously than the branded products and would be cost-effective relative to those, at least in many cases. But we still know that it would be significantly more. And again, the overwhelming majority of patients who would be footing this bill were the healthcare systems covering these patients. These aren't patients at risk for injecting, snorting or illicit delivery.

There would be a decrease in overdose by prescription opioids, I believe, and there's some

evidence to support that. Although, again, there would still continue to be unintended overdose when patients exceed the intended oral intake.

We would see concomitant increases in heroin overdose. Whether or not it be -- whether it be a zero-sum game, probably not. Hopefully not. And perhaps there would be an arms race among those who would abuse these drugs to try to figure out ways to overcome these abuse-deterrent products.

So what about mandating universal abuse-deterrent products? So questions that I have would be would the excess money to pay for abuse-deterrent products mostly for patients where it wouldn't be necessary be better spent for drug treatment centers?

For VA, a five- to ten-time increase would mean an estimated $300 to $900 million a year. Or, use the excess money to implement the recommendations of the CDC for appropriate prescribing of opioids? I think that's a fabulous document that the FDA -- I mean, that the CDC recently released. And there needs to be a lot more education.

I don't know whether educating physicians

would make a big difference. I suspect that it -- you know, I believe it would. But I don't have evidence for that. Or what about using additional money to provide universal coverage of naloxone rescue kits and education?

So to conclude, VA Pharmacy favors the widespread availability for both product formulations; that is, abuse-deterrent products as well as the non-abuse products.

Physicians should be able to prescribe either product formulation; that is, the current products or the abuse-deterrent products based on clinical assessment for risk of abuse and diversion.

And hopefully using some of these risk mitigation tools to help identify those patients most at risk. And to mandate universal use of abuse-deterrent formulations would have staggering costs. Thank you very much.

(Applause)

DR. LIONBERGER: Thank you very much. So our next speaker is Anshu Choudhri, from Blue Cross and Blue Shield. Let me bring up the slides. So, do

you have slides?

MR. CHOUDHRI: I do have slides, yes.

DR. LIONBERGER: All right.

MR. CHOUDHRI: All right. Well, thank you all for joining today. I'd like to thank the FDA for inviting me to present the private payer perspective on abuse-deterrent formulations. My name is Anshu Choudhri and I work with the Blue Cross Blue Shield Association.

By way of background, the Blue Cross Blue Shield Association, we represent our 36 individual Blue Cross and Blue Shield companies across the country. Collectively, our companies cover 105 million Americans and we're the only private insurer to be offering coverage in every ZIP Code around the country.

And because of our deep and local community ties -- and we do offer coverage everywhere -- we have seen the effects firsthand that the opioid epidemic has had on communities around the country. And so, we're definitely committed to being a part of the solution and working with both public and private

stakeholders to get to that end.

Back in February of this year, at the National Governors Association meeting, Andrew Dreyfus, who's the chief executive officer of Blue Cross Blue Shield of Massachusetts, he spoke at the NGA meeting, sharing some of the details of the program that our Blue Cross plan in Massachusetts has, which has been very successfully so far in working with clinicians, working with patients on reducing the number of opioid scripts that are out in the community, making sure that there's greater adherence to evidence-based guidelines, safer prescribing.

And the Massachusetts program has received a lot of acclaim around the country, and on the heels of that meeting and that presentation at the NGA, our other Blue Cross Blue Shield CEOs got together and decided that, you know, we collectively as a system need to be doing more and we need to work together to share some of the lessons learned and the best practices. And so, our CEOs developed a workgroup where they appointed designees from all of their plans to work with us at the association to share best

practices and develop some different solutions as far as playing the role that we can play in addressing the epidemic.

And our approach is really focused around awareness, education of opioid risk, ensuring access to appropriate medication and treatment for opioid use disorder and then also encouraging and supporting the enactment of well-informed public policy to prevent misuse, abuse, fraud and diversion.

We've been engaged both at the federal level as well as at the state level. And you know, as I mentioned, we have the CEO-appointed workgroup. We're also working with PBS on a documentary which will be released in the coming months. And then also one of the biggest assets we have is our data.

So we have 105 million members. There's claims data there and, in conjunction with states' prescription drug monitoring programs, there are opportunities to work together to help identify those that may be at risk for use -- or sorry, abuse, as well as those that may be already there.

As I mentioned, you know, working with a lot

of state and national efforts. And the one thing that we've learned through a number of these efforts over the last few years is that there's no single solution to this. You know, abuse-deterrent formulations are one tool. But it's going to take many tools in order to make progress on this front.

We provided comments to the FDA earlier this year in May looking at the draft guidance for generic abuse-deterrent formulations. And you know, in general, we were supportive of the measured approach that the FDA was taking to promote the adoption of generic ADFs. We also were supportive that the FDA will continue to assess the state of the science.

So as our knowledge of ADFs and whether or not they are truly effective and actually are reducing substance use disorder and the potential for abuse, particularly at the costs that they are being priced at, you know, making sure that the regulations keep up with our collective knowledge of the issue. We also recommended that the FDA conduct post-market surveillance of abuse-deterrent products to make sure that they are actually making a positive impact on the

epidemic.

And by having more abuse deterrence in the community, is that actually leading to the desired end result? And also making sure that the cost of abuse deterrence are monitored.

As you all know, drug pricing's been in the news quite a bit the last few years. Drug prices have shot up at unsustainable rates. And so, we want to make sure that there's monitoring going on so that vulnerable populations, as well as public and private payers aren't put in the position where the costs of these abuse deterrents will hinder access in any way.

So our view in general about abuse-deterrent formulations, as I mentioned, we're strong supporters of access to appropriate treatment for individuals that need opioids for acute pain management as well as for chronic conditions.

We do agree with the FDA that the technologies still have not been proven to be successful at deterring the most common form of abuse, which is just swallowing the pills. As Dr. Good had mentioned as well, from what we've been seeing, you

know, in our claims data as well, the majority of those that are substance use patients that are abusing, it's not from injection. It's not from snorting. It's just from taking pills orally.

And so, I think there is still a great deal of education that needs to be done around that and that ADFs alone are not the answer to solving the epidemic.

While it's important to create a pathway for generic ADFs, we think that's -- you know, we'll always be supportive of generics and we think that that's good, just being mindful again that generic ADFs alone are not necessarily the silver bullet here. And we are opposed to any sort of coverage mandates for ADFs for some of the reasons that I'll get into here.

So additional thoughts, kind of reinforcing some of the things that I just said, that, you know, we've seen that, you know, taking opioids orally tends to be the most common form. The literature has proven this as well. And so, injection -- abuse-deterrent formulations that are helping impede injection or

intranasal use, that's not necessarily going to get at the majority of the population that is abusing opioids.

You know, I think there needs to be great work still to prove whether or not the additional costs of mandating ADFs and having more opioids out in the market are actually leading to decreasing substance use disorder overall.

The literature has also shown that because ADFs are a tool and not the tool, they should not be a primary prevention strategy for opioid addition. And we'll be looking forward to the ICER study that's coming out in March of next year that will be reviewing abuse-deterrent formulations as part of integrated pain management.

So as I mentioned, you know, there's literature that states that ADFs, they can be useful. They are useful in a subset of the population. But they do have limits in mitigating the overall opioid epidemic. This particular study here, just citing that the extent of their effectiveness does have clear limits, resulting in a significant level of residual

abuse and that also opioids -- abuse-deterrent formulations should not be considered a primary prevention strategy.

Other clinicians have weighed in here as well, looking at -- and sort of reinforcing the point that tamper-resistance is important. But also, it's still not addressing those that ingest opioids orally. And there are several videos and blogs on the Internet that demonstrate ways to bypass tamper-resistance. And so, that would make the main benefits of abuse-deterrent formulations not as effective.

This is just a small subset of just some screenshots of a few of the blogs that are out there. There are many more that show this. And so, just reinforcing that where there's a will, there's a way and individuals are finding ways around some of the benefits of abuse-deterrent formulations just by using simple household products.

So challenges in the current environment, I think this -- there are a few different areas that we think as the discussion around ADFs continues to evolve, and then this is from our perspective, we

think that there's more provider education that's needed on these.

I think the drug manufacturers, and to any that are in the room -- I mean, I'm sure I'm not a popular voice right now -- but we do think that the drug manufacturers are aggressively marketing these and not necessarily completely disclosing the limits to ADFs. And we think that also is coming into some of the pressures at the state level as well as the national level around coverage of abuse-deterrent formulations.

As I mentioned, provider education being needed, this is a study that came out earlier this year in the *Clinical Journal of Pain* and kind of a couple of the key takeaways from this study were that only two-thirds of physicians that were surveyed reported that the most common -- that correctly reported that the most common form of abuse was opioid, swallowing pills -- or swallowing opioids whole.

And nearly one-half erroneously reported that abuse-deterrent formulations were less addictive

than their counterparts, which is not true. And so, we think that there's definitely a need for greater provider education in this space.

And I think there's also a lot of confusion around terminology, which factors into that. As you can see from the slide here, many of the different professional societies are defining things slightly differently. You hear a lot of terms being used interchangeably -- misuse, abuse, overdose.

And as policies at the state and federal level are being developed around this, there are downstream ripple effects where, you know, the intended use of a term in state and federal policy could conflict with clinical diagnosis or payment codes, which will complicate utilization management compliance and research and evaluation.

So this is just an example of a site from one of the manufacturers promoting the use of abuse-deterrent formulations as the solution. As you can see here, there are members of a care team that look like they're ready to play football. And in order to step up their game, they need to prescribe more abuse-

deterrent properties, according to the site.

And on this site as well, the manufacturer has decided to assign some roles and responsibilities to the different stakeholders in the system.

And if you take a look, you know, there's a lot of sort of suggested advice to prescribers and pharmacists and payers and policymakers that -- you know, that they need to do more around education and training and, you know, making sure that you are safeguarding prescriptions at home from children. And the manufacturers believe that their single role is to develop more abuse-deterrent formulations.

And so, this education has also made its way to the state level on ADFs. And so, a lot of states, as I mentioned, have been under a lot of pressure because of the opioid epidemic really hitting them at home. They've been under a lot of pressure to pass comprehensive reform in this area.

And so, we've seen I think 13 states this year have passed some sort of mandates on abuse-deterrent formulations and another five states have passed mandates on treatment for opioid addiction.

And so, you know, while -- you know, it's very important that policymakers are taking the right steps, I think, you know, going back to one of my original points, mandating coverage of abuse-deterrent formulations, also as Dr. Good had mentioned, comes at significant cost.

We still don't know the effectiveness of whether or not they are actually going to improve the overall health of the population as well as reduce substance use disorder.

A few states have taken a more cautious approach on this. These are Governor Christie, Governor Cuomo, we have a Democrat and a Republican who have looked at this.

They vetoed legislation in their states, citing that while the intent was laudable and they both had very similar reasons for vetoing the legislation that they saw mandating ADF coverage, they acknowledged that the effects -- the effectiveness of these drugs are still under review and it's still too early to tell whether or not mandating coverage is going to achieve the intended effects. And so, and

also being payers in their state, they also acknowledged that the cost at this time -- it's unclear whether or not the additional cost will justify the end result.

So closing thoughts, you know, as I mentioned, it's going to take a multifaceted approach. So it's not just more abuse deterrents out in the market. It's not just PDMPs. It's not just prior authorization from insurance companies. It's not just provider education.

It's going to take all of these types of tools and different tools are going to work on different populations. You know, collectively I think we need to consider how to, you know, prevent addiction while also looking at ways to building support for those that need treatment.

One of the things that we're looking at on the insurance side, we know that in the past with some of our coverage policies for things like medication-assisted treatment therapy -- or medication-assisted therapy, looking at there are some potential barriers to non-pharmacological treatments and some of our

coverage polices that were created in the past.

We're taking a look at those to see are there ways that we can help there on the coverage side of things so that there's less of a reliance on opioids and there are other avenues available to individuals who need treatment.

You know, ADFs are improving and while they will benefit some individuals, the fact remains that they still can be abused and that, you know, the evidence really needs to catch up with the marketing of abuse-deterrent formulations at this point.

And we're all for innovation. And we think that the incentives should be in place to encourage the development of innovative, effective abuse-deterrent formulations. But before widespread coverage is going to be embraced, there needs to be more evidence.

And another area where we would like to see more development is abuse-deterrent formulations for short-acting opioids. They're all in the long-acting space right now. And long-acting opioids should not be the first method of treatment for individuals. And

so, we'd like to see more innovation in that space. And as I mentioned before, education is essential and I think it's going to take multiple types of organizations to work together in order to make a difference here. Thank you.

(Applause)

DR. LIONBERGER: Thanks very much. So we'll be -- we'll take a break and we'll resume at 2:15. I'd like to ask the people who have signed up to speak in the open public hearing to make sure that they'll be seated in the front row so we can have smooth transitions between all of the speakers in the open public hearing.

So we want all of the open public hearing speakers to make sure that you identify yourself to either myself or Michelle to get you organized and set up for the 2:15 start. So, thanks very much and we'll be back at 2:15.

(WHEREUPON, the foregoing went off the record at 1:53 p.m., and went back on the record at 2:15 p.m.)

PUBLIC COMMENT PERIOD

DR. LIONBERGER: -- Welcome to the public comment period of today's meeting. So we will be calling the speakers and if you're a speaker, when I call your name, then you can proceed to the main microphone and speak from up there.

And we'd also ask when you get up -- when you get up to the main microphone, please identify yourself and this will help with people who are watching via webcast and it will also help our transcribers accurately indicate who said -- who said what at the meeting.

So we remind you to do that. Even after I've introduced you, please reintroduce yourself to make sure that they capture your name. so with that, we'll begin. Each speaker will have -- will be allotted a block of 10 minutes. After 10 minutes, as you get -- after 10 minutes, there'll be a red light and then the microphone will be cut off and we'll go on to the next person.

If you finish early, we'll continue to the next speaker. If the speaker's not available, we'll proceed to the next speaker and come back to people at

the end of the time period if you weren't here for your allotted time. So our first speaker is Michelle Harford. Okay, so our second speaker is Alexander Kraus.

DR. KRAUS: Can you hear me okay? Oh, yeah. Thank you. So my name is Alexander Kraus. I'm employed at Grünenthal USA in Morristown, New Jersey. I would like to make some disclaimers first. Grünenthal has developed abuse-deterrent technology for opioid stimulants and other scheduled drugs of abuse. Technology and patents are licensed to manufacturers in the United States and the opinions expressed in this testimony are my own and not necessary those of Grünenthal and statements made are not by or on behalf of any of our partners or other drug manufacturers.

At Grünenthal, we believe that ADF technology are a valuable tool to reduce prescription drug misuse, abuse, and diversion and when the necessary quality requirements are met, provide additional safety and benefit to prescribers, patients and society. We applaud the FDA's effort to support

the development of abuse-deterrent opioids.

The fact that FDA, since 2010, had approved seven extended-release opioid products with abuse-deterrent labeling and since 2014 repeatedly and consistently and even today has provided a perspective and roadmap for transition to an all-abuse-deterrent opioid market is encouraging to companies like Grünenthal that are investing into the development and continuous improvement of abuse-deterrent technology and products.

This meeting is about the guidance and requirements for the development of generic products in the case where the RLD has abuse-deterrent properties as identified by the FDA and referenced in the product label of the originator.

It is well-understood that the development and approval of high quality affordable versions of innovative products is desirable to provide patients with more choices for treatment and consider differences in the access to medication based on formulary structure in their respective health insurance plans.

However, we are concerned that the draft guidance as presented is not sufficient to ensure that generic versions of abuse-deterrent RLDs will be no less abuse-deterrent than the originator. In our view, the applied formulaic and schematic process as laid out in the draft guidance does not fully address the need to present the necessary level of therapeutic equivalence as it pertains to the abuse-deterrent product.

We consistently heard in the presentations that were given earlier today that abuse-deterrent formulations and technologies are complex. In the general sense, therapeutic equivalence typically requires more than in vitro testing for non-complex products and can -- and the assessment of therapeutic equivalence cannot solely be based on in vitro testing.

And we believe that this should also apply here, which means that we therefore strongly encourage the FDA to, in addition to category one in vitro studies, will require category two pharmacokinetic and category three human abuse potential studies in the

review of all newly developed products with abuse-deterrent properties to inform whether the product has sufficiently robust abuse-deterrent properties, and in the case of a reference to an existing RLD, is not less abuse-deterrent than that.

This is even more important in cases where the generic product subject to the ANDA review is utilizing a new technology or formulation approach which is not identical or sufficiently similar to the RLD product. We have discussed this also earlier today. I think this will be a very important subject to define identity and similarity of technologies.

In such cases, FDA should consider the part of the ANDA review which relates to the determination of abuse deterrence equivalent to the innovator product, which means, according to the requirements and considerations later on in the guidance for ADF opioid development and labeling in its final form dated April 1, 2015.

Grünenthal is aware of the need for more abuse-deterrent opioid products with high quality abuse-deterrent properties to come to market soon.

However, the proposed pathways and existing incentives for such developments are not deemed sufficient.

For example, the current process for labeling of abuse-deterrent products is insufficient as to the fact that the product that has been determined to be abuse-deterrent is not easily identifiable in the product label and makes it harder for prescribers and patients to understand whether and what the product actually has been recognized for in terms of its abuse-deterrent properties.

Improvement in this regard is urgently needed and will support prescribers, caregivers and patients to be able to make the appropriate choice when prescribing an opioid pain medication with abuse deterrence when it is considered beneficial.

Also, the existing regulatory pathways for the development and approval of abuse-deterrent products are not considered supportive enough to effectively progress the transition to an all-abuse-deterrent opioid market and this is the reason why.

The currently approved products with abuse-deterrent labeling are all branded products, as we

heard earlier today. Some are reformulations of existing brand name drugs for which the NDA decided to add abuse-deterrent properties to the product.

However, most of the products are newly developed versions of an existing molecule and have been approved as an NDA via the 505(b)(2) route. This requires the product to be positioned in the end and marketed as a new branded product.

Given the current healthcare environment -- we heard about that too -- new brands in this category typically face significant barriers to access for patients due to market access hurdles imposed by the reimbursement entities.

As a result, the uptake in utilization of these products in the market leads to a much slower penetration of abuse-deterrent products into the market than it would be desirable from a public health perspective.

The fact that the new products typically compete with multisource generic non-abuse-deterrent versions in the same molecule class does not help the transition and substitution of those by the abuse-

deterrent product.

There are two important follow-ups from this situation which should be mentioned also. First, the fact that the share of abuse-deterrent products is not increasing significantly leads to a limited impact in the reduction and prevention from abuse.

This observation is sometimes even used to argue the value of abuse-deterrent products and to continue limiting their access which provides a vicious circle for the utilization and market penetration.

The argument that abuse-deterrent products are of limited value as abusers might just decide to abuse other non-abuse-deterrent version of the same molecule has even been brought forward as a reason to substantiate the negative vote on the potential approval of an abuse-deterrent product in the recent FDA outcome.

Second, the fact that the abuse-deterrent products are positioned and marketed as brands might have created the perception that the pharmaceutical industry, instead of transitioning the existing

products to abuse-deterrent forms and thereby supporting the change to improved and safer products, is trying to grow the overall market, which is truly not the case.

The situation in our view will not substantially change when FDA is going to implement and starting to apply the proposed draft guidance for generic development of abuse-deterrent opioids.

Besides its insufficiencies to ensure that generic versions of the reference product should have no less abuse-deterrent properties than the RLD, it also will not substantially support the transition to an all-abuse-deterrent market.

Abuse-deterrent products approved as an ANDA will only compete with the existing originator ANDA abuse-deterrent product via substitution within the very limited market share of this product.

As long as the bulk of the non-AD -- non-abuse-deterrent products -- and these account for the vast majority of the prescriptions today, as we saw earlier -- will not be effectively replaced by abuse-deterrent forms, the transition will likely not happen

or it will take much longer than the urgency of the situation would deserve.

The conundrum is that as of today, no real incentives exist to reformulate products whose branded reference or RLD has not been reformulated as an initial step. Only in those cases, ANDA filings for abuse-deterrent generics can reference to those.

It is therefore proposed that FDA may establish a new regulatory paradigm that allows sponsors to develop products with AD properties according to the final guidance from April, 2015 and if bioequivalence to the respective non-ADF RLD can be demonstrated, will be approved as an AB substitutable alternative.

We would be happy to get into the dialogue and assist FDA and the industry as a whole in advancing the science of abuse deterrence and to develop meaningful standards and concepts for in vitro, pharmacokinetic and abuse liability assessments.

Grünenthal's abuse-deterrent technology is suitable for all forms of opioids and as a technology

provider, we will be happy to work with every potential partner, be it branded or generic, to provide broad and reliable access to affordable abuse-deterrent products for patients who need them. Thank you for the opportunity to testify today.

DR. LIONBERGER: Thank you. Our next speaker is Susah Oh.

DR. OH: Hello. My name is Susan Oh, assistant director of pharmacy affairs at the Academy of Managed Care Pharmacy. Thank you for the opportunity to provide comments today. The Academy of Managed Care Pharmacy is the nation's leading professional association dedicating to increasing patient access to affordable medicines, improving health outcomes and ensuring the wise use of healthcare dollars.

Through evidence- and value-based strategies and practices, the Academy's 8,000 pharmacists, physicians and nurses and other practitioners managed medication therapies for the 270 million Americans served by health plans, pharmacy benefit management firms and emerging care models in government.

AMCP is concerned about the need to ensure appropriate access to opioid medications while avoiding abuse, misuse and diversion. AMCP members use managed care pharmacy tools to ensure selection of safe and effective opioids for a patient population. These tools include pharmacy and therapeutics committees, drug utilization review boards under Medicaid.

These organizations review current clinical and scientific evidence derived from randomized controlled trials and real-world evidence to make selections for formularies or drug product lists. AMCP supports allowing P&T committees to review tamper-resistant or abuse-deterrent formulation to determine safety, effectiveness and comparison to other medications without these properties.

AMCP appreciates the general principles for evaluating the abuse deterrence of generic solid opioid -- oral opioid drug products drafted by the FDA and supports the proposal to implement tier-based approach to testing. To bolster the availability of evidence, FDA should mandate that manufacturers

conduct reasonable post-marketing surveillance studies that help assess the impact of these products on reducing misuse and abuse and evaluate the overall rate of abuse from these products.

In addition to the work of FDA, AMCP appreciates that a new law, the Comprehensive Addiction and Recovery Act, signed by President Obama in July, 2016 provides new resources, programs and opportunities to reduce misuse, abuse and diversion of opioids, particularly allowing for Medicare Part D plans to establish drug management programs for at-risk beneficiaries and increases funding for prescription drug monitoring programs.

However, the work is not finished. Additional legislative and regulatory efforts are necessary to ensure that pharmacists, physicians and managed care organizations have access to real-time PDMP information that is integrated into an electronic health record. Thank you again for the opportunity to present on this important topic.

DR. LIONBERGER: Thank you. So our next speaker is Ajit Roy. Ajit Roy? Okay. So moving on

to the next speaker, Jack Henningfield?

DR. HENNINGFIELD: Good afternoon. Can you hear me? I'm Jack Henningfield. I'm an employee of Pinney Associates. Pinney Associates consults in this area. Today, I'm not being paid by any of our clients -- they haven't had any input -- but rather, by my team at Pinney Associates. Tomorrow, Ed Cone, my long-term colleague, will be commenting on primarily category one testing. I want to comment a little bit more on the place of category two and category three testing in this area.

The starting point for category two and three though is category one. It is in vitro studies, to best understand the product at hand. And so, that's important in helping to design the category two PK studies and the category three, if those are needed. And the category three oftentimes includes clinical studies that are basically abuse potential studies, but adapted in creative ways to the product at hand.

So from our perspective, the draft guidance on abuse-potential assessment and the generic guidance

go hand in hand. We look forward to the final guidance coming out on abuse-potential. But right now, this has been very helpful to have out.

As in the case of category one, as we heard this morning, there has been a lot of standardization in category two and category three. And so, one of the exciting things in my field -- I grew up in abuse-potential assessments.

I'm a product of Nixon's war on drugs -- is that we have a ton more data on abuse-potential testing than we did just 15 years ago. And you folks and your companies are paid for a lot of that. But thank you. You're serving the nation. You're serving the world because now we have lots more studies. The field has moved tremendously in the last 15 years.

The other thing though, as you heard this morning, is that we're not close to the point that we can just look at the product and predict what's going to happen in a PK study. We're getting closer, or go from a PK study to a human abuse-potential outcome. We're getting closer and we're getting better.

Now, that's good news and that's bad news

for the generic industry. And the good news is, as Ed Cone and I testified last year, I think in a lot of cases we can streamline the process of generic drug development and testing. But the bad news is we don't have a simple recipe, do exactly this, this is the roadmap. That would have been the easy way out.

And two years ago, Ed Cone and I recommended that FDA work to streamline the process, but advised that you can't just automatically say you have to or you don't have to do category three testing. And so, I think that recognizes that you've got to take it case by case.

It's I guess the FDA is adapting the Supreme Court's definition of pornography. We'll know it when we see, or we'll know what to do when we see it. And I think that we've got to live with some amount of flexibility there. The only alternative is just saying everybody do everything.

And the problem with that, it doesn't recognize the important role that generics have in transforming the marketplace. And Dr. Throckmorton this morning talked about the long-term goal of

transforming the marketplace to abuse-deterrent products.

A few years ago, I would have said that was decades off. And now, you know, I don't know what the timeline is. But it's moving a lot quicker than any of us expected. I don't think we're within five years of starting to rescind approval.

But you know, 10, 15 years at this pace, we might much more quickly get to that point like we did in the auto industry where cars without seatbelts, without safety glass are a thing of the past. And by the way, that was one of CDC's greatest top 10 public health accomplishments of the 21st century, not unlike what we're going through here.

Regulation, incentives working with industry, education, better highway signage and so forth, all of that meant we do a better job of preventing and reducing accidents per mile. And when people do have accidents, there's much lower risk of serious injury and death. And I think that we're seeing this here much more quickly than a lot of us thought was possible.

My first AD drug, so to speak, was a buprenorphine in 1980 that I worked on. And now, the pipeline is moving very quickly. So the things that FDA is doing to help incentivize industry and that industry is doing, like being here today and taking it seriously, is actually working. When you're used to the government getting dumped on by everything, I'd put this up as an example of what's working and what can happen.

So I think that we can streamline the process. I think we have to make every effort to streamline the process because generic development is critical. But that's going to make -- mean it's not a simple one-size-fits-all formula.

Finally, you could see this morning the struggle that the Blue Cross Blue Shield and VA are going through to address this. And it's a balancing act. At least to my listening, VA has moved a little bit more in the direction of being more supportive than two years ago and really putting out the comprehensive kind of programs that we need nationwide. And when I see, especially treatment

being left out, that's really unfortunate. We need nationwide more what VA is trying to do in its system.

So let me conclude by saying that my colleagues at I at Pinney Associates, who've been involved in this stuff for decades, support the efforts of FDA to help our nation transition from non-AD opioids to AD opioids. We've already started to see the success with products.

We predicted that if it was working, we'd see some migration to heroin. FDA can't solve that problem. Developers can't solve that problem. To solve that problem, we need the comprehensive efforts -- and again, you saw a nice slice of it at the Veterans Administration. That's what we need nationwide if we're going to deal with the entire problem.

I think we have to get much more quickly to better education, better diagnostic procedures for substance abuse, looking at early warning signs, diverse treatment on demand when the person says, doc, I'm ready for help, what do I do. They need diverse treatment available then. That's part of the reason

why Nixon supported the program I was trained in. He was told that it worked, and it does. It does work. No magic bullet, but it works.

And let me conclude with the words of my mentor and hero, former surgeon general C. Everett Koop. He said we have to make it as easy to get treatment as it is to get the drugs that kill people. We have a long way to go. But I think this is a critical part of that.

And so, FDA, when you get beat up in the press, that your answer is just approving new drugs, we need new and better drugs to replace the old ones. Thank you.

(Applause)

DR. LIONBERGER: Thank you. So our next speaker is Penny Levin.

MS. LEVIN: Thank you. Hi, I'm Penny Levin, and I'm speaking on behalf of Teva Pharmaceuticals today. Teva is a manufacturer of both branded and generic products and strives for a balanced regulatory policy that appropriately incentivizes innovation while also facilitating the development and timely

approval of affordable generic products for the American public. Teva is committed to ensuring the highest standards of safety and quality for our pain therapies.

Abuse-deterrent technology is a valuable, evolving and dynamic field that will aid in addressing the abuse and misuse of medicines. In addition to providing both innovative and affordable generic pain treatments, we are exploring numerous ways to increase the proper use of our medicines, including through drug delivery technology, secure patient packaging, patient and provider education and advocacy.

Teva believes FDA should require opioids, both short-acting and extended-release, to have abuse-deterrent properties and require generic versions of the branded opioids to have abuse-deterrent properties that are equal in quality, but not necessarily identical to that of the brands.

We also believe that for a generic to be considered interchangeable to an abuse-deterrent branded product, the generic must meet the traditional standard of bioequivalence and also that the abuse-

deterrent properties of the generic product and qualify for the same abuse-deterrent labeling as the branded product possess the same abuse-deterrent mechanism such as physical/chemical barrier, agonist/antagonist combination, et cetera, and are no less abuse-deterrent than the brand, as determined by FDA.

Teva recognizes that just as ADF products and technology vary, assuming FDA's recommendations for both the safety and effectiveness of the branded products and the equivalence of the generic versions in this context, Teva envisions that depending on the mechanism of abuse deterrence, the closer the formulation, the nature and grade of excipients and manufacturing process of the generic is to the branded product, the more heavily weighted FDA's recommendations may be toward that of in vitro testing.

Conversely, depending on the mechanism of abuse deterrence, the greater the degree of significance of difference between the branded and generic products, the more likely that additional in

vitro as well as pharmacokinetic and perhaps human abuse liability studies may be warranted.

Since the previous public meeting on this topic in 2014, we've observed significant advancements in the field, with now seven approved branded abuse-deterrent opioids. The technology continues to rapidly evolve and the science in many instances faster than can be kept up with by regulatory guidances.

This has resulted in the current state, where there are no generic ADF approved opioids available for the American public.

It is imperative that the FDA begin immediately the drafting of product-specific guidance, reflecting the currently approved branded ADF opioids and follow suit in a timely manner with subsequent approvals of future innovative products to foster a level playing field where we can continue to incentivize innovation while also facilitating timely development and approval of affordable ADF generic opioid products for the American public.

Teva welcomes the opportunity to discuss

this important issue with FDA and share with you the technologies and data we are developing to help FDA further the development of guidance for both branded and generic products. Thank you.

DR. LIONBERGER: Thank you. So our next speaker is Simon Budman.

MR. BUDMAN: Thank you very much for this opportunity to speak. I'm Simon Budman. I'm the chief strategy officer of Inflexxion. My disclosure is that I'm an employee of Inflexxion. We work with the pharmaceutical companies around post-marketing surveillance for opioids and stimulants. But I'm here not in that capacity and I'm being paid by no pharmaceutical company. We also now work with the FDA providing data -- post-marketing data.

What I want to talk about is the complexity of the ADFs and the fact that abuse and abuse deterrence is far more complex than simply the chemical properties or the physical properties of a particular product. The information that one can get from an in vitro study or house study are simply not enough to understand the abuse deterrence of a given

product.

You've heard about this before, but by pill count, about 96 to 97 percent of opioids prescribed are generics and the ADF market at this point, most of those that are prescribed are dominated by OxyContin. However, abuse in the real world is determined by multiple factors, not simple factors.

We've developed a model to try to understand what actually goes on with products in the real world. The red factors are formulation-related qualities. The others have to do with other factors, as I'll tell you.

The first factor is availability. A product simply can't be abused, will not be abused if it's not available, if you can't get a hold of it. There's no abuse. The best form of abuse deterrence is not having the property out there -- not having the product out there. That ensures abuse deterrence.

The second factor is the quality of the high - liking, speed and intensity, E_{max}, t_{max} of that product. Then there's the issue of effort, the preparation time and the waste that goes into being

able to break down that product.

Then comes the issue of local cost. What does that product cost in the local area or how much are people paying for it from other people to -- from dealers, from other people in order to obtain that product. Then there's the abuse ecology. These factors are dynamic factors. They're taking place in the midst of a bunch of other things that are going on in the abuse environment.

What are the alternatives available? If I don't abuse this product, what other product can I get? How much is it going to cost me? What am I going to get out of the high from that product, et cetera, et cetera.

Then there's the issue of social network and personal environment. Who's abusing what in your environment? And also, are you working? Are you having to go to work each day? In which case, you'll take a different kind of product than you might if you're not working.

Social network is very important. Most injectors are induced into -- or get involved in

injecting through other people. It's very rare that you find an injector who's injecting without having some sort of involvement with other injectors.

It doesn't happen that somebody sits down one day and says, gee, I'm going to inject this product. There's a great deal of data in terms of heroin abuse that indicates strongly that heroin abusers -- injectors -- are involved with other heroin injectors.

Then there's the severity of the addiction. If you're addicted enough and don't have anything else, you'll find, you'll use anything. And again, depending on the degree of your severity of addiction, then all that comes together in terms of abuse. And the relative contribution of these factors may vary under different circumstances.

One of the parts of the post-marketing work that we do is Internet monitoring. We monitor a number of Internet sites where recreational drug abusers look at and use different kinds of abuse-related products. We look at the recipes for abuse. We look at how people describe and discuss different

products.

What you're seeing here is the drug discussion for -- a drug discussion forum related to the introduction of a new ADF. And these are recipes for abuse that they're looking at. So in the first 79 days of the introduction of this product, the bottom line, the deep blue line is the number of threads that people are discussing this. The light blue area above that is the page views.

So what we see is in 79 days, this product had 80,000 page views. These are dynamic processes. They're not static processes. What we're talking about in terms of the abuse of opioids and abuse deterrence of opioids is a process of hacking.

It's not that somebody sort of sits down, you develop an abuse-deterrent formulation, then people say, oh gee, I can't abuse that and then they go on to the next thing. What happens is that people are looking at each product as it comes out trying to find different ways to abuse that product.

And this is again a dynamic process where people are sharing recipes and talking about what can

be done to abuse the product. What you see below is a post. This post is about oxymorphone. "The best thing I can offer is to make sure you get the generic. The name brand has been reformulated and are these plasticky convex pills that you can't crush. People were passing them whole; the body wasn't even breaking it down. If you have had them before, the generics work like the old stop signs."

These are recipe trends for the reformulation of OxyContin. And again, I just want to indicate here that a successful recipe only indicates that you can get to the API. It's not that you're going to use that recipe, but that people are finding recipes that work. They may cost a lot.

Then they take a long time and then they end up being that you can break them down. But you wouldn't want to spend that time, money and effort to break it down. And just about every ADF has some recipes that we've found that you can use for breaking it down.

So there were 688 recipe-related posts for OxyContin in the two-year period following its

reformulation, 319 posts with successful results. Again, you may not use those successful results. But they were -- they were there. And there were the top six successful recipes.

Okay. This is an example online of a successful recipe for an ADF product. And what you see is as you follow the trend over time, there's more and more discussion of the successful recipe.

What you see with an unsuccessful recipe is the recipe starts fairly low. People talk about the recipes. They comment on one another's recipes. They comment on whether it works, whether it doesn't work, how well it works, et cetera, et cetera. And that recipe goes low and stays low. When it comes up again, people say, oh, you didn't catch the other thread. The other thread, we told you we can't really do that with the product.

Here, a few modest proposals and these proposals may make nobody happy, but I'll say them anyway, that we need a basic minimal, maybe open source, plain vanilla ADF technology that should be required of every generic opioid. It's like -- it's

like selling cars that don't have seatbelts. You just can't do it and expect a change to happen.

A branded product that demonstrates two years of real-world abuse deterrence, category four, should get an additional year of exclusivity or it should get two years or three years. I don't know what that should be. But there should be some sort of incentive for developing a really, really good product.

Dynamic labeling, labeling needs to be reevaluated every three to five years because the environment is dynamic and the environment is changing. Ongoing epidemiological real-time assessment of every opioid product. The environment is changing and you need to be tracking it and the FDA needs to be tracking it.

And finally, generics must be physically, easily distinguishable from the branded product. There's FDA guidance on the appearance of generics. That -- for this area, that guidance is misguided. If you have products -- if you have generics that look like the innovator's product, there will be no way to

distinguish those in post-marketing studies. You won't know what you're getting. And they have to be distinguishable. That guidance can't be applied under these circumstances. Thank you very much.

(Applause)

PANEL DISCUSSION: GENERICS ADF GUIDANCE AND POTENTIAL FUTURE IMPROVEMENTS IN THE EVALUATION OF THE EQUIVALENCE OF PROPOSED GENERIC OPIOIDS TO RLDs WITH LABELING DESCRIBING ABUSE-DETERRENT PROPERTIES

DR. LIONBERGER: Thank you. So we have a call for Michelle Harford. This is a final call. We have a final call for Ajit Roy. All right, seeing as those people aren't available, that ends the open public comment period. We'll now move on to our panel discussion.

So I want to introduce a few -- so the panelists sitting in front of you consist of the speakers as well as a few additional members that weren't speakers. So down, juts going on the end, we have Patrick Raulerson, from the Office of Regulatory Policy at CDER.

We have Ellen Fields, the deputy director of

the Division of Anesthesia, Analgesia and Addiction Products in the Office of New Drugs. And we have Daniel -- next one -- yeah, no, sorry. Then, after one of our speakers, we have Daniel Cohen, representing the branded industry, correct?

MR. COHEN: Correct.

DR. LIONBERGER: Okay, and at the end, we have Gregg DeRosa, from Teva Pharmaceuticals, representing the generic industry. So I'll put up -- so Avena, can you put up the discussion questions? The other PowerPoint?

So to begin the panel discussion, what we'll do is we'll put up on the -- we'll put up on the screen behind us the questions that were asked at the -- you know, in the Federal Register notice. I think these will help organize the discussion.

So the first question that we asked was based on any testing that you've attempted to perform or performed in accordance with the March, 2016 guidance, are there any aspects of the guidance that need clarification or improvement?

So this is really a question to the -- to

the industry members of the panel to try to identify any real-world experience that they would be willing to share to say that this is -- again, you know, we tried to do it and we just couldn't do this aspect of the guidance or we weren't clear how to do it.

So we're really looking for that practical feedback on implementing the approaches outlined in the draft guidance. Yeah, so again, this is really a question, you know, first to the industry members and then we'll let other people respond and --

MR. DEROSA: Well, I think -- I think -- can anybody hear me? Okay. I think we felt there was a little bit of a lack of, you know, clarity and perhaps a bit of lack of details that we felt were missing here. I think we kind of felt that, you know, some of the nomenclature was not the same as the brands and we'd really like that to happen.

You know, we thought that, you know, this was a good first draft. But as with every draft, there's always going to be need for some sort of, you know, updates. You know, I think we were looking for a little bit more clarity around the PK and the how

studies. When will we need to do these? Probably a lot more clarity tomorrow. They're going to be talking a little bit about the in vitro clarifications that we're seeking. But my colleagues will talk a little bit more about that tomorrow.

I think we were also a little bit concerned about what are we going to do with the current ADFs. I mean, people have ADFs that are sitting at the agency now. Where do they fit? How do we --

DR. LIONBERGER: So, sorry. Do you mean generic applications?

MR. DEROSA: Generic applications I'm talking about --

DR. LIONBERGER: Referencing a current --

MR. DEROSA: Referencing a current ADF. You know, where does that go? I mean, we've done testing. We've submitted some of them. Are they -- how do we go about it now? How do we get those approved hopefully?

And then, in the short-term before GDUFA II, how -- you know, how are we going to, you know, go about -- without this -- without, you know, real

clarity around this guidance, how are we going to go and submit anything that we're going to submit in the real near-term?

Are -- you know, are we going to get acceptance for filing if we do something that's a little bit different than this draft guidance? I think we're really yearning for the idea of having, you know, more of a sit-down with FDA about how we're going to go about some of this stuff.

I think -- you know, from our perspective, we've been doing a lot of things through controlled correspondence. At some point, when GDUFA II hits, hopefully we'll be able to have some sit-downs where it's a face-to-face sort of interaction on, you know, a pre-ANDA meeting.

I think we're really looking for some product-specific guidances too. I think that will be -- because as everybody had talked before, there are attributes of each of these brand products that are a little different. And there is no one-size-fits-all perhaps.

So having a product-specific guidance that

gives us some idea about what category testing needs to be done or if we are different in any way from let's say cat one, do we go to cat two. If we are, you know, the same at cat two, is that enough? I think we just -- we really are yearning for more clarity on how these things are going to get reviewed and approved.

DR. LIONBERGER: Okay, so --

MR. COHEN: Thank you. Let me pick up a little bit from where Gregg left off, that when we're talking a look at the guidance -- and obviously on behalf of the branded industry, we haven't attempted the generic guidelines by definition.

But if we take a look at the guidances themselves, you're trying to create a dynamic -- a marker in a very dynamic space of development. And by definition, a guidance itself tends to be fairly static in its application.

So at the first level, we certainly encourage flexibility in the guidance. Having product-specific or, as Jeff Dayno suggested this morning, abuse-deterrent method-specific guidance

would be an appropriate standard that would be particularly helpful.

That flexibility is key because, as manufacturers, we have to know our products and we know them best as to how their capabilities are and where they work. And as discussed this morning, category one guidance may not be sufficient.

When we take a look at a very simplistic level, if the proposed generic product is identical in every respect to the reference product, then the manufacturer might appropriately make application for a lower burden of evidence.

And if the product itself -- to the reference product, as suggested I believe in Doug's speech earlier this morning, has a unique application, that really is an NDA and doesn't fall in there.

So where we're really focusing on right now is that gray area where there is a similar mechanism of action in abuse deterrence but not an identical mechanism of action. And there, when we see small variations in the in vitro level, we can sometimes see very large variations in the PK level.

And the same applies to small variations in PK, maybe large variations in the HAL data. So the importance of that mechanism of action and flexibility becomes very critical to put in the guidance.

And then, the last thing, going back to the development of the guidance, the guidances themselves tend to be focused on products that have physical/chemical barriers as the -- as was developed initially and have some very applicable portions to the agonist/antagonist approach.

You need to make sure that the guidance also accommodates new molecular entities, prodrugs, the gel-based technologies, patches. As the innovators, we're trying to bring entirely different mechanisms of action for abuse deterrence to the table. And the measuring everything by the same yardstick is not going to effectively provide alternatives for the marketplace.

MR. DEROSA: I just want to, you know, kind of clarify too that I think we are after the same sort of things. I mean, we want to develop a product that is no less abuse-deterrent, right? And wherever the

science takes us, you have -- FDA has the data, right? Especially at least on the seven approved products. You have the data and, you know, hopefully we could develop something at least for those seven to give us an idea of where we need to be.

I mean, I think we saw a great example with Hysingla where I think, you know -- you know, the data was very sequential and that -- you know, the cat one was relatively predictive of cat two which was, you know, predictive of cat three.

Now, I'm sure they're not all like that. But you know, I think where they are, it could be -- we could develop, you know, a product-specific guidance relatively quickly that would give us some guidance on how we should go.

And you know, as the technologies evolve, obviously, you know, I think the guidances or the product-specific guidances can, you know, help plug any of the holes that really don't get described in this guidance.

DR. LIONBERGER: So I mean, I think one thing I saw -- I heard mentioned from you is that if

the formulations are very similar -- so that means Q1, Q2, similar nomenclature, that means having the same active and inactive ingredients.

So maybe Steve or Xiaoming can comment on some of the things you've seen in the laboratory where, if you have a formulation that has the same components, how much effect does the manufacturing process have on some of the abuse-deterrent properties?

DR. HOAG: Well, based on my experience, if you saw that data, those were similar products. If you look at the formulation -- yes, the formulations were very, very similar. The API was different.

But there was a very large difference in how they behaved in terms of thermal processing and also in terms of particle size reduction, which is critical to the abuse of these and how much energy you needed to break down the product.

So that matrix, the processing -- and I believe that that difference was coming out of how they were formed. And I believe -- I don't know this, but I believe one was hot melt and the other was like

centered. And based on -- I believe that based on patent review and things. But that had a very large impact on the properties of the materials.

DR. XU: Well, we have seen with in-house, looking at in-house prepared formulations, the -- if the formulation component in a composition are similar, the process, for certain applications, it does have an impact on the performance or the properties.

But I think this is more dependent now -- a lot depending on the type of the design of the formulation, how it should be processed. But it may not be generalized. But the process together with the formulation, I think they are equally important.

MR. DEROSA: So I mean, I think differences between, you know, Q1, Q2, Q3, you know, the process, wouldn't we see those sorts of differences when we were designing our product, right? I mean, cat one testing would bear that out, right?

I mean, and we're -- you know, we're after the idea of developing a generic product that is no less abuse-deterrent. So I mean, I don't know that we

could -- we could or would develop a product that had such significant differences because our goal in the end is to have a product that has the same abuse deterrence as the brand.

MR. COHEN: And then, obviously we agree with that approach Gregg. The point that I was making is that cat one data in and of itself is not predictive, even if it is on a similar product, if the results are similar of the cat two or cat three level, as my membership has told me on a regular basis.

And Robert, to your question, it really comes down to, as one of our former presidents once said, it depends on what your definition of is, is. So how close the similar product is to the RLD or to new technology really is going to be informative of what level of testing is going to be appropriate to define an abuse-deterrent that is at least equivalent to the RLD.

MR. DEROSA: Sorry. Yeah, I'm just going to leave it here. Yeah, I think, you know, we're thinking along the same lines. I mean, we want to have a product that has no less abuse deterrence. So

I mean, in the end, if cat one is not sufficient, then, you know, in certain cases I think we would wind up doing that.

But I also, you know, like to think back to the example we saw with Hysingla, right? I mean, there are going to be those examples where I think cat one is seemingly going to be sufficient to establish that.

DR. LIONBERGER: All right. So I have a -- so some comments on the category one in vitro testing. So one aspect that people seemed like they were confused about in the comments on the draft guidance is the differences in the different tiers of testing.

And so, I'd like some comments on the idea of thinking about when you look at the in vitro testing that you do, the level of time and energy that you try to capture in those in vitro tests, right? Is there -- and you know, I'd like to hear both from the -- you know, the brand perspective, as you're developing a new product, right?

You're testing your product. You're looking for ways that you can make it fail, right? I mean,

obviously the more time and energy you put in, you'll be able to find ways that it can fail. But where should you draw the line in terms of now I've found enough and I don't have to go further in the time and energy?

And also, you know, from the point of the testing of the generic products, right, if you're looking for points of -- you know, looking for points of failure, you know, how much time -- how do we -- do we -- how do we gauge the time and energy that we involve in in vitro tests, right? You know, if we go -- like Xiaoming gave the example, right, if you had just these simple examples here, you could easily generate 10,000 different in vitro tests that you might want to do.

So how do you group those into appropriate sets that lead to an -- you know, and I think this is a question for the development of both types of products.

MR. COHEN: Well, and certainly the iterative process is all about testing to failure. And that's something that we're used to. The real

question, I think, is to find the testing mechanisms to make sure that the testing themselves are relevant and applicable to real-world applications for the products themselves.

Abstract testing to failure and means and methods to break down the abuse-deterrent that ultimately have no bearing on real-world activity -- and now I'm back to the question of what is, is. So then, there's also a balance in there. But that becomes a burden on the development of ADF rather than a blessing.

MR. DEROSA: I think we're really going to get into this tomorrow. You know, we're pretty prepared to talk about the details. But I think for us, you know, we're going to look to their product first, right, and we're going to understand how they did their testing from a cat one perspective.

And we're going to try and mimic those sort of things and have hopefully from, you know, a guidance and an understanding of how similar is similar, right? What statistical approach do you do to say, yeah, we're the same and knowing that there's

inherent analytical variability in a lot of these things. So I think we're looking for guidance from FDA about, you know, where are the boundaries, right? We're going to do a lot of the same testing that they've done and how do we determine how -- you know, what's the same?

DR. LIONBERGER: Any other comments on this topic? So then, I want to move to a little bit different section, you know, under the same subtopic, moving a little bit to the in vivo PK studies.

So we've -- I think it's been a -- there's been a common comment, we want more clarity on when in vivo PK studies are part of the equivalence evaluation and more details on their study design and conduct.

So I think we've been -- you know, in both my presentation and Liang's presentation, we identified a few places where we're considering revisions to them.

So I'd like to open up for some comments on the in vivo parts of the profile -- of the PK comparison, you know, I think specifically some of the things we identified were, you know, what type of

patient population is appropriate to use to evaluate specifically nasal abuse because that's something that every currently approved abuse-deterrent formulation has.

And if you read the guidance, you know, if you're -- if you can make your product into, you know, a deliverable powder, right, you have to do an in vivo PK comparison as part of the current guidance. I don't think that's unambiguous at all.

I mean, it pretty clearly points to you have to do -- there either is a PK part for every product that has nasal, you know, deterrents. So I'd like some comments on the details of those -- you know, of those study designs. What aspects should we be clear about in this guidance?

You know, we've identified a few patient populations. How to prepare the materials for those PK studies, right? It's not like a -- that's a much more significant investment than an in vitro study. So you want to make sure that you're testing the -- you're manipulating the material, right? You have to prepare it in an appropriate way for comparison. So

we'd also like comments on, you know, what's the appropriate way to prepare both the brand and generic for a nasal PK, you know, comparison that would be most effective for equivalence evaluation.

MR. DEROSA: I think when it comes to the study itself, grinding a product down to a powder and then asking a healthy, normal individual to snort it, I find that -- I think that's going to be a really tough thing to find because, I mean, there's going to be variability around that in and of itself.

And now, you have somebody that doesn't really know how to snort something. And it might not be the most pleasant thing in the world to snort.

Personally, I think if you want to do these sort of studies, I think they're going to have to be done in, you know, recreational abusers because I think those are the people that understand how to, you know, snort powder in a more consistent manner because, you know, you don't want to get any crazy PK data that, you know, is really driven by, you know, the individual. So I think that's probably going to be something we're going to need to --

MR. COHEN: And that's part of the challenge because the population that abuse-deterrent is for, is directed to is the opioid-naïve patient, not the abuser.

I agree with Gregg entirely that we're going to have to use recreational abusers to do these tests because they need to be experienced enough to be able to perform this type of behavior, which in and of itself is rewarding. You wouldn't want to do that obviously in naïve populations and an abuser population is a wrong comparator.

MR. DEROSA: The only thing I think we worry about as well is, I mean, these abusers, if you're going to go down that road, they're not the most available people in the world. And there's only a few, you know, contract research organizations that can do this work.

So if we're going to have to go down that road and, you know, it's going to be difficult. I mean, we're all going to be fighting for the same group of people.

MR. COHEN: And by the same token, we also

have to make sure that the mechanism of action of the API itself is appropriate for intranasal abuse. The technologies that have the indication, abusers do want to get high through it.

But future technologies in prodrugs, for example, it would not be as relevant a comparator when trying to get high through insufflation is a less relevant measurement and marker.

DR. HOAG: I was going to -- I don't have access to FDA data. But from reading the literature, I often see these studies where they say they ground it and it was coarse and they ground it and it was fine.

And perhaps you maybe require more data, but I would say some characterization of what that thing they actually gave the patient is important other than qualitative, it was coarse or fine.

DR. LIONBERGER: In terms of -- you know, any comment in terms of preparing the -- you know, I think the point's well-taken in terms of characterization of the material.

Any comments on the question of what -- how

do you know -- what's the preparation for the material that you should use in that type of sort of pivotal in vivo comparison for both -- you know, for both of the brand and the generic products. How do you ensure that you're doing the sort of fairest comparison?

MR. COHEN: Well, one of the best markers for that would be to give the recreational abuser the option and the ability to prepare his own preparation using a variety of tools that would be most common. And while I agree --

DR. LIONBERGER: I mean, is that what you do with the new drug development?

MR. COHEN: We ask where would you like to go.

DR. LIONBERGER: Okay.

MR. COHEN: So that would be a more appropriate real-world comparator if we -- I understand standardization and Stephen's comments and I agree with him, by the way, about the characterization. But at the same time, we want to be able to have products that have real-world applications. And so, that portion of the testing

also I think is worthy of your consideration.

MR. DEROSA: I mean, I think we're after standardization. I mean, I think we -- you know, we would like to have, you know, a standard set of tests that we would do, both generic and brand. And you know, according to the guidance, there's, you know, a certain, you know, particle size cutoff. I don't know if that's the right cutoff or not.

But you know, if we were finer than the brand, I think we would really like to get some sort of standard set of, you know, testing and tools so that we could -- you know, we could be much more standardized. I mean, from a real-world perspective, you're probably right. But when we're doing the comparison of test and reference, I want something standardized.

DR. LIONBERGER: So are there situations when -- and anybody on the panel maybe can identify situations where the category one-type studies might be sufficient for these nasal routes, for products that have the nasal claim. And I'm thinking specifically of products that might be very, very

similar in formulation or are there new methods or testings to be more predictive of nasal availability that we might want to investigate or be aware of.

You know, and some -- from the product development perspective, are there things, you know, when you're developing a formulation to be abuse-deterrent, you don't want -- I mean, from my perspective, right, you probably don't want to have the only way you're going to find out what the effect of that formulation on nasal availability is, is to do one of these expensive studies where you can't find the patient.

So what -- you know, as you're developing the product, what are you going to do to at least be sure that you're close to the product before you do that pivotal study. You know, what are the most -- what are the most promising in vitro characteristics that you see -- that the panel sees are, you know, potentially linked or potentially predictive of the nasal availability?

MR. DEROSA: I mean, I think this is going to get more into what we talk about tomorrow. But you

know, I think we're focusing on particle size, right? I mean, we'd like for -- if we are -- if it's above a certain particle size -- and again, I don't know if the number in the guidance is the correct number or not.

But you know, the coarser the product, I think we would believe we wouldn't necessarily have to do insufflation. Or if that product gels very, very quickly in the presence of water, I mean, I think we would tend to think that the cat one would be enough.

MR. COHEN: And as Gregg said, we'll be talking about this in greater detail tomorrow. And I think I'd rather leave it there with folks that are more expert in the cat one arena.

MR. DEROSA: Yeah. Agree, agree.

DR. LIONBERGER: So let's move on to the second question that we asked. So are there current -- are there any characteristics of the currently approved abuse-deterrent RLDs for which issuance of product-specific guidance beyond what was described in FDA's March, 2016 draft guidance which would facilitate the development of abuse-deterrent opioid

products?

And so, leave this open for questions but also point out maybe one aspect that people might want to comment here are on both products that have aversive agents or products that have antagonists as part of their abuse-deterrent mechanism to identify specific aspects that people might want to see for those particular products, just so to spur some discussion.

MR. DEROSA: Well, I think this guidance is generally probably refers more to the -- you know, to the crush-resistant products. It would be nice to have a little bit -- I mean, there is some mentions. But it would be nice to have -- you know, maybe it even needs to have separate guidance.

I don't know where you have a guidance on one technology or one platform versus another because they're different. And I don't know that there's necessarily a one-size-fits-all.

DR. LIONBERGER: Yeah, I think it mentioned this in response to my questions earlier that, you know, the current draft guidance, you know, doesn't

envision in any way a pathway for crossing technologies.

MR. DEROSA: Right.

DR. LIONBERGER: It doesn't say that there's going to be any pathway to say, well, I have an antagonist now.

MR. DEROSA: Right.

DR. LIONBERGER: I'm as good as a crush-resistant product. It's really comparisons within the same type. I mean, it doesn't -- you know, I would say that -- admit that it currently doesn't say that. But I would say it doesn't provide any guidance on any of those type of approaches.

MR. DEROSA: Right, right. Yeah.

DR. LIONBERGER: You can kind of take that for what it implies about what we think about those -- about that approach -- you know, that -- those types of substitutions. So implicitly, it is saying, you know, you have to stay within the same mechanisms. But is it -- is there a sense of agreement that, you know, the area that needs more -- an area that needs more clarification are the antagonist -- are the, you

know, the both category one and category two studies for the antagonist combinations?

MR. DEROSA: Yeah. I don't think there's -- there's not a whole lot of information there at all.

MR. COHEN: Absolutely, and by the -- and my earlier comment as well, that we need to make sure that we're including for the possibility that the agency will be approving other new formulations beyond the two approaches that already have a label, as those products' NDAs are already before the agency for consideration as we're meeting here today.

MR. DEROSA: That's why we really would love to have product-specific guidance.

MR. COHEN: Or mechanism-specific guidance.

DR. LIONBERGER: Yeah, so like I think, you know, when we say product-specific guidance, we really mean specific to that RLD, right?

MR. COHEN: Correct.

DR. LIONBERGER: Right, and that's what you're looking for --

MR. COHEN: Correct.

DR. LIONBERGER: Like, so you would like a

specific -- you know, and correct me if I'm wrong -- a specific set of tests to say for, you know, this particular RLD, you do these types of category one tests and these comparative PK studies.

MR. COHEN: That would be ideal. I mean, just like you have bio study guidances now, it would be nice to have something that's specific to that product.

DR. LIONBERGER: Does -- you know, does any of the panelists see any concern about being that, you know, specific, that it's -- you know, I think one concern that I would identify would be our guidances have to be general enough to cover the range of different technologies that a generic applicant would use, right?

So we can't assume they're using exactly the same polymer. It's a different polymer. I'm going to use a different amount. I'm going to use a different manufacturing process. So you know, I'm --

MR. DEROSA: Well, I think you could be general enough. I mean, I think you could. But I think what we're really looking for is an idea of, you

know, for this specific technology, what are the tests you envision. I mean, we can probably guess. But it would be nice to get some guidance.

DR. HOAG: I was going to make one -- I do occasional consulting. And you see the generics and innovators and they're all trying to avoid each other's patents and things. And there are these slight changes of how different companies do things.

It'd be very useful to have very specific statistics. Like if something has like a C_{max} and a t_{max} or an AUC, those things, you know, may be too broad and someone may be able to meet something, a very broad statistic. But the product may actually perform differently. So --

DR. LIONBERGER: No, I mean, I think the challenge that we're torn with is sometimes people want to be very specific. But then, they want some flexibility if they don't actually meet exactly one of those criteria.

So I think we recognize that that's, you know, a challenge. And I would say that every guidance that we've put out, not just draft guidance,

every final guidance that we've put out says that alternative approaches are always -- you know, are always acceptable.

So guidances, right, they're not regulations. They're not intended to be rigid, the only approach that's possible, right? It's trying to give the best possible advice that we can across -- you know, across a range of different product circumstances, right?

There could be a range of different technologies that a generic company is using to have a crush- and extraction-resistant product. And you know, there's a challenge between, you know, being very specific and being broad enough to cover the range of things that we possibly could receive from generics companies.

MR. DEROSA: I think -- I think -- oh, sorry. Go ahead.

MR. COHEN: I was just going to say I think the area where Gregg and I will find some agreement though is your statement is aspirational. And we appreciate that. But in reality, the guidances

themselves tend to be inflexible in their application.

MR. DEROSA: Well, and I think, you know, let's use -- let's say we use Hysingla for an example, just because we've had the example. It would be nice to know if the agency believes that cat one is enough to get an approval for a generic product.

You know, if you're similar enough from your, you know, technology and performance in cat one, is that enough, you know, because there are going to be other ones, I would suspect, that you're going to say it doesn't matter how close you are with cat one. You've got to do cat two as well. So I mean, I think that's the kind of flavor in guidance we'd really like to see.

DR. THROCKMORTON: Can I ask a question?

DR. LIONBERGER: Sure.

DR. THROCKMORTON: Can I ask a question about that? So we listened this morning to Xiaoming and Steve say very small differences in manufacturing can basically take you from something with a certain set of abuse characteristics to something very different. So I'm just wondering about the potential

for writing that kind of a very prescriptive, product-specific guidance now. It seems challenging on face to a non-chemist.

MR. DEROSA: But wouldn't -- you know, some of the descriptions -- so some of those tests in cat one would be very different, right? If I had a very, very different process, that might yield extremely different cat one testing results.

So I mean, you know, when we're developing these products and trying to assure that we have a product that has no less abuse deterrence than the brand, that would probably disqualify us from continuing to further develop a product that had very, very different characteristics.

MR. COHEN: But Gregg, I know you want to use Hysingla as an example because it works for the paradigm. But you know, cat one testing itself just hasn't shown that it's predictive enough for cat two or cat three continuation at this point. I mean, perhaps your direction more appropriately lies with more experience in that we have more testing initially, particularly with the current RLDs, and

then use that experience to inform an adjustment. And Robert, this type, I will go to your aspirational view of the guidance where we can use the knowledge that we learn and change over time as appropriate based on the evidence.

MR. DEROSA: Yeah. I mean, I think in the end, there is data today that exists for seven products and we could hopefully -- there's that data that could drive a product-specific guidance for those seven products to tell us, you know, whether you believe in those specific products that cat one is, you know, enough or do we need to do something different.

DR. THROCKMORTON: Dan, I'm sorry. I've got to -- I've got to challenge you. So you've now said four times, at least to my count or something, cat one does not predict cat two, does not predict cat three. Is that information public? Because I mean, it's one of the things that we called for in the draft guidance. It made its way -- the draft brand name guidance. It made its way into the final guidance, this need to understand the relationship between the

in vitro testing, the PK and the pharmacodynamic we're all interested in. So the data underlying your assertion that you've now made several times, I'm just wondering are those available to us because it would be really helpful to know what you're pointing at there.

MR. COHEN: Yeah, and by in large -- and we'll talk about this tomorrow as well -- but by in large, you're in possession of more data than the individual companies are sharing among themselves at this point.

DR. THROCKMORTON: So we would have the same data you're drawing on?

MR. COHEN: Yes, you should.

DR. THROCKMORTON: Publicly?

MR. COHEN: I think unquestionably.

DR. THROCKMORTON: No. No, it was just we were missing something. That was -- that was --

MR. COHEN: Okay. Fair enough, then.

DR. THROCKMORTON: Thank you.

DR. LIONBERGER: So we'll move on to the next question on our notice -- so this next question

is a little bit future-looking. Are there approaches or technologies for evaluating abuse deterrence of generic opioid products that were not included in the March guidance that should be?

So are there different approaches to -- Yeah, so I would say that -- so I would say that if you use a little more flavor to the question, the guidance says that you could do comparative in vitro testing with -- so the guidance talks about -- oh, this is a great microphone.

So the guidance talks about, you know, different types of comparative in vitro testing, looking, you know, mainly at endpoints of drug release or drug extractability, syringability. It talks about, you know, PK studies that look at drug availability after the particular routes of administration.

You know, it talks a tiny bit about drug-liking as a possibility, but not really recommended. So are there -- you know, is there any other type of approach that we should use or are there different in vitro comparisons or that we should look at? I know

that Steve mentioned some of these things about, you know, looking at, you know, a diffusion cell so it helps tell you nasal availability or are there ways to measure, you know, for example, he talked about, well, the gelling properties are important.

I mean, none of these in vitro -- these tests are very performance-based, right? Are there other characteristics of these products that we should move toward a more physical property-based where you look at instead of -- I mean, some of our talks from both Xiaoming and Steve both talked about this, moving toward testing and comparing mechanical properties rather than a drug release property.

But you know, are there any other aspects or in terms of particle size and particle size characterization? Is that -- is that -- are there any of these things that are more appropriate endpoints for the type of testing that are in the guidance that we maybe should be considering is, you know, one aspect of this. Or are there different types of pharmacokinetic study designs that we should look at?

The third example -- and you know, this is a

little bit more complicated one, is that a lot of times when we look at manipulation, we look at endpoints of how much drug is extracted. Are there ways to look at and compare not how much drug was extracted but either the time and energy it took to extract that amount of drug from two different products?

So if you want to say, well, I've caused complete release from the brand product and I've caused complete release from the generic product, are there ways to consider the amount of effort or energy that it took to get that?

So comparing the amount of input rather than the output measure itself. So those are some of the ideas I'm looking for here. So any comments from the panel?

MR. DEROSA: I mean, I think tomorrow we have our in vitro experts and they might have -- you know, might have some comment on that. I mean, I would defer to the brand guys. I mean, mainly you guys have more experience in this. We're just starting to understand. And I mean, from a -- from,

you know, an in vitro perspective right now, the guidance seems reasonable.

MR. COHEN: The additions would be back to the real-world scenarios of what deterrence is. So time and effort become an important part of the calculation as to whether or not the product itself is deterrent.

So those measurements would be important. Also taking a look not just at the vast scales that we're currently using, but taking a look at a comparator. Not a question of take drug again, but take drug compared to the drug we're comparing it to.

If there is a difference there, those types of measurements should be important as we're -- you know, again, more analysis of real-world scenarios that a potential abuser may be looking at in addition to the scientific measures that again we'll talk about more tomorrow.

DR. LIONBERGER: So --

DR. HENNINGFIELD: Hi. I'm Jack Henningfield. Thanks for the introduction to what I was going to say. You started out by saying time and

effort. So the guidance is pretty heavy -- have been heavy on the technology, what kinds of tests, the statistics.

But the guidances talk about how much work effort, how much does it take. And that's the really big thing. There's a whole technology of that. It's called behavioral economics. And in our field of substance abuse, that has advanced considerably.

At our group, at Pinney Associates, we worked with behavioral economic experts, did some pilot studies. We've got a pilot scale. But that's only the beginning.

And I think that by talking about quantitative methods of estimating the work effort, you're going to bring more people that are out there that are expert into doing that because it's not just work effort. It's how do you measure it quantitatively. And guess what? There is a science for doing that.

So I'd encourage you to at least get the word behavioral economics -- that's not in our scale, by the way. But the principles are the same. It's

how much work. How do you quantify it? How do you compare it across drugs? And there's a science for that.

MR. COHEN: And it also has to be a dynamic effort as you work through that because initially, any type of effort to break down a product compared to a non-abuse-deterrent product is going to be a deterrent at least to the level of substitution, when we're only dealing with 4 percent of the market space out of 250 million scripts last year having an abuse-deterrent property.

And over time, those types of measurements are going to need to change. When we reflect on the ideal world and the future that we're striving towards, which is a transition of the market to abuse-deterrents, time and effort measures will be different at those points than they would be today.

DR. THROCKMORTON: So that would apply to innovator development as well as generic -- brand name as well as generics, right? So Jack, you're suggesting you're sort of testing -- let's call it preference testing of a kind would be applied to the

brand name product development and then carry over to the generics comparisons?

DR. HENNINGFIELD: (Off mic)

DR. LIONBERGER: Can you please go -- sorry. Can you go the microphone so that we can make sure that everyone can hear?

DR. HENNINGFIELD: It's going beyond preference testing to having volunteers, like we do in abuse liability testing. How much would you pay for this drug? That seems like a pretty simple measure. It happens to be fairly predictive. And there are more quantitative ways of doing this when you're comparing commodities.

My group does this at Johns Hopkins. NIDA does it. But it's a whole area of science that by simply bringing it in a little bit more clearly in the guidance, you bring more scientists in the field to help you be able to come up with numbers. I mean, our preliminary alert scale, that's what we're doing. We're coming up with numbers.

By what quantitative metric is this more difficult to abuse than that? You know, we heard

earlier today there are lots of recipes out there. But you know, there are recipes for making French baguettes. But nobody does it. It's too much work.

MR. COHEN: And Doug, to be specific, my answer is yes. Even though we're talking about generic guidance today, I'm also implicitly talking about the branded guidance as well.

And for a branded product, if we have as reference a non-ADF product that we're using as the comparator and we can test our ADF formulation against the non-ADF product on a preference base, a time and effort base, an economic base, we think those measures are significant to help you, as I've talked about real-world results, as to whether or not the abuse-deterrent is going to be effective when it's deployed in the marketplace.

DR. Tolliver: In terms of additional category one studies to consider would also be the -- particularly for agonist/antagonist and also for the aversive products is looking at the destruction of the antagonist versus the agonist and looking at the destruction of the aversive agent. And these kind of

studies are done as part of abuse-deterrent assessments. And you know, the whole idea is to change that ratio of agonist to antagonist.

And if you can increase that ratio of agonist, decrease the antagonist, then you have to wonder what effect that will have on the abuse-deterrent characteristics.

The same thing goes with an aversive agent. If you are able to find ways -- and such ways may exist -- in order to preferentially destroy or reduce the amount of the aversive agent that is in the product, then again, you have the -- you have to ask the question, well, what is the impact of that on the abuse-deterrent characteristics of the product.

DR. LIONBERGER: So I'm not sure if people can answer this. But I mean, has that been identified -- has that been identified as -- you know, certainly if that happened, that would be an issue. But has that been identified as a potential -- you know, a potential mode for people avoiding that aspect of abuse-deterrent technologies?

DR. Tolliver: It has been examined and

under certain -- for certain innovator drugs, yes. It has been looked at as a way to beat the system. Is that what you're asking?

DR. LIONBERGER: Yeah, yes. Thank you.

DR. LOSTRITTO: Yes, it has. That's why I'm specifically stating this, because of experience with it.

DR. LIONBERGER: So, a comment?

MR. HEFFERNAN: Thank you. I'm Mike Heffernan, with Collegium. And I want to go back to the I think important question that Dr. Throckmorton asked about data that we're aware of that requires an iterative approach. So I'll speak right to our product, Xtampza, and some of the data that's available, and it's publicly available. But if you look at -- I'll go category by category.

If you go category one, for example, if I use a mortar and pestle to crush it and I do it for two minutes, it's different data than if I do it for three minutes. If I put one capsule in the mortar and pestle, it's different data than if I put two capsules in the mortar and pestle. It's different if it's a

ceramic mortar and pestle. It's different if it's a metal mortar and pestle. All of that data you learn in the iterative approach to figure out what the best method of manipulation is, which you then take to category two.

So if I'm not using the best method of category one to get to category two, then I'm not really testing the product to failure. Moving to category two, we're talking about particle size and particle size is the driver when you think about the hard to crush tablets or hard to crush products.

The problem with that is what if something has a small particle size and has low solubility or is lipophilic and is not delivered through the nasal passage? Particle size becomes irrelevant and if I don't do a PK study, I don't know the answer to that.

And then, when we move to category three, something like Xtampza again as an example, with Xtampza in category three, if I crush using the best method of crushing found in the lab, I'll get a certain PK profile. If I chew, where I would argue that the teeth are not as useful as crushing, you're

going to get a higher PK profile and a PK study. You would not predict that by category one data.

So the issue is it's so product-specific, and there are examples in everybody's dossier of where these products would not be predictive -- category one, category two, category three. Thank you.

DR. LIONBERGER: Yeah?

DR. ZHAO: I just want to comment on the comment that was just delivered. I think we have to acknowledge that there is not much detail for the PK study. But we are under good guidance leadership from CDER.

So we have to take advantage of the data available through the past years. We are conducting some internal meta-analysis. So regarding with the PK profile, so any PK metric we are going to recommend in the product-specific guidance will be data-based, evidence-based.

Also, I think I use the case Hysingla. But based on the current state of knowledge, I am not saying that for Hysingla, category one data will be sufficient to support the abuse-deterrent claim. It's

mainly an example used to demonstrate that the PK metrics do predict the PD response. So with category one or two/three, we are trying to escape, you know -- at the generic program, we are trying not to defeat the purpose, trying to get away from category three studies.

That's why, category two PK studies, the meta-analysis is very important and guides us to develop guidance. I think we are in good hands under Dr. Throckmorton's very much open-minded to support innovative approaches in this end. And you will see more kind of research rolling out from FDA.

DR. LIONBERGER: All right. So I want to give people an opportunity to comment. I have one specific thing that I think has been mentioned several times. So, as I recall, the current draft guidance doesn't really ever say the word chewing. So I'd like to open up for comments for people to just -- what should our guidance say about chewing products -- chewing tablets? I mean, I guess we've given product abuse-deterrent claims for chewing. So what should -- you know, like I think I was -- personally, I think we

have to consider -- we have to say something. And so, here's an opportunity to comment on what should we say about abuse by chewing?

MR. COHEN: (Off mic) -- is that considered a --

DR. LIONBERGER: Yeah, that's a comment. The comment is -- you know, I think the comment there is chewing is different than grinding because you do it sort of applying mechanical force and sort of a solvent extraction at the same time. So let's let the panel comment on it.

MR. COHEN: Yeah. Well, sort of the short answer to it is, well, oral abuse, as we've already talked about, is the most prevalent form of abuse. Chewing the tablet orally is the first form of manipulation along the abuse pathway. And so, you should be referencing it in there.

I know there are products that have put together the hardness profile that prevent or limit the ability to chew a product. And that by itself is a deterrent to that form of abuse and is deserving of 9.2 language.

MR. DEROSA: Well, I think if a product is not abuse-deterrent by the oral route, you would assume that by chewing it in some manner, you probably will get a higher PK than if you ground it, if it was meant for, you know, abuse deterrence for insufflation. You would assume that you would probably get a higher PK.

I mean, if the product is labeled for abuse deterrence by chewing, I think that generics are going to have to do something to support that. But if it is not, you know, I don't -- I don't know that we would be obligated to do so. I haven't really thought -- I mean, we didn't even discuss it, frankly.

DR. HOAG: I could say chewing is a well-understood process. So it would be something you could develop tests.

MR. DEROSA: Yeah.

DR. HOAG: When we looked at the Internet -- and again, we didn't do an exhaustive study, but we didn't see of the newer formulations, we didn't see that much discussion of chewing. But that's not a scientific -- you know, I can't validate that. But,

so we didn't consider that. But it's something that can be done. You know, the dental world, oral processing, there's a lot of ways of evaluating that.

DR. THROCKMORTON: Rob, can I make sure I understand the question? So are you asking whether chewing should be added to the sort of panel of routes that would be looked at as a part of the generics assessment?

DR. LIONBERGER: Yeah, I mean, I think --

DR. THROCKMORTON: I mean, is that what you're looking for?

DR. LIONBERGER: Yeah, that's basically the question. I think the current draft guidance doesn't specifically say, you know, what you should do about chewing.

But we have mentioned chewing in some of the labeling claims that have been given and I think that's, you know, a sort of key gap that like -- you know, I think we probably will intend to say something and we want some input into what we should say.

MR. COHEN: If it's a known route of abuse and it's prevented, it's appropriate.

MR. DEROSA: Yeah. I mean, I think it just gets down to what are the routes of abuse for the product. I mean, and what is the technology that the brand has. I mean, if it's not -- if it's not necessarily abuse-deterrent by the oral route, I don't know.

I mean, you'd have to have something that the brand would have had to have done from a chewing perspective for I think the generics to have to be, you know -- have to do work on it.

DR. LIONBERGER: So let me again --

MR. COHEN: And Robert, again, within your question, the implication is that the guidance is drafted doesn't accommodate that. And that part I'm not sure if that's necessarily an accurate statement because, again, we want to focus on the routes of abuse --

DR. LIONBERGER: Right. There's oral -- I mean, there's oral -- I mean, do people feel that oral route already covers -- you know, covers chewing or is chewing sort of a septate than sort of preparing something and swallowing it and having it absorbed?

So that's your sort of point that we need to clearly differentiate.

DR. DAYNO: Jeff Dayno, chief medical officer at Egalet. I think it's important when we look at the oral route, especially with regards to abuse, because it's also the intended route of how these products are taken intact in terms of providing efficacy. So, and it's also important because the most common type of oral abuse is taking too many tablets intact. And that's important.

So when you refer to the oral route of abuse, it's through manipulation of the product initially and then assessing the impact, whether PK profile or drug liking. So it's manipulated oral abuse. None of the current technologies can address taking too many tablets intact, which is much important from a public health perspective.

When it comes to the methods of manipulation, it also reflects the iterative nature of this field. Some of the products are labeled. The oral HAP studies were based on chewing as a method of manipulation.

But we also know that if we take these platforms to failure, then other types of physical manipulation is more aggressive such as crushing, cutting, grating, grinding. And then, you'll reduce particle size further and other products have been tested through the oral route with those more aggressive methods of manipulation. So chewing is important, as well as other methods of manipulated oral abuse.

DR. LIONBERGER: So I want to -- you know, something that comes to mind -- you know, comes to mind around the question of chewing and what's -- I think people -- this was mentioned by our generic industry panelists in terms of having things in the label. So for example, if a product has a claim about resistance by chewing, there's some positive evidence about the chewed product and what the change in drug exposure and drug liking was that supports that, right?

So that's a -- like I just want to get some input on the conceptual idea that in cases where there's a positive claim that's supported by data,

should in the generic comparison there be a different set of data then, you're screening for the risk.

Like say for example a product doesn't have a claim for abuse by chewing. But you're just trying to sort of screen out risks or vulnerabilities in the formulation for sort of very severe dose dumping risk. So that's the -- if you look at our guidance, it says evaluate data across all the routes.

But should there be a different expectation for routes that have a sort of positive claim, right? So for example, an antagonist combination where it says if you crush it, then the antagonist is released and you obtain certain plasma levels, that that's a very positive -- you know, that that's a positive statement rather than a product that doesn't get any claims in that area and you're looking at -- you know, does that -- so maybe the way to formulate my question is does the fact that something has a positive label claim affect whether or not different levels of data should be evaluated for the generic equivalence in terms of the need for category one or category two, in vitro or PK data. Is that a factor that we should be

considering?

MR. DEROSA: I mean, I think the first thing we're going to look at is what the label states, right? So if there are labeling claims that talk about insufflation or chewing, I mean, we're going to do tests to provide data to show that we're no more abuse-deterrent in those label claims than the brand would be. I mean, that would be clear.

I think where we're a little -- probably need a little bit more clarity is, you know, if the product is not abuse-deterrent from an insufflation perspective, I mean, how much testing then does the generic need to do to show that, you know -- there's no claim there, all right?

I mean, we obviously don't want to be ground to a fine powder so, you know, you can snort it. But where does -- where does that end for us? You know, from that perspective?

DR. LIONBERGER: Yeah, I think we definitely hear that comment and I think we want to be very clear about.

MR. HEFFERNAN: I was just going to mention

that, you know, when we talk about chewing, we talk about abuse. But we also talk about safety. And I think, you know, every one of these products has a black box warning that says, you know, don't chew, crush, grind and so on.

So even regardless of your claim, you've got a safety issue with these products. And so, I think chewing is one of the key things that needs to be evaluated in all of these products just from that perspective.

MS. FIELDS: Hi. Ellen Fields, from DAAAP. From the RLD perspective, we tell sponsors that we want them to evaluate all the routes of abuse because we don't want to be in a situation where a drug is abuse-deterrent by, say, the nasal route but not abuse-deterrent by the IV route and then abuse shifts from a less dangerous -- well, they're all dangerous, but from a less dangerous route of abuse to potentially a much more dangerous route of abuse.

And I think that's the way we do it. And I think that would be an important thing to think about for generics as well. You don't want something that

could potentially result in more abuse -- unintended abuse -- an unintended consequence of more abuse by a more dangerous route.

AUDIENCE MEMBER: Ravi -- yeah, to your point that if there is positive label, the RLD should be required to do more testing, I don't think that's necessary. As such, I think the in vitro proposed tests are fairly detailed.

There are RLD label claims that are positive or negative. It doesn't matter, as long as we do those series of tests sequentially and show that we release the drugs -- even the antagonist to the same extent as RLD, that should do it, I think.

DR. LIONBERGER: Thank you. Yeah, I mean, the guidance is clear. Yeah. You know, so as Doug's pointing out to me, you know, our current guidance says you have to test all of the routes.

But I think there may be some question about what level of evidence within each route you need. Do you need -- are you more likely to need category -- you know, PK data for cases where there's a positive claim. Did it affect our level of evidence that we

need to go from in vitro to in vivo data, depending on what the claim is for those routes?

I think we're very clear and the scope of the guidance is you've got to provide the data for all of the routes. And that's for the point -- the reason that -- the reason that Ellen one points out, that that's the set of data that we need to make a decision about the product as a whole.

We need to see all of the data for all of the different routes. But there may be different sets of data that you need depending on labeling or that's at least the question that I was asking for us to consider.

All right, so let's move on to the next question for the panel. So the next question is what additional actions --

DR. THROCKMORTON: Rob? We've got a comment.

DR. LIONBERGER: Oh, sorry. Sorry.

DR. MENDOZA: Sorry to inject, sorry to interrupt.

DR. LIONBERGER: No, that's --

DR. MENDOZA: So, Mario Mendoza, with Pfizer. So one quick point of consideration for the antagonist comment or question that you've put out there.

So keep in mind, as I think most of the room knows, not only is it really antagonist release but assessing how much of the antagonist in the blood, right, will lead to withdrawal, a decrease in any of the positive subjective measures, like drug liking , take drug again.

So that ultimately depends on the opioid tolerance in the individual, which is why that category three data needs to be assessed. So it's not just manipulation, antagonist release and you're done. So what do you do with that really depends on the recipient.

DR. LIONBERGER: So but when you're developing a new drug product, right, you have one product. You have lots of people who have different responses to that same drug exposure. So how do you -- like --

DR. MENDOZA: Exactly. So you look at that

population --

DR. LIONBERGER: Right.

DR. MENDOZA: -- in the case of category three data. You're looking at a subset of an abuser population, an opioid user population. Thanks.

MS. LEVIN: I think it would also help if -- looking beyond the label, in the summary of basis of approval because we've seen branded companies try numerous studies where sometimes they were successful and got certain claims in the label, but the data wasn't robust enough in other areas to make it in the label while it was still indicating there were routes of abuse.

That would be helpful from a generic perspective to know that's a route they need to explore as well, just for consideration.

DR. LIONBERGER: I mean, I think, you know, the generic guidance says you have to cover all of the routes once they're in the label. So I think that's sort of -- I think we did say that also to get away from things like this ambiguity, right? Should I look at this route or only that route? Should I only look

at it if the RLD looked at it in their application?

You know, so I think we determined that the path that provided the most clarity for the generic companies was to say, you know, the default is you've got to look at all of the routes. Right, so --

DR. THROCKMORTON: The summary basis of --

MS. EDWARDS: This is Candis Edwards, from Amneal. Just to further support what Penny just said, you know, as a generic, we're not necessarily in the business of discovery as much as we're in the business of equivalence.

And so, the work that the innovator has already done to put, you know, their data in different buckets as to what claims I can get from the label versus what other potential claims might be there or did occur or didn't, I think that information is valuable to support the development that we do as generics.

And I think that leads to some of these product-specific guidances where the agency is able to bring forth some of that information to define not only what we should be doing, but areas where there

may be other potentials for abuse that we need to consider when we develop our products.

DR. DAYNO: I just also want to clarify with regards to, you know, the labels in category one, as we all understand the reason in terms of not giving away recipes, all of the details and all of the work that go into the category one testing are not included in the labels.

And it is important to understand, it is the reason when the innovator companies are going in front of advisory committee meetings, the first part of those meetings are closed and we are discussing the full scope and battery of work that goes into the category one studies to find the optimal methods of manipulation to go into category two and category three in those closed sessions to reflect, you know, all of the iterative work that went into those programs.

AUDIENCE MEMBER: (Off mic) -- Shah, from -- Pharma. I think I would bring one point that we have discussed thoroughly in 2014 meeting in open session that the need for meaningful, discriminating

standardized tests. That is what the generic industry is asking for. So we would appreciate from agency that will provide product-specific guidance and those tests are standardized, meaningful and discriminate enough so that we can differentiate that RLD and test are equivalent. Thank you.

DR. LIONBERGER: All right. So let's move on. All right. Let's move on to the next question, which is a little bit broader question. What additional actions could FDA take to encourage the submission of ANDAs that reference an opioid drug product whose labeling describes abuse-deterrent properties?

So I think we've heard that people really want specific product-specific guidances. So you know, in addition to that, are there other aspects that we could -- and I think people have also mentioned that they want, you know, complex product meetings as well, so --

MR. DEROSA: I mean, all the stuff that's described in GDUFA II, obviously we'd love to have that now. Well, and I might as well say it again. We

want product-specific guidance.

DR. LIONBERGER: Okay.

MR. DEROSA: it would be nice -- it would be nice to get, you know, perhaps, you know, as part of this, you know, expedited reviews. It would be nice to, you know, maybe if we have to go down the route of having to do more than just cat one, maybe cat two and in some cases maybe cat three.

Maybe we get reduced fees for submission. You know, I think this -- you know, this is a very new area for all of us and, you know, we're looking or some help and guidance. And I think all of those things that I just mentioned would be helpful.

MR. COHEN: And Robert, we'll do our part if you help us by approving more NDAs so there are more RLDs for the generic industry.

DR. LIONBERGER: I think it is the wrong end of the table for that.

DR. THROCKMORTON: Penny, this morning you raised the specter of either reworking or doing away with the human abuse potential study. I don't know if this is the right time to ask you to sort of embroider

on that a little bit.

MS. LEVIN: Well, I don't -- I certainly don't have the solution. But I could recall when we all started those studies some years back, that there were concerns about the population we were looking at and was it really the right surrogate for human abuse in our patients. And I'm not sure we really have the answer today.

And also back then, naloxone was not approved. So there were ethical issues of really looking at the patients and what those might look like and when do they become at risk. So we're making -- you know, we're trying to make safer opioids. But if we remember who they're really for, they're for the patients.

But we're using the human abuse liability study that has a lot of shortcomings from a design perspective and challenges with them. And we're all going for the same patients. Someone said three, maybe three or four labs in the country run them. That being said, forgetting the operations, I go back to what we're trying to accomplish from an

epidemiological perspective. I'm not sure we're getting that answer.

I don't know the answer. But I wonder if there's an opportunity to revisit, maybe even a registry. We've got seven approved products.

Do we follow a perspective cohort out and those patients -- again, looking at the patients using these opioids, do they get naloxone ready if they need it or are there characteristics now that we've heard from some of -- from the VA colleagues, a lot of the things that they're using with their patients. Can we build that in?

I'm just not sure that continuing to do the study that we've all identified issues with -- and maybe some of the brands have found other solutions in this time or have advanced or modified those. Again, I just feel that we should start looking at perhaps other ways to really capture what does that abuse look like in the patients.

That's who we're really trying to get to. And we are trying to deter these obviously from -- we don't want addicts taking our drugs. But we want the

patients using them to know they can safely use them.

And it would be really interesting to me from an epidemiological perspective, when do our otherwise healthy patients, other than having pain, become at risk for perhaps developing addiction or abuse? And be mindful of that so that we can care for them and capture them before that would happen. That to me would be relative risk and we'd have a real -- a real answer. But I don't know what the study looks like.

DR. THROCKMORTON: So to be clear, what I'm hearing you say -- what I'm hearing you call into question is the endpoint of the studies. It's VAS liking of one kind or the other as a predictor of abuse risk. Is that -- is that the nut of your concern, that that as an endpoint isn't the best way for us to be determining whether or not in a comparative liking way, whether one of these abuse-deterrent products is more or less likely to be abused?

MS. LEVIN: Yeah, I think that's part of it and I think the population isn't adequately enough to

illustrate that. I don't think I have the same risk profile as that of an addict to determine my liking. We're not really comparing apples to apples at the baseline to then draw these conclusions and then make a long-term population-based conclusion on it.

But I don't know the study design. I just, you know, think we can put our heads together and perhaps knock something else around that might be more indicative.

DR. LIONBERGER: Sorry, if you have comments, can you please come to the microphone?

DR. LUKE: There's a possibility that you can build a patient-reported outcome-type of construct around that kind of study. I think you'd have to send a consult over to the appropriate folks over in CDER to think about doing that. Doug, you're shaking your head. Did you --

DR. THROCKMORTON: It'd be complicated.

DR. LUKE: It is, exactly.

DR. HENNINGFIELD: I think my call for flexibility earlier is that I think it's premature to say we always need human abuse liability or we don't.

You get to the human at times and you find things that you just didn't anticipate earlier on. We've seen that time and again, and especially as the technologies are evolving.

I think this is something that FDA needs the flexibility to say, you know what, we're completely comfortable with everything you've got, with the design, with how it was done, with the category one, with the category two, that you don't need it. And I think FDA should have that right and should streamline whatever possible. But I think it's a long way from writing it off.

AUDIENCE MEMBER: Regarding question four, I think that two more points come to my mind. One is what if a generic, when they start testing, they find that their formulation is better than the RLD? Would they be risking going to 505(b)(2)? Or if the FDA clearly thinks that this is not something to be considered in pushing them to 505(b)(2)? That's --

DR. LIONBERGER: So I think the guidance is reasonably -- to me, reasonably clear that the standard for the generics is no worse than, right?

But the ANDA approval pathway, if you're successful, you end up with the same label as the RLD.

There's no claim benefit for being superior. There's no sense in which the ANDA review process, people are even going to be evaluating superiority or making that judgment or have any intention to make that judgment, right? I mean, we're looking for, you know, are you substitutable, be no worse than. That's the standard.

You know, I mean - you know, so certainly it envisions products that aren't identical. So, but you know, it's not a preclusion that you're better. I think sometimes when you're better, FDA's concern is by being better in one aspect, you introduce other effects -- you know, like you could say, well look, my product gives you a higher C_{max}, you know, than a normal product.

Usually we say that's not equivalent because we think there are sort of concerns about higher drug exposure, maybe different adverse events, right? So you have to be -- if you're too different, you have to be careful that you're not introducing a clinically

relevant difference in some other unexpected aspect. But the guidance is very clear that the standard -- you know, that the evaluation of these standards for the abuse-deterrent aspects is be no worse than the currently approved RLD, right? It's not an equivalence standard like the BE part of the studies that you have to do.

AUDIENCE MEMBER: Right. Sure. Thanks.

DR. LIONBERGER: Right.

AUDIENCE MEMBER: And one quick question on the aversive agents. I think the guidance is clear that it can be same or it can be different than the RLDs. Can we say the same thing about the antagonist? They have to be same as an RLD or they can be different?

DR. LIONBERGER: I think this is just basic understanding of the ANDA process. The antagonists are official active ingredients of the product. They're covered by the absolute generic product statutory -- have to have the same active ingredients. The antagonists are active ingredients. They have to be the same. They have to be the same. They have to

be the same amount, same strength. Every standard requirement for the generic drug approval. That's just the basic -- you know, just the basic rules of the generic drug program. You know, it's clearly and absolutely an active ingredient in the product.

AUDIENCE MEMBER: Right. But unless you put up a suitability petition, because in combination of two drugs, there is a provision in the petition that it can be different, right? I don't know how --

DR. LIONBERGER: I mean, if you have a suitability --

AUDIENCE MEMBER: Yeah. Yeah, it's a little complicated. But I just wanted --

DR. LIONBERGER: Hypothetically. But I -- like --

AUDIENCE MEMBER: Yeah.

DR. KOVACS: Elisabeth Kovacs, from Apotex. I have a question. One of the talks and the slides that have been presented today was a comparison between fed and fasted PK study. And the conclusion was that really you cannot use the PK study to predict the likability because although the C_{max} was lower in

the fasted study, the likability was higher.

Now, the fed, then a couple of hours later, we are looking at another slide which says clearly that the preference is it's a lot related to the time to onset. Well, you don't need a lot to put two and two together because essentially, a t_{max} difference between a fed and fasted is two hours.

So clearly the onset and the fasted condition is going to be significantly faster than contributing the likability studies. So I don't know under these circumstances do I really need the likability study to get to that conclusion.

DR. LIONBERGER: I mean, that's part of -- I think this is an open public debate. People present data and their interpretation and we're I think very happy to hear, you know, alternative analysis of those data sets. I think if people have comments -- if someone's presented something and you don't agree with it, please make a public comment to the docket. Write your explanation and counter-explanation to those points.

This is an open public discussion of points

and we encourage this type of debate. We've put data out there. We've put this guidance out here for everyone to comment on. We're happy to hear all the inputs. But if you comment on it and you put information out, I think expect comments as well.

DR. ZHAO: Yeah, and I do have a response to your comment. This is really a good one. I think you are referring to the plot presented this morning where you see a C_{max} for the dissolution profile you know, for slow -- a higher C_{max} for slower dissolution profile or for the lack -- the drug -- a drug liking score, you have higher C_{max} in PK.

But you have lower likability. I think when you look at that, it is consistent with our investigation, like whether partial AUC can be used as a measure of the quickness of the -- the rate of the drug onboard. So when you look at the partial AUC dealing for that PK curve, actually the partial AUC is higher for the one corresponding with the higher drug liking score. That's not inconsistent with our finding.

DR. KOVACS: I'm sorry. Maybe I wasn't very

clear. What I was suggesting is that you can make inferences from the PK study with respect to the likability if you link the time to onset or the partial AUC to the potential for likability. You don't really have to run the likability study. That's what I was trying to say.

DR. LIONBERGER: You know, I think we've clearly -- like I think Liang mentioned this and also the current final guidance on new drug development mentions that, you know, I think we need a better understanding of the relationship between the pharmacokinetic and pharmacodynamic effects.

And you know, if we understand that better -- and you know, considering the variability of the pharmacodynamic measure as well, I think, you know, there's potential to make progress there.

But that's certainly a research activity that, you know, FDA is certainly very interested, as I'm sure industry is very interested in as well. And you know, I think certainly we think that a lot of the effect -- you know, in some ways, it comes from the drug. But what are the right PK measures and is there

one that gives you that better linkage?

AUDIENCE MEMBER: I think Steve mentioned and, Bob, you also mentioned earlier about the diffusion study in lieu of the nasal diffusion, trans-diffusion cell studies.

So considering the complexity of these category two studies, I think if we believe that a product is designed based on physical/chemical principles and not other aspects are involved, that a plain diffusion study isn't discriminating initially the control immediate-release product. I think that could add significant value for the generic products.

DR. LIONBERGER: I mean, I think it's valuable for both brand and generic development products. I think nobody wants to do a nasal drug liking PK study without knowing what the results are going to be.

And the better in vitro tests you have that tell you this formulation is the one that I should use, you know, I think everyone benefits from having that better understanding of characterizing your products before you do human studies. I mean, human

studies are expensive and difficult --

AUDIENCE MEMBER: Yeah, we do appreciate that when you use antagonist or agonist, that may not apply. But if the drug is designed -- the product is designed simply based on physical/chemical principles, I think that diffusion studies should be very helpful.

DR. LIONBERGER: You know, I think just one thing that we've noticed there is, you know, the nasal route -- if something's more difficult than the oral route because the oral route, we have lots of normal products -- huge numbers of oral products that are designed to deliver through the oral route.

So we have more understanding of what makes an oral product bioavailability. You know, a nasal powder is not a common standard pharmaceutical dosage form. So there's not this level of understanding of that as a sort of standard delivery mechanism that supports the in vitro and characterization.

Like there's not as much literature or scientific understanding about what makes a nasal powder bio-available. How do different gelling excipients, at what concentration, affect availability

or resonance time and, you know, all of the factors.

I mean, I think, you know, we have research programs supported by the user fee program into nasal delivery, but mainly focused on nasal suspensions and actually products intended for use through the nose. There may be some, you know, knowledge from that that gets transferred to this.

But the nasal powder is not a common delivery -- you know, drug delivery platform. And I think that makes some of the in vitro/in vivo challenges with that route much more complicated because there's less data on the normal use that's available.

AUDIENCE MEMBER: Yeah. One more comment on question number three. If I look at 2015 guidance and also the 2014, this open discussion, Steve, you presented very well nice data that when a certain product is subjected to heat, the abuse-deterrent property is lost.

I have not seen the heat aspects into the guidance. So if we can include the heat test, if the product is subjected to heat, what will happen --

DR. LIONBERGER: No, let me -- your base tests include -- as you go further down, include adding heat, temperature changes in combination with other types of manipulation. So those are higher levels of complexity.

But they are included in there. And as, like you said, as the brand products get better at being resistant to simpler manipulations, the testing goes into those more complicated, you know, approaches.

AUDIENCE MEMBER: Yeah.

DR. LIONBERGER: So as we're nearing the end -- sorry, I think we have to move on to the next question. So moving on to our final question --

AUDIENCE MEMBER: What I'm talking about -- microwave testing as well as heating in the oven, I think those aspects were presented but not included in the guidance. Yeah.

DR. LIONBERGER: So let's move on to the final question. So are there potential consequences of the development and introduction of abuse-deterrent opioid products that warrant further consideration?

So here, you know, this is a broad question as to are there -- as we move further toward implementing the generics guidance, are there other aspects that we need -- and this gets to some of the input we heard about some of the broader impacts of the effect on payers and other aspects of the healthcare system as well.

So this is really a more open-ended question to say, you know, are there things doing -- are there things that we're doing here that may have impact in other areas that we may not be aware of. So this is an opportunity to flag some things for our attention that maybe, you know, you've noticed that maybe we haven't noticed as we're going through this process here.

So it's rather a broad, open-ended question. But I think it's a good way to sort of bring this panel discussion to an end, so --

DR. CHOUDHRI: So I think that, you know, I mentioned before some of our general concerns. I think, you know, we are supportive of the development of ADFs. You know, I don't want that to get lost.

But it was the coverage mandates was one that we're very concerned about at this point because the evidence hasn't quite caught up yet.

And you know, I think there's an opportunity for the FDA, through this exercise, in helping with the education piece and the education gap that is out there, particularly for clinicians and for patients.

I think the term abuse-deterrent, it is -- it can be confusing for many, maybe not in this room, but I think outside of this room, the term abuse-deterrent implies that, you know, the drug is addiction-proof or, you know, if you take it, it's safer and you may not become addicted.

And I think, as I may have shown in one of the studies on one of my slides, you know, that a lot of physicians aren't completely clear on this. A lot of patients and families aren't clear on this as well.

And so, I think, you know, clear explanation in labeling an explaining its abuse-deterrent -- this particular drug is abuse-deterrent because it's crush-resistant or because it's, you know, injection-proof, I think that level of, you know, qualifying

information I think is important to continue to educate others on what it really means to be abuse-deterrent.

DR. HENNINGFIELD: Henningfield, again. I think there are two. One we talked about earlier today, and that's that you can't solve the problem of opioid abuse and overdose in America just focusing on here. There is migration to other substances. There will be.

You need comprehensive -- again, the VA model, that's the sort of thing we need nationwide. The single biggest tool is that when a person with an abuse problem says, you know what, I need help, they should be able to get it now and not just be forced into a one-size-fits-all treatment. We've known that for decades. We only had one president that actually tried it; Nixon, ironically enough, although Obama is trying it now.

The second thing though is that, you know, what's the answer to the question? Do we under-treat or over-treat pain in America with opioids? Well, if you look, go back to the I1 report, the answer is

both. There are people that are suffering that are not getting the treatments that they should be. And that's especially underrepresented populations, minority populations.

And I think a better opioid -- abuse-deterrent opioids may help us make the decisions more on the basis of need and not fear. My mom had no problem with getting her opioids the last few years of life that helped her function.

But a lot of people of color, that's another area I work in, have a much more difficult time for a whole variety of reasons. And I'd love to see that be elevated a little bit more in the discussions.

DR. BUDMAN: Simon Budman. The thing that I would urge you to be looking at as you move forward is the epidemiological data.

You've got to look at the epidemiological data because, so far, we've been -- when we've been looking at abuse-deterrent formulations with branded companies, as we said before, you're talking about 4 or 5 percent of the market. That's a pebble in the pool.

Once we have and move towards abuse-deterrent generic formulations, you'll be talking about throwing a boulder into the pool.

And what effect that boulder has is going to be very important, both in terms of intended and unintended consequences. And you have to be looking at that data in real-time, as it's going along, rather than finding the problem two years hence, three years hence or never.

DR. LIONBERGER: Any final --

MR. COHEN: As a final thought, and to my friend from the payer industry, I would wager to bet that there is no one in this room that abuse-deterrent products make a product less addictive. The abuse-potential of schedule two products are the abuse-potential of schedule two products and we all recognize that.

What we do want to do is make the products less abusable and to deter that form of abuse. We do want to keep in mind who our population is. It is not the abuser. It is those that are opioid-naïve, those that are at the early end of the manipulation and

deterring crisis. We are a part of the solution, not the silver bullet.

And lastly, as we consider this, whether it's for branded or generics, we have to make sure that the perfect is not the enemy of the good, that our requests for technology development don't outstrip the technology capabilities that we have today.

The abuse-deterrents that are currently before the agency have components and capabilities that are likely better than the abuse-deterrents that were initially approved.

And those NDAs that you're considering today and eventually the ANDAs that you'll be considering tomorrow will not be as good as the products that we hope to put in front of you in the next five and 10 years.

And make sure that this product remains dynamic, that the guidance doesn't lock us into any particular technology or any particular route and that the outcome is the most important measurement.

DR. LIONBERGER: All right. So I would like to conclude today's meeting by, you know, thanking

everyone for their participation. I want to explicitly also mention people who made this logistically possible. That's Michelle Eby, who you might have had contact with, also Gail Schmerfeld, Trang Tran from OGD policy, Kris Andre and Avena Russell from my office, people working behind the scenes to make sure that this system worked, that we had this hotel room and all of the logistical parts for this to be successful.

But personally, I'd like to thank everyone who participated today. I think this has been a very valuable meeting. It provided us lots of thoughtful input as we move forward with the guidance revision and finalization process for the draft guidance on generics. I also look forward to our discussion tomorrow on some of the more details of the standardized in vitro test conditions.

So again, I'd like to thank all of the participants on the panel and the speakers and all of the comments that we've received from the audience as well. It's been very helpful to us. Thank you very much, and enjoy your Halloween. Be careful as you

drive home.

(Applause)

(WHEREUPON, the foregoing adjourned at 4:33 p.m.)

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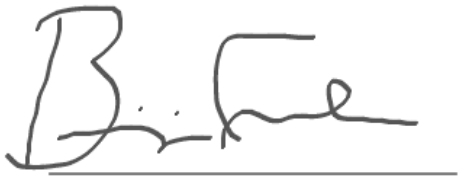

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