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

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Chesapeake Room

Hyattsville, MD

Reported by: Samuel Honig

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TABLE OF CONTENTS

P R O C E E D I N G S

DR. LOSTRITTO: This morning we'll be hearing formal presentations from government experts as well as both brand name and generic industries. Today, there will be two opportunities for public comment. FDA has established a docket to which comments may be submitted. We encourage comment and discussion, and FDA will consider comments at this meeting and submit it to the docket before drafting or finalizing guidance on this topic.

I would also like to identify the FDA press contact, Sarah Peddicord. Sarah, if you're present. There she is right there. Hello. Good morning.

Now some housekeeping stuff. If you haven't registered or checked in at the desk, please make sure you do so, so that we know everybody who's here. For those who weren't here yesterday, restrooms are located down the hall to the right of the meeting room, and across from the common restaurant.

The buffet lunch will be available in the Patuxent Room at noon. I believe it's $15.00. And if you would like information on local offsite

restaurants and so forth, you can see the hotel concierge.

The parking in the Marriott garage is for free. I assume if you're here, you've parked already. And if you use shuttle service to the Metro, please see the staff outside. And if you have any emergency, please contact the staff at any time.

We ask that you please silence your cellphones so that it keeps the continuity and the flow of the meeting uninterrupted to the extent possible. There is complementary Wi-Fi available, and you can get the pass code from the meeting registration desk.

We ask that you don't interrupt the speakers with questions or comments. There will be a public comment period and they will be taken only during the open comment periods as identified on the agenda. You are asked to request to speak at the time you register, and FDA has notified you if you'll be talking during one of the comment periods, and your name will be called during that comment period.

There are still a few spaces available if

folks do want to have public comment. And if you would like to speak to the new technologies, formulations, abuse deterrents from 11:00 to 12:00, please see Michelle Avey (ph) if she's here. She was here a few minutes ago, but she'll be back there in that corner soon if she's not there already. Okay.

And this meeting is also being audiotaped. Transcripts and tapes of the meeting will be made available on FDA's public website. Speakers will mention any financial conflicts of interest that you may have before you begin your speech. And please note that we are not aware of conflicts of interest for FDA speakers. You have been provided an agenda, and we'll stick to the schedule as best we can. And please return from breaks promptly, which will be announced.

So, with that, let's get started. I want to make sure I didn't miss anything. And I think I covered all of the topics that were on the list. So now, I have the pleasure of introducing myself, and moderating for myself.

Vision for Standardizing In Vitro Testing to Evaluate Abuse Deterrence of New Oral Opioid Drug Products

DR. LOSTRITTO: So, I'm Rik Lostritto. I'm the Acting Associate Director for Science in the Office of Policy for Pharmaceutical Quality, otherwise known as OPQ, at the Agency. And I have a longstanding interest in the topic we're talking about today, and as some of the speakers have mentioned.

I am also a pharmacist by training originally. I've worked in two different drug companies and served in academia as an associate professor of pharmacy for nine years before joining the Agency 21 years ago. So I have several perspectives in addition to the government perspective on this as well.

So today I'll be talking about the vision we have for standardizing in vitro testing to evaluate abuse deterrents of opioid drug products. And I say vision because we're basically starting with a blank sheet of paper. And we have the guidances that are already posted or in draft form, and we're looking to you today to help provide some input to guide our

process as we go forward.

So here's an outline of what I plan on discussing today. The scope of what that vision might be. Our current state, which I'll summarize briefly because I think we're all fairly well aware of the vision that we have and what would be necessary to bridge the gap between now and what we would like to see for both new and generic drugs, some examples in the summary.

And I'm applying the principles of my talk today to both new and generic drugs, and there will be some differences obviously, and those will be discussed, but we're trying to be all-inclusive and build what's on what's out there already.

So the scope of what we're talking about here in this talk is the testing of solid, oral opioid drug products, both at the initial approval and throughout the product life cycle. And for those who may not be familiar what I mean by product life cycle, the product life cycle doesn't mean in this case to switch from an RLD to a generic. What I'm referring to is the life cycle of that individual product as it

may go through changes in things like packaging, site of manufacture, source of raw materials. That's the normal consequence of the life cycle as things change within a given drug product.

Standardizing in vitro testing. So we'll take input from this meeting, the published guidance that you've seen, both the one that's already out there and the one that's draft on evaluating generic opioids, and other sources may be used to develop the future guidance, recommending common in vitro methods to evaluate NDAs and ANDAs for these products.

Let's take a quick look at the current state. So we have a guidance that's out there now, Abuse-deterrent Opioids Evaluation and Labeling. It's been out there for a little over a year. And we have the draft guidance which we've been talking about yesterday, General Principles for Evaluating the Abuse Deterrents of Generic Solid Oral Opioid Drug Products.

We have some FDA lab experience, which you heard about yesterday. You're going to hear more about today as well. As well as external research and development experience and other. And you are part of

the other, giving us the benefit of your experience as well. And other stakeholders outside this room that may contribute eventually as well.

So for NDAs versus ANDAs, there are some similarities and differences regarding the assessment of abuse-deterrent properties. And I have a number of topics, and we'll compare them. So if you look at pharmaceutical equivalence, this is not required for a 505(b)(2) NDA, and it's not applicable to a 505(b)(1) NDA because it's a new entity. But for an ANDA, it must be pharmaceutically equivalent to the RLD.

In terms of bioequivalence, it's required for ANDAs, and could be a key basis for the approval of a 505(b)(2) NDA. And it's not applicable to NDAs because again, it's a new thing and it's not necessarily equivalent to anything else.

In terms of labeling, as was mentioned yesterday, the ANDA must match the RLD with limited exceptions. And NDA pre-market data must show a product's abuse-deterrent properties can be expected to result in a meaningful reduction in that product's abuse to merit that claim in the labeling.

In terms of the technological approach to abuse deterrents, for ANDAs, again as was discussed yesterday, and a number of good points came up yesterday that sort of salt the talks for today and discussions for today. For ANDAs, the proposed generic should use the same abuse-deterrent technology approach, or actually, as the RLD. And this came up not only in the talks yesterday, but in some of the comments that were discussed and so forth.

And the OGD guidance provides -- OGD, Office of Generic Drugs -- the OGD guidance provides recommendations for evaluating abuse deterrents relative to RLDs, within the same category of abuse deterrent technology. So for example, the same physical chemical approach to resist crushing could be used, but a different polymer may be used to achieve that same result. That's the sort of thing described in that guidance.

Both the NDA and the ANDA should meet certain standards for abuse deterrent performance, which include, where feasible, assessment using similar standardized approaches. And the abuse

deterrent properties for the claimed route, and also should address abuse across all routes to ensure -- again, something that was mentioned yesterday and that we all know -- that you don't have an unintended consequence of a more facile abuse by a different and potentially more dangerous route.

Right now there is no bridging to assure that abuse deterrents performance is maintained throughout product life cycle, or actually throughout the shelf life of the product itself.

So, let's take a quick look at the guidances that are out there in terms of the abuse-deterrent opioids evaluation and labeling guidance from last April. This guidance anticipated the evolving landscape that we have seen, and that we see right now. It deals with the physical chemical barrier approach; agonist/antagonist combinations; aversive agents; delivery system approaches; new molecular entities and prodrugs; combination of these mechanisms; and novel approaches being considered as well. It's a very broad effort.

And again this came up yesterday as well, is

talking about Category 1 pre-market studies, the in vitro manipulation and extraction discussions that are in this guidance, and the studies are asked to include a design with the specific physical chemical knowledge of the product and mechanism used. That study should be designed to consider the abuser approaches, and the degree of effort required to defeat. And degree of effort came up yesterday in some discussions. We'll talk a little more about that today and what we think about that going forward.

It could include heat and cold pre-treatment conditions, crushing, grinding, grating, cutting, et cetera. And some of these discussions came up yesterday and how the different properties, the viscoelastic properties of a solid form could be amenable to particle size reduction by cutting, not necessarily by grinding or by mortar and pestle. And you can have different materials can give you different results and different approaches can give you different results. And also, of course, particle size distribution, for example as in insufflation for nasal abuse.

Now, I'm not going to talk much about the abusive deterrents of generic solid oral opioid products because this was really very thoroughly discussed yesterday. I'll just give you, for those that weren't here, a little brief summary. It is a decision tree/tiered approach, and has a use of controls, which was talked about a lot, and we're going to talk a little bit more about that today as well.

And in that guidance, it compares a test product T, reference or RLD product, and a control product under discriminatory conditions where T is the test product in question, the ANDA product. R is the RLD or reference product, and C is the control product for abuse deterrents performance comparisons.

So now I want to talk about our vision. Again, we're starting with a clean piece of paper, so the ideas I'm putting out there today are just that, ideas, and we need to flesh them out more fully. What we'd like to have is to quantitatively assess abuse deterrent properties and NDAs and ANDAs, using standard methods that would start with the OGD

guidance that are relevant to methods of abuse. So we have a very good foundation there that we can build off of.

We would like the future state to provide abuse deterrent performance criteria across all known routes of abuse. We'd like to have better confidence that the abuse deterrent's performance is maintained throughout shelf life, and across the product life cycle for new drugs. And that's an entirely new thing, and that is something we think is very important going forward. Abuse deterrence is in a sense a critical performance attribute, and as such may need to be looked at during shelf life and product change.

We'd also like the future state to be flexible enough to address product specific issues and new abuse-deterrent technologies. And both these topics came up yesterday as well during the public comment period and during the discussions.

The future state should integrate well with other guidance. Not only the other abuse deterrent guidances that we've been discussing, but with other

guidance that deal with product quality as well. Size, shape came up yesterday, and so forth. We have guidance on that and other related product guidances that we would want to integrate with, and at least not contradict or obviate. And, of course, the future state has to have further impact on abuse deterrents.

Now, I want to talk about failure point situations. A lot was discussed yesterday about taking a product to failure. And I'm going to put a slightly different spin on it today as we go along. And it's a bit nuanced, but I'll try to explain it. The failure point may be considered to be the point where enough work -- as energy, knowledge and time -- has been applied to the abuse deterrent product to defeat the abuse deterrent mechanism so as to likely permit abuse against that abuse deterrent claim.

Now that sounds a lot like what we've already done and talked about, but I'm looking at it in a slightly different way -- and I'll go on and by the time I get to the bottom of the slide I'll add a little more to it -- because these failure point determinations involve multiple considerations.

It's not just whether you can get a given particle size. If you defeat the abuse deterrent approach, such as particle size reduction, will the result be liked by abusers and abused by various routes? So there's multiple things to consider first of all, and it's not just a matter of getting it down to a particle size, for example. It has to be liked in order for it to be abused.

Also, if you're comparing two different products, it may not be the best thing to do the exact identical conditions to both products to see if one is better or if they're the same or not. It may be that it may just take a slightly different condition to get this one to be defeated from this one. So for example, maybe cold water here, maybe warm water here, to get the same result. Both are relatively about the same amount of energy and work and knowledge to get into place, but they're different conditions.

So it's a little like comparing apples and oranges, but at the end of the day what we're measuring is how much sugar is in the fruit, and that's kind of the idea. So it's going to look like

an apples and oranges thing, but what we're looking for is instead of the same conditions in some cases, the same outcome. So that's my distinguishment there.

So how can we bridge the gap between where we are now and get towards that vision? So, we're going to continue a focused scope for now on solid oral opioid drug products. If we expand beyond that, we feel right now for this next round of guidance development it might be a lengthy process and we're trying to get something done in a reasonable period of time. We're looking for input from not only here, from the Agency, industry, academia and other stakeholders.

We'd like to compare new drug product and appropriate comparator at the failure point, as well as at other points as well. And there's a reason for that we'll see as we come along. We want to compare proposed generic products to the RLD to assure the generic does not fail when the RLD demonstrates abuse deterrence performance.

And it's going to have to be balanced in practice. We need a mix of standardized approaches

that are adaptable to product specific situations, and that's a tall order to do in any sort of guidance effort, such as this, or any effort at all. We'd like to have some assessment under standard conditions, and assess the effort needed to reach failure, again under the conditions for that product to reach failure if so achieved or relevant.

Somebody mentioned yesterday that you could take any of these mechanisms to failure, and that's true. And if it's a heroic measure it may not be relevant to an abuse scenario, so that's part of the thinking in terms of the work, energy and knowledge and time, and so forth.

So what else do we need? We want to build on the existing guidance documents. We want to add these sort of apples-to-oranges failure point assessments. And we'd also recognize that the fullest testing for an NDA would be during development to support an abuse deterrent claim at approval.

Determination of quality attributes that serve as relevant surrogates for abuse-deterrent performance over shelf life, and which can support

supplemental changes over the product's life cycle, will be something very new and very important to add here.

There are also issues, as was mentioned yesterday, that there are issues with statistical and sample size considerations. This is another -- and it's not just here. It plagues all sorts of testing and what tests you're going to use, sample size and so forth is a science in and of itself. And the effective use of control and comparator products.

So building on existing guidance, we want to capture these mechanisms of abuse deterrence, the physical chemical barriers, which reduce the ability to manipulate mechanically, the agonist/antagonist combinations, aversive substances, prodrugs, and so on. Applied to these approaches to abuse, or routes of abuse, oral, insufflation or snorting, injection, and smoking. And the tier-based approach to evaluation makes sense. If you can defeat it using tap water, you don't need to test it necessarily doing 40 percent ethanol in water.

Let's look at some examples. You'll see

some repetitive theme in these examples because I'm trying to make a specific set of points. So determine the failure point to get a powder, if that's at all feasible. So you can look at different mechanical approaches, and we talked about this yesterday, crushing, grinding, milling, grating, cutting, et cetera. And the effort and time and energy needed to get it.

Is the material likely to be abused orally, by insufflation, injection, et cetera? This is an important question. Again, just because you get small particles that can be snorted, doesn't mean it's going to be snorted or be like to be snorted, or that the drug may be released by extraction or so forth.

What pre-treatment is necessary and how complex is that? One thing I tried to avoid doing, we talked about this yesterday and somebody mentioned we don't want to give out recipes either in a public forum or in any sort of public document. So if it looks like I'm sort of beating around the bush here and there, it's deliberate. So I talk about pre-treatment. We know that some very sophisticated

household approaches have been used for pre-treatments with some success.

The FDA labs may also assess these conditions to failure as well in some cases, both connected to product or connected to research. If an aversive agent is used, is it easily separable and what does it take to do that? If an antagonist is used, know the conditions that release it and that have had that effect. And that also came up yesterday as well.

We want to determine the quality attributes that can be tested at release and on stability to assure that abuse-deterrent's performance is maintained throughout shelf life and across the products life cycle. So this is an important consideration.

And what I mean here is not necessarily, certainly actually not to go through the entire process you went to evaluate abuse deterrents in the beginning, but rather, as you go along and gain knowledge about the product, and some of you talked about yesterday, the speakers from industry have an

exquisite knowledge about your product that is not public, then you should have an idea what quality attributes, or performance attributes of that product may correlate with abuse deterrence to serve as a surrogate for it. And you can show that.

Maybe it's hardness. Maybe it's dissolution. Maybe it's something else that you can do. But that approach should be relatively facile and doable in a laboratory, and it should be able to be a routine sort of testing kind of thing. And that's what I'm talking about. That's the goal. That's the kind of thing I'm trying to frame here.

So in order to do that, you have determine those aspects of the formulation, the excipients, the manufacturing process, and even the container closure that are critical to assure that the level of abuse deterrence performance during a product's life cycle is maintained.

And I don't want to get too into the weeds here, but I often, when I get the chance, I want to say, I can't stress enough how important container closure can be in the maintenance of quality

attributes for a given drug product. It doesn't matter if it's abuse deterrence or any other product, the container closure excludes moisture, and light, and oxygen, and whatever else may be necessary to preserve the quality of the product. Don't overlook it.

So, I'd like us to consider an ICH Q8-like approach. I'm not going to go too much into that guidance, but I would recommend you take a look at it. And it's not meant to be applied to abuse deterrent development and testing, but as a paradigm or a model I think it has some utility.

The failure point approach may be combined with a tiered approach. And the conditions for aversive agents and antagonists also need to be accounted for in these kinds of studies. So let's look at extraction now as another example. And you have two cases, with an aversive agent or an antagonist, or no aversive agent or antagonist used.

So again, you can determine the failure point by extraction scenarios using the listed solvents, using even differential solvent treatments.

The time, temperature and other conditions necessary to reach a failure point. Now what's the failure point? How much drug needs to be extracted before you call it a failure?

Well, I think in part that determines on the potency of that opioid how much mass you're getting out, what concentration it's going to be, how abusable it may be in terms of liking and so on. So in one case it may be a given percentage of drug. In another case it may be a higher or lower percentage. And I think in that particular case it's going to be drug substance specific, you know depending upon potency and so forth.

If an aversive agent or antagonist is used, you want to determine the failure point scenarios using the listed solvents and simple differential methods. And again, the time, temperature and other conditions necessary to reach a failure point.

We want to determine the quality attributes there as well that can be tested at release and on stability to assure an acceptable failure point is maintained. And it may be an entirely different

quality attribute than making sure that particle size reduction can't be achieved.

So it may be more than one quality attribute that you're interested in, in keeping the abuse deterrents across the board, not only for your label claim but maybe not for allowing a more facile route of abuse as well, or a more dangerous route of abuse.

You want to determine those aspects of formulation, excipients, manufacturing and container closure that are critical to assure that level of abuse-deterrent performance during your product life cycle. Again, using an ICH Q8 approach.

So ICH Q8 provides guidance on how to utilize the knowledge gained through development, through the application of scientific approaches and quality risk management to development of a product, its manufacturing process, and life cycle changes. This guidance and its concepts give approaches that may be used to enhance abuse deterrence product development throughout the product life cycle and throughout shelf life.

So for example, if you take a look at the

guidance, there's a section there that says identifying potential critical quality attributes, or CQAs, of the drug product, so that those product characteristics having an impact on product quality can be studied and controlled. And whatever that is for a given product, you can substitute abuse deterrence in here and have the same type of thinking.

So the ICH Q8 model suggests an approach that may help clarify how to go ahead and come up with these critical quality attributes. So in this case, the impact could be directed towards abuse deterrence performance in an ICH Q8-like manner.

Another example for smoking. Again, determine the failure point for smoking as feasible. What pre-treatments may be necessary to get it to a free-base form if it's a salt or so forth, and the temperature range and the conditions of failure, and the combined manipulations that may be necessary to smoke, or volatilize the material any number of ways.

And then determine the quality attributes that can be tested at release again and on stability to assure an acceptable failure point is maintained.

And as relevant, you can again consider an ICH Q8-like approach.

So, Dr. Buhse is going to talk a little bit more about the role of the FDA labs. I just want to highlight a few things and kind of salt her talk for her a little bit. The FDA labs may verify applicant data and assessment approaches. You should be aware of that. So not only application data, but also research data as well, and their own research and so forth. And the FDA labs intend to continue their research into abuse deterrent technologies, testing and assessment standards development.

A little bit about statistical and sample size considerations. So, in terms of statistical relevance and power, typically the burden is on the applicant to justify sample size, the physical test, the number of batches to assess abuse deterrent properties, consistency of abuse deterrent performance, and so on.

This is a tall order and there isn't always one right answer. I was involved a lot with parametric tolerance testing a while ago and there are

a million ways you can get to the same result and a million permutations. It's important that whatever approach you use though is justified and has statistical relevance to the issue at hand.

It may be possible to standardize some acceptance or rejection criteria based on the delta or the confidence interval of a given test so that we have a uniform criteria for performance in terms of confidence.

In terms of annual stability studies, if you're going to be, in the future, hopefully, making sure that abuse deterrence is maintained throughout the shelf life of the product, you are going to have to look at this on stability. But you may also have a large number of strengths and so forth, so the concepts of matrixing and bracketing and the testing time points and so forth that we use in other quality attributes may be applicable here as well. They should consider that.

And you saw this yesterday. I'm not going to repeat it. But basically this just shows sources of variability can not only come from the product, it

can come from the sampling technique, the number of batches, the method itself, how, in this case here coarse and fines are separated and studied.

The effective use of comparator products. So preferred is the use of an immediate release product for a modified release product. And somebody brought up yesterday, what if the new product's an immediate release product? What if there's no (inaudible)? These issues came up yesterday.

So what if there is no corresponding immediate release product for an NDA? What's the comparator? Should you make a research formulation for this purpose? Use a product approved elsewhere? Anywhere? From an ICH country? Should you use the API, just a neat API? Should you use an immediate or modified release product for another drug that follows the same type of formulation or mechanism type? And these are all things we want your input on because there are no hard answers to that right now.

What if the NDA is for an immediate release product? Which immediate release product should you use to compare it to? We'd like to see develop

standard performance characteristics that may eventually take the place of the control formulations as we learn more. And that would be another goal for the future state, is to clarify and take care of that.

So, in summary. There's a gap between the current state and the vision. There's a need to have assurance, through testing, that abuse deterrence performance is maintained throughout the shelf life and over the product life cycle, for example to support supplemental changes, for new and generic drug products.

It's useful to consider ICH Q8-like approach in determining the product quality attributes that assure abuse-deterrent performance as part of routine testing. And the use of relevant statistics, such as sampling plans and confidence intervals and so forth, the confidence we want to have a test to have and so forth, to support abuse-deterrent properties has multiple challenges.

In addition to abuse deterrent standard performance characteristics for new and generic drugs, which is to be determined, these products also need to

be tested to failure across all routes of abuse as part of the initial assessment, and the failure point may involve sort of apples-to-orange comparison, as I talked about earlier.

But we certainly can build on existing guidance and experience, and the FDA labs may verify some abuse deterrent assessments and contribute to future guidance development, develop standardized techniques, and perform abuse deterrence performance assessments for opioid drug products.

And I want to thank you very much and we're going to move on to our next talk here. Thanks. So our next talk is Dr. Lucinda Buhse. I only call her Lucinda when I introduce her, it's really Cindy. She's the Director of the Office of Testing and Research in OPQ, which I also serve in. And the title of her talk is Office of Pharmaceutical Quality Science and Research Abuse Deterrent Formulations. Welcome. Let's see if we can get your slides up without me deleting them.

Office of Pharmaceutical Quality Science and Research: Abuse-Deterrent Formulations

DR. BUHSE: Okay. I have them on a stick if you need.

DR. LOSTRITTO: Well, they should be here. So, Rob, this is where I need you because I can't find her slides here.

DR. BUHSE: Maybe look in the folder. See a folder there. Okay, now, there's my name right there.

DR. LOSTRITTO: All right, we'll go with that.

DR. BUHSE: We'll hope that those are mine.

DR. LOSTRITTO: There we go.

DR. BUHSE: Oh, he said it's already open. Too late.

DR. LOSTRITTO: Okay.

DR. BUHSE: Do the little symbol.

DR. LOSTRITTO: This one?

DR. BUHSE: This one right here.

DR. LOSTRITTO: So you're seeing how much of a lud (ph) I am.

DR. BUHSE: Right there. It's that one right there.

DR. LOSTRITTO: I'll let you do it.

DR. BUHSE: Yes, thank you. We don't let him in the lab either. Thanks, Rik. Thanks a lot. Okay. Thank you very much, Rik, for the kind introduction. And I'm going to talk a little bit about science and research as it might relate to abuse deterrent formulations.

I think, as has been stated in the last few days, there's certain expectations that somebody has when they think abuse deterrent formulations. We expect, of course, technologies to evolve. We are kind of at the infancy, hopefully, of what people are going to be developing or thinking about, and we want to make sure that anything we do encompasses new ideas and innovation.

We also believe that any new technologies should not be at risk for introducing new vulnerabilities, making an opportunity that maybe wasn't there for a given drug to be abused, et cetera. And we also expect that when testing your product, you should not only look for its strengths, but also look for its vulnerabilities so what we know that as an Agency, and we don't have to discover it ourselves in

our lab, which we often do.

And toward that end, we, as an agency, will need knowledge and capability to assess the technologies that are new, and also to do testing to verify results submitted to us by applicants, and also to look for these new vulnerabilities.

So, Office of Pharmaceutical Quality, Science and Research, that's the same office Rik is in as well, we have the laboratory, Office of Testing and Research. And that lab not only does research and testing for the Office of Pharmaceutical Quality, but also for the Office of Generic Drugs. We support development of standards and policies, and toward that end we have helped develop the generic guidance as well as working with Rik on the concept of the new guidance as well.

We also identify and try to assess new technologies to try to determine if they will do what they're purported to do. Often advertised as being wonderful and we try to evaluate them and see what their weaknesses and strengths are.

And then we also support the review

scientists. If they get an application for an abuse deterrent formulation and they have questions about the data, or they'd like some of the data repeated, we help them do that as well.

And then we also collaborate, I think you saw yesterday with the talk from NIPTE, we do a lot of collaborations with universities, academia, small business, et cetera, to try to also leverage their expertise in assessing new technologies or doing research.

So today I'm going to talk to you about three different things. One is our emerging technologies team, which is a great way to get new technologies into the Agency. And then we'll talk a little bit more about the method verification program, which Rik brought up earlier. And then also our abuse deterrent research.

So first of all, emerging technologies, that's an area that is very important to CDER and the Office of Pharmaceutical Quality. We want to make sure that we have a smooth pathway for people to bring new technologies into the Agency. We don't want to be

the barrier as a regulatory agency if somebody has a great new idea that's really going to help the patient.

So emerging technology that may have impact may be a new dosage form. It may be a new way to manufacture something. It may be a new analytical method. It may be a new control strategy, et cetera. And any of those could apply to abuse deterrent formulations. Someone may have a great new idea about a way to deliver an opioid and it might be a new technology and they want to ensure that that new technology gets a quick review and doesn't run into any technology barriers.

So the emerging technology program is the collaborative approach that we have in the Office of Pharmaceutical Quality with the field labs, which do the inspections, to assess technology and determine that everybody who is going to be looking at the technology, from the review to the inspection, understands the technology and really play an active role in shepherding that technology through the Agency.

So there is a draft guidance that's in the process of being of being finalized that talks about this process and the emerging technology team. And so this is a great guidance to go to if you think you have a new technology that you would like to bring to the Agency. Go ahead and see if you think it would apply to this guidance, and then you can submit it to the emerging technology team and then they can help you shepherd it through the Agency.

So what happens when you get accepted to the emerging technology team? Well what happens is you get really early on engagement. You get face-to-face meetings with the team, which includes reviewers and includes inspectors. If needed, they will come and do an early inspection to see if there's issue that you want raised early on.

And then someone from the emerging technology team ends up on the integrated (ph) quality assessment of the review application as well so that they can quickly bring up to speed any of the reviewers that are on your application. And so that really helps shepherd everything, makes everything go

very smoothly and get new technology onto the market as quickly as possible.

And then the actual inspection itself is also done by people who have been involved from the beginning, and so you're not trying to explain your new technology to someone who has never heard of it.

So, now you have your new technology and you have it approved by the Agency. Or maybe you don't have a new technology and you've submitted your application for review. And I just want to talk a little bit about the method verification program that goes on in our laboratories and how we assess your product.

So you can see more about the method verification program and the analytical procedures and method validation for drugs and biologics, guidance for industry that was finalized a little over a year ago. And this has a section on how the agencies will assess NDAs and ANDAs. And we look at your methods, whether those methods be for release or to assess abuse deterrents, and we see if they're acceptable for quality and control and regulatory purposes.

What we will do is the laboratory will send your request for samples and for maybe standards or any unique supplies or reagents that you may have. And then we will take them into our laboratory and see if we can repeat the method that you've developed.

So, when do we do the method verification? When do we ask for samples? It's not every application. Obviously I don't have the capability to do that. We often do it for new molecular entities. We often do it for novel analytical methods or products, take a look at something that's new. We also do it if it's a critical method, and this often comes up with abuse deterrent formulations. If there's been some testing, something unique that's been looked at by the applicant, we'll go ahead and assess it in our laboratory. And we often, obviously if the reviewer has a concern about a method, or a concern that the method might not be working, et cetera, they may often ask us to assess it as well.

So for abuse deterrent formulations, what do we do with those when we request them from your product? A couple of things we do. One of them is

definitely take a look at the testing that you've done and see if we can repeat some of that. But in addition to that, we also try to do potentially, depending on maybe if we see gaps in what's been done by the applicant, we may also try to do that, do an assessment of that as well.

So obviously it's all the in vitro testing that we're doing, Category 1 testing, extraction, milling, grinding, et cetera, simple heating, freezing, et cetera, and try to see what we can get, how we can extract the product out of the formulation.

Just as an example, we may see an application where they're grinding the product in a coffee mill and they show that their product can't be ground potentially. We may get the product in-house and we may find that actually if you pulse instead of keeping the grinder on, it actually ends up being easily ground. We may find that if you put it in the freezer for 10 minutes, it can be easily ground.

So we do try to, as Rik mentioned earlier this morning, we do try to find the failure point and determine is that how far away from a non-abuse

deterrent formulation really is the failure point. And we want to make sure that the data submitted to us isn't just only the data that makes the product look good. I think that's why I mentioned at the beginning, and I think Rik mentioned as well, we're interested in the vulnerabilities of your products. Where is the edge of failure, not only interested in where they have their strengths.

The other thing we look at is trying to make sure that the methods being used to assess the abuse deterrent are really appropriate. I think Xiaoming showed this slide yesterday, but the dissolution method that you're using to release your product may not be the most appropriate method to determine the release after the product's been manipulated. Here you can see that once you grind the product, it actually swells up in the basket and you're not getting any release.

And maybe you're not getting release because it's caught within the gel and not necessarily because it wouldn't release in the body. And so the basket method may not be appropriate for the evaluation of

this product after its been ground. Potentially you might want to use a panel method for that, et cetera. So we want to make sure you're really thinking about, after I've manipulated the product, how should I assess it. And it's not necessarily being it should be assessed by the same methods that you used to release the product.

I'm going to talk then a little bit about our abuse deterrent formulation research. In addition to verifying the methods that you, yourself, develop in submitting your application, we also do our own research to try to understand abuse deterrent formulations. We do contract work, as was shown yesterday. And then we also do our own work.

Some of the more details were talked about yesterday by Xiaoming, so I'm just going to basically talk about our capabilities a little bit. So we have the ability to actually manufacture tablets and capsules in our laboratory. We have a lot of bench scale equipment, and we do make a lot of abuse deterrent formulations. We take a look at what's going on in the literature. Take a look at what's

going on in applications. Try to repeat it. Try to determine what are the variables that are important to the abuse deterrent properties.

I think Xiaoming talked a lot yesterday about the fact that it's not just what excipient you're using, it's also the process you're using to manufacture the tablet that can really affect the abuse deterrent properties. And we really want to try and understand that, so when we assess your application, we assess your manufacturing process, we can make sure that it's robust enough to maintain these abuse deterrent formulations.

In addition, of course, once you've manufactured, you have to also do an analytical assessment of what you've made. And so we have that same capability in our laboratories as well. We have the ability to look at hardness, to look at all kinds of properties from rheology to particle size, et cetera. And we try to do that at both after we manufacture products, and also after we've tried to manipulate them as well, to try to understand in a more fundamental level what's happening with these

abuse deterrent formulations.

I think as Rik talked about, there's also challenges about how much sampling should you do, how much testing can you do. Especially when you start looking at some of these, I call them kitchen tools I guess, to manipulate formulations. If you're using a pair of scissors to cut something, or if you're using the coffee grinder, how reproducible is that? And if it's not very reproducible, then obviously you need to increase your sample size to really be able to see differences and to decide whether one formulation is better or not than another formulation.

The other thing we sometimes see is depending on the formulation, maybe you can potentially easily separate out the opioid. Maybe if you do a quick grind, for instance, potentially the larger particles or the smaller particles may contain more or less opioid. And if you do a simple sieve, you can often get a higher concentration of opioid.

So we look for these kinds of things and try to determine what are the vulnerabilities of certain technologies that are being used for abuse deterrent

formulations, and trying to understand how they can be defeated, and understand the best ways to strengthen them if that's possible.

And then of course there's the fundamentals. This is an example of a formulation where it's actually the manufacturing process that ended up making this abuse deterrent. Method two here on the right is abuse deterrent and method one is not. But they're the exact same formulation, the exact same excipients.

And to Rik's point about making sure that every lot you make has the same abuse deterrent properties, we want to make sure that you're release testing. You don't want to do necessarily abuse deterrent testing at release. But potentially if you've linked your abuse deterrent properties to the characteristics of your properties, either microscopically or with a hardness test or something like that, then that can be your release test and that can help you with the assurance that your product does have abuse deterrent properties every time you manufacture it.

And you need to really make sure you have those control strategies in place throughout not only the whole manufacturing process, but also with your excipients to ensure that any of these combinations of excipient variability and manufacturing variability don't result in an end product that may have lost its abuse deterrent properties.

So in summary, I think as everybody knows, abuse deterrent features can be defeated, varying degrees of difficulty. And that's why I think that we all need to continue to think about new technologies and new ways to improve on the existing abuse deterrent technologies. We also need to understand what those vulnerabilities are, because I think that will also help us determine what potentially we could do to bolster those up.

So to support development of ADF products, we've committed resources to a variety of things: contracts with academia and small business; the emerging technology team to try to ensure that if you do have a new technology, we can help get that through the Agency in an expeditious manner. And also to

ensure that we are ready to review new technologies in our review and inspection and divisions if we have the capability in-house, if we have the ability to understand it, we can help educate reviewers and inspectors as well.

Appropriate of course in vitro assessment, we talked yesterday I think about in vivo versus in vitro. Nobody wants to do in vivo if they don't have to. So the more we understand about in vitro testing and what it does and doesn't tell us, I think will be very valuable to us. And we really try to do that in our laboratory and really understand what things about the formulation, what things about the manufacturing process really affect the abuse deterrent properties. And if we can do that and have some good in vitro testing, then that will really help us in the long run in understanding these products and understanding what's critical.

And I think as Rik mentioned, abuse deterrent features and testing should be applicable to life cycle. You should know that at release of your lot that it has abuse deterrent properties. And you

should know that at the 24-month shelf life, that it still has abuse deterrent properties. And so we need simple ways to be assured of that, whether it's a control strategy that you may have during manufacturing or during release, et cetera, something needs to be linked to the abuse deterrent formulation characteristics of the product.

In addition, we need ways to ensure that if you do make changes moving forward in your manufacturing process, in your manufacturing site, or in your excipient supplier, et cetera, you really need ways to ensure that you've still maintained your abuse deterrent properties with those changes that you're making throughout the life cycle of your particular product.

So with that, I'm going to turn it back to Rik.

DR. LOSTRITTO: Thank you, Cindy. We are a few minutes ahead of schedule, and we debated whether to forge through and take a break later, but we decided we're going to take our break now, early. So we'll meet back here, precisely begin again at 9:45.

Okay? Thank you.

(Whereupon, a recess was taken.)

DR. LOSTRITTO: All right folks, we're back. All right. A couple of housekeeping things. We have three folks for public comment, and I'd like them to come please sit here in the front reserved row and check in with Michelle over here. Alexander Kraus, Nathan Langley, and Andrew Barrett, if you could please sit in the front row here and check in with Michelle. And we have room for more public comments during this period coming up, after the talks. So if you want to check in with Michelle, now would be the time.

We thought since we're a little bit ahead of schedule, at the request of some folks, that we would have a few minutes Q&A for the two FDA speakers. So I'm going to ask Cindy Buhse to come on up here and take all the blame.

DR. BUHSE: I was going to blame you, Rik.

DR. LOSTRITTO: So, we're going to open it up to questions. I know Dr. Throckmorton is really chomping at the bit to ask a few questions, so I'm

going to start with him.

DR. THROCKMORTON: So, Rik, I want to clarify something you said. You talked about needing to characterize the abuse deterrent characteristics of the products, or throughout the life cycle. I want to just make sure you're explicitly saying, from your perspective, that you'd expect abuse deterrent performance to be assessed as a part of shelf life determination and things like that. And the place I'm going with that is that that would be another -- it would make the argument for simple testing.

DR. LOSTRITTO: Yes.

DR. THROCKMORTON: Would reinforce the need for that, right, to the extent possible?

DR. LOSTRITTO: Absolutely. We wouldn't want to have the whole milieu of testing every testing time point on a stability study for either the annual batch or during for the development batches that are going into an NDA or into an ANDA. So what we would like to have is through something like an ICH process come up with surrogate tests, whatever they might be.

Like I said, it could be hardness, it could

be dissolution, it could be something else that's not in the standard test milieu but that which is feasible to be done on a routine testing basis, yes. To support shelf life and also to support changes to the product that might occur, such as to packaging or supplier source, that sort of thing. Yes.

DR. THROCKMORTON: So you're not talking about repeating the full battery of the testing that was conducted for the abuse deterrent evaluation and some subset of that?

DR. LOSTRITTO: Correct. Correct. A feasible, hopefully a feasible subset.

DR. THROCKMORTON: Hopefully we'll get some comment if people have ideas along those lines.

DR. LOSTRITTO: Yes, I hope so too.

DR. THROCKMORTON: Okay. Cindy, got a question for you. Tell me a little bit more about the qualification, the program, the technology program that you have in place. So, are any of the outputs of that publicly available? Because you could see where it would be valuable to have industry understand our willingness to accept certain technologies, you know

respectful of commercial confidential information and things like that, but to understand that certain techniques and certain approaches we've evaluated, found them to be scientifically robust under a certain set of circumstances, kind of along the lines that we do with biomarker qualification and animal model qualification in other parts of what CDER does.

DR. BUHSE: So the emerging technology team, when they've assessed new technology and we've approved new technology in an application, typically what happens is there is a press release, usually by the firm, that whoever had the new technology, does a press release. And then if they agree to that, then we'll often go public, saying yes, we did this through the emerging technology team.

But we, as an Agency, do not initiate any kind of public acknowledgement that we have -- just like any other drug, right, we don't come out and say this was the way this was manufactured. For instance, if it's a manufacturing thing, a new manufacturing process, we wouldn't come out and say this new drug was just approved and it has this new manufacturing

process. We would consider that somewhat proprietary. But if the firm wants to do that, then we are happy to come out as well.

DR. THROCKMORTON: I just wonder if there's a balance there between avoiding the proprietary but still making it known that new approaches are things that we've been looking at.

DR. BUHSE: And often new technologies are coming in as a partnership between somebody who has the new technology and a pharmaceutical company, for instance. In those cases the company that has the new technology of course has a lot of incentive to want to advertise the fact that now their product is part of a new drug.

So I think a lot of what goes through the emerging technology team does end up out there in the public sector, but I don't think we as an agency initiate the advertisements or the publicity.

DR. LOSTRITTO: So we have about seven or eight minutes left if folks want to queue up to the microphones. If you have any questions for Cindy or I right now, we'd be happy to address them. If you're

bored to stultifying -- oh, there you go. Ravi? He made it first, Keith. Go ahead, Ravi.

AUDIENCE MEMBER: Okay. Yes, I just had a question regarding the evaluation of -- analytical as well as safety evaluation for products where they might be smoked and there is an abuse deterrent excipient. Does one need to consider the combustion products as part of the evaluation of that product from an analytical perspective as well as a safety perspective?

DR. LOSTRITTO: I'm going to put on my old pulmonary hat, which is what brought me to the Agency in the first place. And, you know, if the combustion products are toxic, cytotoxic, or irritating above and beyond just aversion, I think that might be something you may want to explore as a safety concern, I would think, rather than just leave it unexplored. That would be something you'd want to talk to the clinical division about if that's a realistic thing happening in your sphere. Do you want to add anything to that?

AUDIENCE MEMBER: Okay. The question on stability testing, right, there was some good

discussion. The way I see it is based on your quality target profile, which defines what abuse deterrents a product should have, you come up with CQAs, the critical quality attributes that directly assure those target product profile based on CQAs we already have, the list of tests in your specifications.

So if we show that all this is linked together, and the list of tests that are chosen for stability testing, they are surrogates for all these performance characteristics of ADF, then do we still see that we need to do more testing on stability, or we can justify whatever chosen tests are there for stability, they're enough to assure the performance throughout the shelf life?

DR. LOSTRITTO: That's a good question, Ravi. So I think you're kind of hitting the idea on the head is what we're talking about with the ICH Q8 approach. So in that what you're saying sounds reasonable, but you know as is always, the devil is in the details and the case would need to be made that these particular tests are surrogate for these abuse deterrent properties.

And if they're already existent in the stability program, then maybe that's -- maybe that would be something you could make a case for, for being adequate. It may in some cases involve a different type of test, so maybe hardness or some other attribute, or a different dissolution [test] that's not the regulatory one to show equivalence batch to batch, but that might be useful for another purpose. So yes, I think the goal is to be creative and yet comprehensive without adding a lot of effort. And you're kind of thinking along the right track, I think.

AUDIENCE MEMBER: Sure. One example is alcohol driven dose dumping for extended release products.

DR. LOSTRITTO: Yes, exactly.

AUDIENCE MEMBER: Right, we typically do it one time, testing. We don't necessarily continue throughout the shelf life unless something is warranted. So that's all for me.

DR. LOSTRITTO: Unless something is warranted, yes.

DR. MENDOZA: Hi, good morning. Mario Mendoza with Pfizer. So I have a question and comment about both PK and time and effort. So what I heard from this morning's presentations is that, let's say along a paradigm of failure point testing, and so I heard Category 1 manipulation failure point as an example, so you test to Category 1 manipulation. And then you assess that, or ultimately we would say, drug-like subjective measure.

So the first question is, will you consider PK testing in that? Because I heard a comment about no one wants to do in vivo studies. And the reason I ask is because you may have then, as you know, either a placebo effect in the drug-like measures. So you have to assess that with drug concentration in the blood.

DR. LOSTRITTO: So I'm going to sort of take the fifth on that. That's not my area and I don't feel qualified to comment on the PK aspect of it.

DR. MENDOZA: Okay.

DR. LOSTRITTO: And the guidance we're talking about developing right now anyway, is going to

be an in vitro guidance. That doesn't mean we won't consider the implications of PK in that in vitro guidance, but right now I'm going to defer on that question, if that's okay with you.

DR. BUHSE: Sharon says she has an answer on that.

DR. LOSTRITTO: Okay, Sharon, if you'd like to address that, go right ahead, please.

DR. HERTZ: Sure. When a PK requirement exists, we're not worried about a placebo effect. The placebo effect would only be part of an actual clinical study, a human abuse liability study. And when those are required, there's a whole -- we already know how to design those studies. They're commonly used in other settings. But if the product under development simply requires a comparison of PK, that's all you need to worry about is the direct comparison.

DR. MENDOZA: Thanks. And my other question is about assessing the conglomerate of time and effort. So I know other people here made comments on the abuse psychology, and I think that that has to be taken into consideration. And so someone spending 15

minutes on average abusing a product in New York City may be different than someone spending an hour in North Dakota, not to pick on any particular state. But it depends on the abuse ecology and perhaps what is around them in terms of access to other abusable products.

DR. LOSTRITTO: Thank you. We actually have time for one more quick -- yours wasn't a question, by the way, it was a statement.

DR. THROCKMORTON: Can I ask him a question though?

DR. MENDOZA: Well the question was about assessing time and effort within the abuse ecology.

DR. LOSTRITTO: Yes, that's part of what we planned evaluating further is what constitutes time and effort, knowledge. So is letting it soak for 24 hours unattended, that doesn't take a lot of effort, it just takes a lot of time. So the element of the patience, as in being able to wait, is an element there.

So there's so many factors to consider that it's, initially anyway, we're looking at this as a

more case by case. As we learn more and trying to make things more standardized, you're going to have to compare various scenarios that maybe, say for example, three minutes in a coffee mill compared to five minutes in a mortar and pestle. How do you compare that? So those are some of the questions we have to grapple with, yes.

DR. MENDOZA: Thanks.

DR. LOSTRITTO: One more question.

DR. SMITH: Damon Smith, Altus Formulation. At least from my perspective it seems we're very much talking this morning about how to assess the abuse deterrent properties of a formulation per se. Whereas in this case we'll be looking at the relative abuse deterrent properties between the RLD and our product. Would you be able to comment a little bit more about development of discriminatory conditions in the in vitro setting?

DR. LOSTRITTO: I believe you're talking more about the generic guidance that we talking about yesterday, right?

DR. SMITH: Absolutely. Absolutely.

DR. LOSTRITTO: I don't have anything specific to add to that, but Rob, if you want to add anything to that, or to that point. He's talking about discriminating conditions.

DR. LIONBERGER: I mean that's an important aspect of the generic guidance. I mean any comparative test that you want to do between the brand and the generic product, you want to have confidence that has a reasonable -- it's got to be informative, right.

So I think you can think of a test being non-informative in several ways. One, if you've identified sort of a failure point, if your brand product fails at that point and you test the generic at that point, why are you testing it? (inaudible) the generic, (inaudible) drug and it failed. So there's aspects of looking at -- and so what we discussed yesterday was, the applicant has to support the justification for here's my comparison of the brand and generic product, right.

And the way you can do that, you know we said control can be part of that, but also looking at

the performance of RLD and your product as you vary the different conditions. So as you change the amount of effort that you apply, what happens to both of the products. That can also be information that says, I'm testing this at a place where I can show equivalence, but if I'm worse, I'm going to show that I'm worse. If I'm better, I'm going to show that I'm better. It's looking at it sort of -- you know sometimes if pharmacokinetic pharmacodynamic or if you look at the sensitive (ph) part -- if you reach the point where the full effect is saturated, products or differences are going to show up the same on a test where products that are different are going to show up as different in your test.

DR. LOSTRITTO: Right. And I think actually your answer in part clarifies your question in contrast to what I was talking about, or maybe in support of what I was talking about. Another way of looking at it, outcomes versus same condition. Same outcome, same condition.

MR. SMITH: Yes. My point is you can develop a discriminatory test that may show a positive

difference between the generic, or at least a no worse difference between the generic and control and the RLD. But how do you demonstrate those conditions are therefore relevant in the abuse setting? We were at a sort of a different design track there.

DR. LOSTRITTO: Yes. Well we're running short on time, but briefly I think what we're trying to do with this next guidance in particular, and also this is done in the OGD guidance, is to have a variety of conditions that would pick up any artificiality that was an artifact of a given test method or approach. If you want to talk about that at all in terms of analytical methods or anything, (inaudible).

DR. BUHSE: No, I think Rob covered it. Well, in the generic guidance, I think the tiered approach, you know if you're equivalent to the RLD and then you take it to the next tier, and you fail but so does the RLD, and then you've shown I think that the tier you went to is the discriminating condition you want to be at, for whatever it is that you're assessing.

DR. LOSTRITTO: Thank you very much. So I'm

going to introduce our next speaker. Recommendations from the Generic Industry Working Group for comments on the draft guidance on general principles for development of generic abuse deterrent opioid formulations, Elisabeth Kovacs.

Generic Industry Perspective on Standardizing Testing

DR. KOVACS: Good morning, everybody. I will be providing recommendations from the Generic Industry Working Group, and comments on the draft guidance on generic principles for development of generic abuse deterrent opioid formulations.

The group of companies that constitute a working group is listed here is Amneal Pharmaceuticals, Apotex, Aurobindo, Lupin, Mylan, Par Pharmaceuticals and Tiva Pharmaceuticals. This is our disclaimer. And we'll be talking on the standardizing in vitro testing to evaluate abuse deterrents.

In terms of the outline of the talk, I will be providing some background comments. We will be looking at the four questions addressed for the second day and FDA announcement for the meeting. We'll have some additional considerations, and we'll close with a

summary.

So clearly the benefits of standardizing testing methodology have been -- I mean we spent a lot of time in discussing those. And we are in full agreement that it's something that it can be extremely beneficial, reduce the test results variability in order to allow more increased relevance of the test results and increased confidence in the results.

We'll allow consistent evaluation of product manufacture for the abuse deterrent formulations for generic product with respect to the abuse deterrence attributes. We'll allow establishment of meaningful performance target for critical quality attributes. And we've been talking about establishing a relationship between the critical quality attributes, which would be a measurable attribute in the product that can be linked to the abuse deterrent attribute. And in order to establish that correlation, reducing the variability of the testing is going to be extremely very beneficial.

We'll facilitate assessment of formulation platforms to other drug products, and we'll allow

meaningful comparison between other generics, among the generics for the ADF products. And overall it will translate to increased confidence for regulators, prescribers, pharmacists, payers and patients.

We looked at maybe dividing the topic in four categories and talking about where we can benefit on more standardization and where potentially we can benefit of maybe more flexibility. Approaches to abuse deterrents, physical chemical barriers combination, antagonist/agonist, prodrug, and of course there are also others. We will be looking at in terms of route of abuse. Testing requirements, or testing protocol, or totality of the tests that need to be carried out. And then we will be talking about the test methodology.

In terms of the route of abuse, they are very well defined. To demonstrate abuse deterrence is a performance driven, and it can be essentially accomplished by multiple technologies for the same approach.

In terms of the testing requirement, we are looking possibly for some discussions to see how we

can be more platform technology driven. We need more flexibility to allow focusing on the critical attributes opportunity. And also it creates an opportunity to develop maybe technology specific guidance, and maybe we'll talk a little bit more about that as we go forward.

In terms of the test methodology, clearly this is where we said we need more standardization. We need to reduce the result variability. We need to increase the reproducibility, changes during the life cycle and moving from one site to another, whatever the requirements would be. In order for results to be compared and the conclusion of the comparison to be relevant and to allow confidence then clearly the variability of the test results also will have to be controlled. Some of the variabilities will need to be controlled.

We'll allow establishment of meaningful performance target for critical quality attributes. We'll allow meaningful comparison between products and consistent evaluation of product manufacture for abuse deterrent formulations for generic product.

So, we are looking now, we start with approaches to abuse deterrence, for example. So, looking at the three examples that we mentioned earlier, physical chemical barriers, combination of agonist/antagonist, and the prodrug, these are well defined paths and crossing for a generic between one approach to another, this is not something that we are recommending. That's not what we are talking about. That being said, however, within the same physical chemical barrier, the possibility of achieving the same performance is available using different technologies.

And the approach will have to dictate the performance targets that a generic product will have to meet. The performance targets however can be accomplished, as we mentioned earlier, by using more than one technology. And ultimately a generic product has to use the same approach to abuse deterrence as the RLD, however for a given approach, the performance of the RLD can be accomplished, as I said, by multiple technologies.

Again, talking about the routes of abuse.

These are very well established and essentially the performance, it's linked to the route of abuse. And for a given approach to abuse deterrence, multiple technologies can be used as part of the evaluation of the RLD. All potential routes of abuse should be evaluated to establish a target for development for the generic product.

From a generic drug product perspective, the abuse deterrent ability can be demonstrated by focusing on the critical performance attributes relevant to the technology used. And the generic product has to be no less abuse deterrent than the RLD with respect to the routes of abuse listed on the RLD label.

And we are looking at one example here. When we are looking for example at the route of abuse injectability. And we are looking at an RLD which is a crush resistant possibility with a viscosity building agent. The generic, it's a different crush resistant matrix with another type of viscosity building agent, or maybe a gelling agent.

So, ultimately some of the mechanical

manipulation, the results would be different, and maybe not entirely comparable. However, when we look into the performance with respect to the route of the abuse, this is the deciding factor and they can be considered if none of them can be or they are comparable then they can be considered being equivalent.

The same concept here. We are looking at two approaches, a low volume solvent viscosity for a gel formation. We are looking at extraction with a biocompatible solvents for hardness. These are technology dependent. However, when we look at the injectability measure or syringeability, or measures for extraction rate and extent, these are technology independent and there are performance characteristics that needs to be met with respect to that particular abuse route, route of abuse.

I mentioned, testing requirements should be standardized around technology platforms. Critical quality attributes focused -- actually I should stop here for a minute and define the reference to the technology just to make sure that we are understanding

the same what we are talking about here.

When we use the concept of technology here, we are using the concept of the combination of formulation composition and process. We are not talking about a different technology in terms of the abuse deterrent ability.

So the example that I mentioned earlier for example is based on crush resistance, the hardness, versus different approach, which is a drug formation. So therefore, these are two different behaviors, two different formulations. And the critical performance, it's linked to the technology used, although ultimately the abuse deterrent ability can be the same.

So the test requirement should be standardized around the technology platforms. The current drug guidance does not necessarily meet this need. It is tiered. It appears to be rigid in sequence of execution, and it's a one size fits all approach. This may lead to unnecessary tests for some technologies or may not provide adequate depth for others.

And last but not least, we'll talk about the test methodologies. And we look at where are opportunities for standardization. For example, the mechanical manipulations, we heard throughout yesterday and today the discussion about the level of effort and characteristics of the output. And both of these are important because the level of effort can be a deterrent on its own but the specific characteristics of the output are also impacting on the ability of the product, the formulation to be abuse deterrent.

So for example, when we talk about particle size distribution, we can't say something like for example, when subjected to the same level of effort, including time, what is the particle size distribution? Or the reverse of it would be is that what is the effort and time in order to achieve the same particular size distribution.

Parameters to consider for standardization are tools and equipment, and we heard the talk about that with Dr. Hoag's recommendations yesterday. Potentially use performance indicators, and I know

this is a very farfetched concept, but it's something similar that we have a performance verification for the dissolution right now, which is very standard.

The concepts that need to be looked at definitely is the number of tablets, or essentially is the mass, tablet mass for grinding, for example. If we have two different strengths which are proportional, we would have 1,000 milligram and a 500 milligram, which if they are proportional and we standardize the number of tablets, we'll end up with half of the tablet mass in the grinder and that clearly would impact on the output.

With respect to the chemical manipulation, extractability, parenteral and oral, the performance characteristic is how much drug is extracted in the solution. So the considerations that need to be added maybe is the solubility characteristic of the API.

If the API is not soluble and within a certain pH range, then that pH range, the deterrence is not a characteristic of the product, but it's essentially the API. If it doesn't dissolve, it doesn't dissolve. And clearly the relationship of the

solubility versus the volume of the solvent used.

The parameters again that we consider for standardization are again the tools and the equipment; sample/solvent volume ratio; particle size; choice of solvent, pH, polarity, accessibility; time of exposure; temperature; agitation.

And when we talk about particle size in terms of the chemical manipulation, the extractability, then again, maybe what we are talking about, define a particle size range that is being used for the comparison, which may or may not necessarily be the immediate output from the mechanical manipulation, although the two are definitely related. We are agreeing to that.

I took the liberty of borrowing this slide from Dr. Mansoor's presentation for the meeting in 2014. And essentially what it illustrates is the very wide range of particle size that's obtained with the various coffee grinders which are available on the market. And clearly with the recommendation of looking into the particle size as a potential area for standardization in order to allow generation of

relevant results which would be also comparable, as I said.

So, I think that this, again, it was discussed earlier today, both Cindy and Rik. In terms of FDA standardizing in vitro testing to help substantiate appropriate and consistent product manufacture that assures abuse deterrence at release and throughout the shelf life. And we are in full agreement. We are not proposing, and in fact what we are saying is that to repeat the tests which are outlined in the guidance, it's not something that we were thinking or planning to do as part of the typical QC release.

Critical quality attributes identified in the product that can be related to critical material attributes in the components, critical process parameters during the manufacture, to establish that link in between the characteristics of the components and process that can be linked to the abuse deterrent attributes of the product. And then that can be monitored both at release and during the shelf life.

And examples of that are antagonist assay or

dissolution, a relationship between the two. Clearly, if you would be looking at a given rate of release, and then one of them it slows down, another one it maybe it speeds up, then maybe that relationship is modified and that needs to be addressed if it's impacting on the quality of the product with respect to the abuse deterrence or not.

And resistance to crush, hardness. Hardness is something again that can be monitored. In fact this is not even a difference because the hardness is being typically monitored as part of the lot to lot variability as well as throughout the shelf life in the ranges that have been demonstrated, established and demonstrated that are adequate with respect to abuse deterrent characteristics. Another example, in mucoadhesive if the quantitative composition is constant, a test for a parameter such as viscosity may be proven acceptable.

So, this question is something that we had a lot of discussion on within the group. With respect to the performance attributes measured by in vitro testing can be quantified and linked to their impact

to the abuse deterrence. Amount of time and delay in defeating the abuse deterrent property. From a generic manufacturer perspective, we are asked, expected, and targeting the same level of abuse deterrence as the RLD that the generic product is developing the equivalent to.

So essentially this includes effort and time in defeating the product. And going back to a previous statement that I made on the slides, the understanding of the RLD is something that is done at the upfront in order to establish the target for development. So essentially that's our option and it's our position here.

Building flexibility into standardized testing that will address a suitable application for emerging technologies. Again, this has to be a collaborative ongoing/iterative process of a joint committee between FDA, the generic industry, other potential stakeholders. The gap between technologies that are covered by the current guidance versus those which are emerging can be addressed through the product specific guidance and or eventually into

technology or platform specific guidance.

I would like to talk a little bit about dissolution. The dissolution that is provided in the guidance, it's a standard dissolution, 0.1 mL normal HCL, different levels of it in oil or water. And we all know very well that a dissolution can be either over discriminating or non-discriminating.

Looking into the dissolution as potentially providing a tool that is going to be correlatable with the performance in vivo would require a different approach to developing a dissolution method to assess the manipulated product. Opportunities to explore different dissolution methods based on the API solubility, using biorelevant dissolution media, this should be available in order to attempt, and hopefully be successful in developing a dissolution method that can be correlated to the in vivo performance.

Furthermore, physiologically based pharmacokinetic modeling options also should be available to establish a biorelevant predictive dissolution method to be used for evaluating the abuse deterrent capability.

This will not only provide an opportunity for science and risk based decision making, but will also reduce the number of unnecessary clinical studies because it's an opportunity to bridge the Cat 1, Cat 2 before the Cat 2 study is required. And in fact, this can be expanded to other concepts as well.

When we are talking about the particle size and establishing a particle size limit for nasal abuse, I understand that -- I mean the guidance right now talks about 10 percent at 500 micron, and that number still potentially is going to be changed.

But ultimately what we are looking at is we are looking at a mix of the active and the excipients. That mix may or may not be representative of what is the theoretical ratio in the product itself. So potentially the fine can be predominately excipient. And there are technologies out there, and I think that we discussed the other day, morphologically-directed raman spectroscopy that can identify, for example, the API (inaudible).

For example, that you maybe would have 15 percent or 20 percent, but only 1 percent of that is

active, the rest of it is excipient. I think that is going to be a sufficiently strong argument for not have to go into the liking (ph) studies.

With that, I would like to summarize. For the same approach to abuse deterrence, performance objectives can be achieved, as we said, for multiple technologies. The generic product has to be no less abuse deterrent for each route of abuse as indicated on the RLD label.

For a given approach, the performance of the RLD can be achieved by a generic using different technologies. And from a generic drug perspective, abuse deterrence can be demonstrated by focusing on the critical performance attributes relevant to the technology used.

In terms of the test requirements, should be standardized around technology or platforms. The current draft guidance does not meet this need. And again, I discussed the dissolution earlier. The standard dissolution methods provided in the guidance should be augmented by exploring opportunities to develop biorelevant and predictive dissolution methods

that they can be used to bride the Cat 1 and the Cat 2 studies. Test methodology requires standardization to mitigate variability that could impact on the test results. And I think with that, I conclude my --

DR. LOSTRITTO: Thank you, Elisabeth, for a very nice talk. And I have to apologize, I did not introduce you properly when I introduced you before, that you are the CSO of Chemistry and Analytical Science at Apotex Incorporated. So thank you again.

I want to call now Alison Fleming, Vice President of Product Development, Collegium Pharmaceuticals, and she's going to talk about the branded industry perspective on standardized testing.

Brand Industry Perspective on Standardizing Testing

DR. FLEMING: So good morning. My name is Alison Fleming, and on behalf of the Branded Industry Working Group, I'd like to thank FDA for the opportunity this morning to provide some perspectives on standardization of in vitro testing for abuse deterrent products.

So first my financial disclosure. I am a full-time employee at Collegium Pharmaceutical. And I

am representing the Branded Industry Working Group, comprised of the 10 companies you see on this slide. This morning I want to emphasize that the opinions being expressed are not those of Collegium or any of the individual companies, but instead best represent the consensus of the Branded Industry Working Group as a whole.

The outline of my presentation today, I'd like to start by reviewing the current status of guidances that are available for in vitro testing of a abuse deterrent products. And also talk about the current status of abuse deterrent technologies we have in the marketplace and in development.

I'd like to discuss the benefits and the drawbacks of standardization in relation to the evolving landscape we have in the abuse deterrent field. Provide some perspectives on standardization and really I'm going to use the generic guidance as a model for standardized testing and provide some examples there of pitfalls and some things that you run into when one tries to standardize tests across technologies. And finally I'm going to provide some

conclusions and recommendations.

So this has been addressed already this morning, but as we know, we have two guidances that have been issued. One for the development of new abuse deterrent technologies, which I'm going to refer to as the innovator guidance. And a more recent guidance, a draft guidance for the development of generic products. And both of these guidances specify that testing should be done to in vitro across different potential mechanisms of abuse.

And there's basically five areas that these tests are divided into. The first two are more general characterizations of mechanical manipulations and chemical manipulations of products. And the other three are more route specific explorations. So injectability and syringeability, assessment for nasal administration, and then smoking studies.

But as we dive into the two guidances, although they recommend testing in the same general areas, and for the same general attributes, there are very different approaches in these two guidances. And I think was already touched on a bit this morning.

But the innovator guidance provides a very flexible and adaptable approach to testing, which really looks ahead at new technologies that might be coming down the pike. And it stresses that a totality of the evidence.

It presents a model of doing iterative testing where you start with simple manipulations and you move to more complex manipulations, so that you're really covering a wide range of parameter space in the testing. And it provides examples of tools and solvents that could be used, but generally provides very few specifics. And then finally, of course, the in vitro results are used to guide subsequent in vivo testing, both for PK and human abuse potential.

Within the draft generic guidance, we see a much more formulaic approach to testing. There's a tier-based paradigm that is introduced, which was described yesterday. And in addition to the tier-based testing, to sort of dwindle down the number of tests that need to be done, there's also a paradigm of discriminatory condition development.

And basically what the guidance outlines is

that you take a reference product and then you take a non-abuse deterrent comparator, test that under a range of parameters, and establish a condition under which you see a difference between the abuse deterrent and the non-abuse deterrent product. And then subsequently, a potential generic is tested against a reference product only at that discriminatory condition. And I'm going to be providing a few examples later at how that works and how that could be a potential pitfall of testing.

And then of course we've heard a lot about this over the last couple days, but the draft generic guidance is very focused on hard to crush tablets. And it's our position that other types of technologies are really not adequately covered by the current guidance. And as I've already discussed, the guidance provides a lot of specifics, specific tools, specific times, specific solvents, which has the potential of excluding potential technologies, which I'm going to also touch on in more detail later.

In terms of benefits of standardization, I think we can all appreciate and recognize that

standardized tests provide very clear expectations for both sponsors on the generic side and also on the innovator side in terms of what needs to be submitted to the FDA. And then of course for the FDA, it really facilitates review to be looking at a range of standardized tests. And also for advisory committees to be looking at comparable testing across products. You potentially can improve the interpretation of results, and you can potentially also eliminate tests that don't provide meaningful data or extraneous tests on products.

But on the potential drawbacks side, if one follows a very limited number of tests, there is a potential to not explore weaknesses of new formulations, or potential generic formulations. And then the other pitfall we have is that if standardized tests are overly specific, they become quickly outdated.

So as new technologies come forward, either new technological approaches or even new products within a technological approach, those protocols cannot be applied to those new products. And as we'll

see hopefully through the examples today, it's a bit impractical to try to design a range of studies that are going to be able to anticipate new developments that are on the horizon in this area.

And lastly, standardized tests can oversimplify the complexity of abuse deterrent features. And so if one is designing products to meet a specific list of tests, there's a possibility that we're not going to see future formulations with more rigorous abuse deterrent properties, or future formulations that continue to have this iterative additional benefit that we would like to see in the marketplace.

I think this list has been presented already a few times over the last couple days. I won't spend a lot of time on it, but these are the seven products that FDA has approved with abuse deterrent labeling consistent with the innovator guidance. And on this slide we see that they can be bucketed into two general approaches, physical/chemical barriers and then also agonist/antagonist approaches.

And what I'd like to do for a couple of

minutes is just talk about these approved products in a little more detail than we just saw in that last slide. I think it's easy to think about physical/chemical barriers, for example, as a homogenous group of products. Or to think about abuse deterrents in general as a homogenous group of products.

But one of the things I'm attempting to do with the picture on this slide is just show that for example the variety of physical forms alone of these products. So we have hardened tablets. We have pellets in a capsule with a sequestered antagonist core. And we have waxy microspheres in a capsule. So just looking at this at a very macro level, you can imagine that the tools you'd have to apply for manipulation, for example, would be very different across this range of products.

And then beyond the physical forms, there's also the inactive ingredients that are applied. So we have gelling polymers, waxy materials, insoluble coatings, all of which have a range of solubility, melting points and other physical properties, which

result in a lot of diversity and complexity among this group of products.

And of course as we consider products that are in development, this diversity grows, right. So in the guidance there are described other approaches, such as the use of aversive agents or prodrugs, or combinations of approaches, which will introduce additional complexity into the area.

And then there are a range of approaches, as I had alluded to before, even within the physical/chemical barrier category. So we've seen in development capsules with viscous liquids, coated particles embedded in a gelling matrix, and injection molded tablets in development, which will require again a different range of tools and testing.

So, I think the point I'm trying to make here, and I think is pretty clear from all of these examples, that as we develop overly specific testing protocols, we're simply not going to cover this range of products. And that's not only true for future developments, but frankly for the products we have before us right now that have been approved.

So in the next several slides I'd like to just walk through some examples, and again using the draft generic guidance as a model potentially for in vitro standardization. And I'd like to sort of illustrate two points. One is in terms of the scope of the guidance, how different technologies and even different products within a technology won't necessarily be covered by the scope of the testing included in the guidances.

And then the second point I'd like to illustrate is what I alluded to earlier, which is how the selection of discriminatory conditions using this reference versus non-ADF comparator, can actually influence the results you obtain, and potentially miss something about a potential generic product.

So first in terms of mechanical manipulation on this slide. The current guidance includes three tools to be applied to products. They are all methods to chop formulations. So there's no tools described in the current guidance to pulverize, such as a hammer, or a pill crusher, or a mortar and pestle.

And in the photograph I've shown here, I

really want to illustrate how the scale of, for example, a standard kitchen grater, and the scale of a microsphere formulation, aren't compatible. So this isn't a tool that you'd apply to this product, so different tools would need to be applied to this product. And at current, with the current draft, two of the three manipulation techniques in the guidance wouldn't apply to multi-particulates.

Also with respect to mechanical manipulation, the current guidance specifies single tool manipulation for five minutes. We know that there are products in development that may require the application of multiple tools. We also know that there are some products for which over crushing could actually have the adverse consequence of increasing the particle size as opposed to continuing to reduce the particle size.

And so in short, the appropriate selection and optimization of a mechanical manipulation methodology for an individual product is really critical. And this becomes especially critical when you think about mechanical manipulation being the

first step in the subsequent in vitro testing for extractability and others. And also in subsequent Category 2 and Category 3 PK and human abuse potential studies.

I'd like to touch a little bit on insufflation and the current guidance treatment of that. And this particular example focuses more on the establishment of a discriminatory condition. So in the current guidance, and I know we've heard that the particle size cutoff may change, but the current guidance basically specifies manipulating the product, and if fines are produced, which are defined as particles under 500 micron, that are less than 10 percent of the mass of the crushed product, no subsequent in vivo testing is done. But if there are fines present in greater than 10 percent presence, then subsequent PK studies would be done.

And in the current methodology, it specifies milling the product. And then if fines cannot be produced by milling, it does allow for alternative crushing procedures. But there is no requirement to use the best method. And it would be possible to

bypass an in vivo study, for example, by applying an inferior method.

And in the example that we have here, we consider that if we had a potential generic product, for example, that was crushed, and you achieved greater than say 15 percent, so you met the threshold, you would go into a PK study with milling, you could do your test in your reference product both with milling, but there could be perhaps another methodology, not something esoteric but something very simple to obtain, where your generic actually had a much greater degree of fines, or much higher quantity of fines.

And so this becomes important because I know that this is a theoretical example, but I think what we can all appreciate, and what we've seen from FDA present on their work in their laboratory, is that when you start thinking about generics potentially having different excipients, or even different processes, we can imagine a scenario where one tool would give comparable particle size distribution and a different tool actually would not give comparable

particle size distribution.

An additional example of selection of discriminatory conditions is in abuse by injection. So if you consider that the way the guidance is currently situated, for abuse by injection, a range of parameters is included for exploration. And again, you explore the reference product versus a non-abuse deterrent comparator over, for example, a range of volumes from 1 to 10 mL.

And so the example I've provided on this slide is one where you have a gelling tablet. You explore that range of parameters between 1 and 10 mL, and you find that at 2 mL, you have a significant difference, you have an abuse deterrent effect of your reference product. And you select that as your discriminatory condition.

Well then, when you go in and you test the potential generic versus the reference, you're bypassing the more rigorous conditions of 5 and 10 mL, or at least that's our interpretation and understanding of how the guidance works.

And so that's important because although it

may be discriminatory when you look at a non-abuse deterrent versus a reference product at 2 mL, you may see differences between a potential generic and the reference at 5 or 10 mL.

And the next example I'd like to provide is more one of scope, not one of a discriminatory condition. So in the current guidance, as has already been discussed a great deal over the last couple of days, there's very limited attention to other technologies, such as agonist to antagonist. And this is again a theoretical example, but it illustrates how, what the guidance calls for, which is characterizing the ratio of the antagonist to the agonist is only one attribute of an extract.

There's also the absolute amount of an agonist that's present in a particular extract. And in this theoretical example, we can imagine a scenario where the ratio extracted is the same or comparable between two products, but there's a lot more agonist in one of those extracts than the other. And that could actually drive and determine the likability of that extract. And with respect to agonist/antagonist,

we also know that biphasic extractions are important, which aren't contemplated by the current guidance.

And so this is my final slide by way of examples, and it contains three examples, which are again directed more at the scope of the guidance in a few different areas. So for abuse by injection, the current guidance calls for extractability in small volumes of water, and syringeability through various sized needles.

So when we think about the scope, we can think of products for which when heat is applied they flow, or melt, and there's no requirement in the current guidance to study syringeability of those heated or melted products.

Also, for products that don't contain a gelling agent, forcing through various gauge needles is not an applicable test. And so the guidance is very focused on that hard to crush gelling tablet, as we've already discussed.

For abuse by ingestion, the percent of opioid is extracted in various solvents, but it doesn't really contemplate the real world

applicability of those extracts. So for example, are you actually preferentially concentrating the active versus your excipients, or is that extract a messy mix of your excipients and your active? And these are characterizations that we know some innovator sponsors have done in fully characterizing their products.

And lastly, for abuse by ingestion, the current guidance, as Elisabeth had pointed out, specifies dissolution in 0.1 normal HCL. We know that there are excipients that are pH sensitive for which 0.1 normal would not be a discriminatory condition. And so there needs to be room for applicable dissolution methodologies for a variety of products.

So those are quite a few examples I've gone through, but I hope what I've illustrated is the challenge we have here, the difficulty in contemplating standardized tests that are going to cover our current range of products that we have on the market, and are going to be able to be forward looking to things that are in development.

So where do we go from here? So, there is a danger of throwing up our hands and saying, no

standardization is possible, but that's not the message we want to convey today. The message we want to convey today is that there are probably areas that we can think about standardizing testing and introducing more standardization. We know the innovator guidance is very flexible, and perhaps is a little light on some of the details that may be possible to pin down. But what we also know is that the current draft generic guidance is too limited in scope and a little too specific in the testing paradigms.

So what we offer here is a potential paradigm for how to think about this as we move forward. And I don't think it's very different than what was presented earlier this morning by Dr. Lostritto. And that's that we establish a core set of tests that really provide a starting point. And as we think about the core, we think that it will likely need to be subsetted (ph) by approach. In other words, the core set of tests for a physical/chemical barrier product wouldn't be the same core you would want to apply to an antagonist/agonist,

but it may be possible to establish a limited core.

But we do want to emphasize that the Branded Working Group believes that this core is really a starting point, and that additional product specific testing, with knowledge of the product, knowledge of excipients, knowledge of the process, is really going to be important to fully characterize the product.

And we also believe that, similar to what has been presented by the Generic Working Group, we do believe that recommendations around specific products probably will benefit from being in product specific guidances. And that this is particularly true when we start thinking about Category 2 and 3 and the in vivo requirements for individual products, it's going to be very important to have product specific guidances around testing.

And one last point on product specific guidances, and this has been brought up already. We do want to avoid roadmaps to defeat products, so that's also part of the balance here.

And one last bullet we have on this slide, which is a little out of place, but we did want to

touch on the question around shelf life and also product life cycle. And as we got together as a brand working group, we had come to the same conclusion about implementing risk assessment type approaches to identifying critical product attributes that one would monitor and be able to use as a sentinel for the abuse deterrent properties of product.

So in conclusion this morning, as a Brand Working Group, we do believe that there is a rationale and an opportunity to incrementally increase the level of standardization we have in in vitro testing of abuse deterrent products, but we need to be contemplating the current range of technologies and future technologies that may come down, again that may be introduced in the next several years. And it's our position that the draft generic guidance is simply too specific in scope and the types of tests that are required to be able to cover more than hard to crush gelling tablets.

We believe that a focused, concerted effort, led by FDA, could help us arrive at rationale standardization recommendations. This meeting is a

start. Also we recognize that a Category 1 focus group that has representatives from industry, academia and FDA, has been convened to look for opportunities for standardization, continues the work of the CCALC group. And beyond that, we think that an actual FDA working group on standardization may also be beneficial moving forward.

In our last comment we just want to reiterate that as we implement standardization, we shouldn't lose the spirit of the original innovator guidance for the development of abuse deterrent products. And that is that robust and iterative testing needs to be carried out to ensure appropriate abuse deterrent properties. And that all sponsors should be providing a totality of evidence to support a product, including Category 1, 2 and 3 studies.

And that's all I have today, and I thank you very much for your time.

DR. LOSTRITTO: Thank you, Alison. Very nice talk. And I want to thank all the speakers this morning, I guess myself too, specifically the other speakers this morning for their nice contributions.

So we're a little bit ahead of schedule and I have a couple housekeeping things here. We're going to start our public comment period in a moment. We only have three folks for public comment this morning, so we've decided that we're going to increase the period of public comment for each person to 15 minutes, from 10 to 15 minutes, if you want to use it. That may leave some time at the end for more Q&A for all of the folks who spoke this morning. So speakers from this morning, be ready for that, but just some housekeeping announcements first.

So this is the public comment period on potential new approaches to abuse deterrents. The FDA places great importance in public comment periods. The insights and comments provided can help the Agency. That said, in many instances, and for many topics, there will be a variety of opinions. One of our goals today is for this public comment period to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please only speak when recognized by the chairperson. Thank

you for your cooperation.

So we have our three folks here. And the first, and I'm going to try and -- I believe Alexander Kraus is first. Is Alexander Kraus here? Okay. I believe you have some slides here.

DR. KRAUS: Good morning. My name is Alexander Kraus. I am employed with Grunenthal USA in Morristown, New Jersey. Grunenthal develops abuse deterrent technology for opioid, stimulants and other schedule drugs of abuse. The technology and patents are licensed to manufacturers in the United States. Opinions expressed in this testimony are my own and not necessarily those of Grunenthal. Statements made are not by or on behalf of any partner or other drug manufacturer that we work with.

This session is about innovation and new technologies in formulations for abuse deterrents. Grunenthal has more than 15 years of experience in the development and characterization of innovative abuse deterrent technology and products, and has, and is continuing to pioneer the development of a crush resistant, physical/chemical barrier approach.

We believe that this approach offers significant potential to reduce misuse and abuse of prescription drugs, opioids in particular, with the benefit of keeping the clinical efficacy and safety profile of the original product in the intended population upon reformulation. The first reformulated products with abuse deterrent properties that have been released into the market incorporated physical/chemical barrier approaches, namely resistance to crushing and gelling. I want to show a first slide.

What we see here on the slide are abuse rate data from the RADARS system, from the time span 2010 to 2014 for the first two products that were introduced into the market using the crush resistant barrier approach, namely oxycodone extended release and oxymorphone extended release.

On the left panel we see abuse rate data from the system from the Poison Center abuse database for oxycodone extended release. And we see a consistent decline of the abuse rates over time. The vertical lines in that chart represent certain points

in the timeframe. The first vertical line shows the introduction of reformulated oxycodone extended release in 2010. And we see that abuse rates after the introduction of the reformulated product consistently and sustainably went down.

The second, or the middle chart shows a similar dataset for oxymorphone extended release. Particular notice here is that after the introduction of the reformulated extended release oxycodone product, the abuse rates in this particular dataset show a significant increase of the abuse of oxymorphone extended release. Upon the release of the reformulated oxymorphone extended release in 2012, which is the second vertical line, and abuse rates after that significantly dropped.

The third chart is abuse rates in comparator opioids and are used for comparison only.

From this dataset it appears that the properties of these reformulated products, namely resistance to crushing in order to avoid form of a fine powder suitable for intranasal abuse, and the gelling properties, impeding preparation for

intravenous abuse, and the overall properties of the products as a whole, would have provided a significant barrier or deterrent effect for abuse of these products.

And while these technologies certainly are not perfect, because there's still the possibility to abuse them, via oral specifically but also non-oral routes, it is assumed that the technology provides a significant barrier.

It's also reasonable to assume that in many situations where inexperienced casual abusers, who might be inclined to experiment with simple manipulation techniques that are easily and successfully applicable to standard non-abuse deterrent opioids, may find that the resistance to crushing provides a significant barrier of protection for these forms of abuse and misuse in these products. Whereas we sometimes focus a lot on the abuse by experienced abusers who spend a lot of time and effort to defeat the formulations, but that's actually not necessarily the target population for abuse deterrent products.

If we assume that the initial barrier to protection in these products can help preventing the progression of abuse behavior into more severe and desirous forms of abuse, including intranasal and intravenous administration, then it can also be a significant barrier into progression of other forms of abuse of illicit drugs, namely heroin.

This concept has actually been discussed by a presenter from the CDC earlier this year at the National Rx Abuse and Heroin Summit in Atlanta, Georgia. And I want to show the next chart, which is reproduced from that presentation. The chart that you see shows the proposed progression pathway from oral abuse of prescription opioids by the initiation of non-oral abuse via snorting, all the way down to the abuse of heroin and the risk of addiction and overdose.

Of particular note is that the crushing of opioid in this progression is seen as one of the key steps, kind of a gateway in the process. If this holds true, which is not confirmed obviously, but was discussed as a suitable model to investigate, if this

holds true, then the broader utilization of crush resistant abuse deterrent prescription opioids should offer a significant contribution to curb not only the abuse and risk of overdose from opioids in the current abuser generation, but even more importantly may have the potential to prevent, at least to an extent, the next generation of abusers to initiate developing their risky habits.

Abuse deterrent opioids are not the sole solution to the opioid epidemic of course. Current abuse deterrent technologies aren't perfect. Therefore coming back to innovation, Grunenthal is continuing its effort and investments to continuously improve abuse deterrent technology and formulations, both for existing and for newly developed products, to make these products better in the abuse deterrent properties and safer in the hands of patients and the community they live in.

Stronger incentives for further development and improvement are needed to support these efforts, and to improve abuse deterrent technology in the existing extended release phase, and to allow

development of new technology in fields where abuse deterrent products are currently lacking, like specifically short-acting immediate release opioid and prescription stimulants.

As we heard yesterday, about 90 percent of the current opioid prescription volumes are for immediate release products whereas none of these currently have demonstrated abuse deterrent properties according to the requirements laid out in the FDA innovator guidance for abuse deterrent products.

IR opioids are, and will probably for the foreseeable future, be a mainstay in pain management, and they will likely continue to see high utilization and high rates of abuse, misuse and diversion. Grunenthal therefore has made efforts to develop new innovative abuse deterrent formulation technology that is applicable to IR opioids across the spectrum of the available solid oral products, including specifically fixed-dose combination products of opioids with acetaminophen.

Of further concern is the increase in misuse and abuse of prescription stimulants, especially in

younger populations of college students. A recently published survey by the Partnership of Drug-Free Kids, a charity organization, revealed that within a population of college students they surveyed, up to 35 percent of the students used prescription stimulants non-medically, with up to a third of them manipulating the drugs. Grunenthal is pioneering the development of abuse deterrent forms for these products as well as we see severe harm potential in this vulnerable population stemming from the inappropriate use of these products.

Thank you for the opportunity to testify today.

DR. LOSTRITTO: Thank you, sir. Nathan Langley.

MR. LANGLEY: My name is Nathan Langley, and I'm an employee of Gatekeeper Innovation. And I'm here to comment on somewhat of a different angle of abuse deterrence than has been discussed over the past day. Gatekeeper Innovation, we provide medicine safekeeping for good health. And our first product is Safer Lock, which is a combination locking cap that

fits directly on existing medication bottles, designed to make sure medications are staying in the right people's hands.

This has been recognized, has the National Parenting Seal of Approval, the Mom's Best Award, and also recognized by the Center for Lawful Access and Abuse Deterrence as a top five technology to reduce prescription drug abuse in the US.

Before I jump into my presentation, I want to share with you why this company was started and why this product was developed. My partner almost lost his younger brother to prescription drug abuse, and it could have been prevented with something as simple as Safer Lock. His mom was in a very bad car accident, has had over 30 back surgeries to date. And as you can imagine, she was prescribed heavy pain medication to cope with this, while my partner's younger brother at the time was a high school student.

And she had the handicap sticker on her car, and when she would drop him off at school, his friends would ask, Hey, what is your mother taking. Well he found out, and people were offering him money to

purchase these pills. While he did not sell the pills on campus, he was curious enough to try them himself. And what he did was take one or two pills at a time, put the bottle back without her noticing, and he liked the way it felt. This curiosity turned into a habit, which eventually became an addiction.

Now his mom did not know this was happening. In fact she went to the extent of accusing pharmacists of shorting her on her medications. I've spoken with several pharmacists, even some in this room, who mention that this is not a unique situation. So by the time that she did find out though, he was already addicted. Long story short, he's been to rehab four times. He is sober today, but it's our mission to prevent as many other families from going through the same experience.

Now we understand that prescription drug abuse is a very complex issue and that there is no silver bullet to solving this. And from this we did some research, and as everybody in this room knows, this was not a unique situation. One point nine million Americans have a substance abuse disorder

involving prescription pain relievers. And according to Drugfree.org, 90 percent of prescription drug addiction starts in the teenage years. And according to the CDC, 70 percent of all prescription drugs that are abused originate in the home, wherein just 3 percent are locked up.

And once again, as I mentioned, this is a very complex issue. It goes into all the elements that we've been talking through over the past day, from drug formulation, proper prescribing of medications, proper disposal, making sure medications are taken as prescribed. We do have a next generation of our product coming out that has an adherence component that communicates with the doctors and patients, but I'm here to talk to you about Safer Lock today, which is the combination locking cap that fits on existing medication bottles.

There are 10,000 possible combinations to the bottle. The patient sets the combination to their preference so it's easy to remember. It is CPSC certified, which makes it child resistant and senior friendly. It's also USP 671 certified, which means

the seal is tight enough to not allow in moisture so the medication is still safe inside there. And if fits existing pharmaceutical bottles.

A question that we commonly get is, well can't somebody just take the whole bottle or smash it. And absolutely. Somebody who is determined enough is going to find their way into anything, but the issue that we're trying to help address is people who are taking one or two pills at a time, putting the bottle back without anybody noticing.

So why aren't patients currently locking up their medications? Well one is misconception, and this goes into the education piece. Because a doctor prescribed it, the medication must be safe. This is a very common misconception. While the medication is important to that person who it is prescribed to, it can often be very dangerous to others.

The next element is denial. My partner's mother went through this. Not my child. Not my brother. Not the housecleaner. Not anybody visiting my house is going to be interested in my medication. It's for me. Why would they want to do that?

And then awareness. One, patients aren't aware of the tools to lock up their medications or to store them safely. Or they're not even aware that they should be storing them safely.

And we have a few key initiatives that we're doing to address some of these reasons why people are not currently locking their medications. One of these, the product is available in retail across the US. Now, while we're happy to make this available to people in retail pharmacies across the US, one of the challenges with our retail approach is that the people who are purchasing this product on their own have already had an issue. And it's our mission to get it into people's hands who haven't an issue yet, prevent it from ever starting in the first place.

So, some of these other initiatives were actually allowing to do this -- or were able to do this. Illinois passed the bill this last year to provide incentives to pharmacies to dispense hydrocodone in four digit locking devices. Recently launched with Cook County hospital systems, also in Illinois, where they're dispensing hydrocodone with

Safer Lock on their medications.

And then also we work with Pernix Therapeutics, where anytime somebody is prescribed Zohydro ER, the doctor actually gives the patient a coupon for a free Safer Lock to ensure that they have the proper tools to make sure that they can store their medication safely and that it's staying in the prescribed holders hands.

Now these are the types of initiatives where we think we can really make a difference, where we're getting it into the people's hands who have not yet had an issue. And it avoids the misconceptions and the denial. They don't have to worry about that because they have it.

Some of the things that we are measuring with our pilot program, it's difficult for us to measure if we've had an impact because it's a very lagged indicator because we're preventing the next generation, so we won't know until the next generation if there's less addiction. But the misconception is one thing that we're looking to measure as far as if it's locked up are people less likely to share knowing

that it has the ability to be dangerous to others.

And these are the types of things we're looking to expand on, work with other county and state programs, other pharmaceutical companies. We've actually gotten a lot of interest from both the branded and generic side, which that's as far as I can go into detail on that, but we're excited about that.

So, our mission is to save lives by preventing misuse and abuse before it ever starts. We have a solution, but we know we can't do this alone. We're looking for partners who can join us in our mission to have every prescription drug stored safely. If you have any questions, this something that might be of interest to you, this is my contact information. Please do not hesitate to reach out. Thank you.

DR. LOSTRITTO: Thank you, Nathan. Andrew Barrett?

DR. BARRETT: My name is Andy Barrett. I am an employee of KemPharm. KemPharm is a clinical stage company developing a number of prodrugs of opioids to treat pain, and prodrugs of stimulants to treat ADHD. Our prodrugs are, by design, abuse deterrent as the

API remains inactive until and unless converted to the active moiety by enzymes in the intestinal tract.

Thank you for the opportunity to speak today. Before I proceed with my formal remarks, I would like to take a moment to commend all those in the room today who have been involved in the effort to address the epidemic of prescription opioid abuse. The efforts of the FDA, the pharmaceutical industry and the medical community to come together to address this very important situation must be applauded.

In this regard, I welcome the opportunity to speak today with the hope of building on this tremendous work and advancing technologies that enable patients to gain relief from pain, while helping to deter abuse of these beneficial medicines.

Without question, the 2015 FDA guidance on abuse deterrent opioids was a watershed moment for the prescription opioid industry. Not only did it serve to establish the FDA's thinking about the studies that should be conducted to demonstrate abuse deterrent properties, it also provided recommendations about how those studies should be performed and evaluated in

product labeling.

With this, pharmaceutical companies and researchers were given a foundation for developing opioid drug products with potentially abuse deterrent properties. The result has been a wave of new products and technologies that collectively offer the promise of substantially curtailing prescription opioid abuse.

Will the problem ever be remedied in full? I think we can all agree that the answer is no, but the efforts of the FDA with its 2015 guidance has served to chart a new optimistic course for the analgesic drug development industry. That said, we are gathered here today because there is an opportunity to potentially improve upon the guidance by taking into account new technologies and approaches that were not fully recognized in the 2015 recommendations.

This is no fault of the FDA or those who have advised the FDA in drafting the carefully considered 2015 guidance. Rather innovation is simply dictating new terms, and this is a good thing. The

Office of Pharmaceutical Quality has put forth a vision for standardizing in vitro testing methodologies for evaluating abuse deterrent formulations of opioid drug products.

Included with this was a review of the efforts being made to standardize in vitro testing conditions for future products along with potential challenges that could be encountered, as well as insight from the OPQ's Office of Testing and Research on its testing of abuse deterrent formulations, including approaches being taken to simulate how abusers can manipulate opioid products.

While I think we can all appreciate OPQ's and FDA's interest in developing standardized practices, it is my belief that standardization presents certain challenges, particularly with respect to innovations that may not have been fully realized at the time such guidance was developed.

Illustrating this point, the current FDA guidance for Category 1 testing is designed primarily to test putative abuse deterrent extended release opioids designed with physical and/or chemical

barriers. This is to be expected since at the time the guidance was drafted such technologies were the furthest advanced and most understood. These parameters were critical for gaining FDA approved abuse deterrent labeling on a number of ER matrix technologies that resist dose dumping. Encouragingly, current data suggests that such products have made meaningful impact on certain forms of abuse. And as a result, such products represent a foundational technology to the field of abuse deterrent opioids.

However, where the Category 1 guidance succeeded in introducing a first wave of abuse deterrent products, it has also proven to be somewhat narrow in scope when applied to newer technologies that do not rely on physical/chemical barriers or agonist/antagonist combinations to achieve abuse deterrence.

For example, prodrugs are being developed that require enzymatic conversion to an active opioid moiety to achieve analgesia. In its 2015 guidance, the FDA recognized new molecular entity prodrugs as one of the seven abuse deterrent formulation

categories, remarking that prodrugs with abuse deterrent properties could provide a chemical barrier to in vitro conversion to the parent opioid, which may deter abuse of the parent opioid.

However, current FDA guidance is focused primarily on the extent to which an abuse deterrent formulation resists manipulations that facilitate snorting, injecting and smoking the opioid. For instance, Category 1 testing that involves crushing, grinding or milling with an assortment of commonly available tools is not relevant for prodrugs where the putative abuse deterrent properties are inherent to the molecule and not a function of a particular formulation.

For a prodrug to be converted to the active moiety, the covalent bond must be broken between the opioid molecule and another ligand. Accordingly, the ability to hydrolyze the inactive prodrug into an active opioid molecule is a key consideration in the Category 1 evaluation of such products. This is but one example illustrating why additional stipulations on novel technological approaches can potentially

deter multiple forms of abuse should be incorporated into future guidance so that such guidance maintains relevance over time.

Moreover, additional considerations should be given to the evaluation of putative abuse deterrent IR opioid products, specifically whether a one size fits all approach should be used, or whether specific considerations should be given to IR opioids that must be immediately bioavailable to provide analgesic benefit. This is especially important given that an individual's first exposure to an opioid is usually an IR opioid, the abuse of which can progress to more potent opioids and alternative routes of administration.

In conclusion, I believe there is a prime opportunity with the generic solid oral opioid drug product guidance to include measures for testing and evaluating abuse deterrent formulations that account for a variety of technologies and target products. While standardization can have its benefits in terms of setting easily understood parameters, it can lead to a narrow casting that can stifle innovation and

hamper the introduction of products that could have a positive impact on remedying the epidemic of prescription opioid abuse. Thank you for your time today.

DR. LOSTRITTO: I want to thank our three public comment speakers for their sincere and thoughtful comments this morning. Thank you very much.

This concludes the public comment period formally, but we find ourselves with the nice position of having some extra time on our hands. So, rather than break for lunch early, I'm going to ask all of our speakers from this morning, Cindy and Alison and Elisabeth, to come on up and we'll take some Q&A.

And if you want to ask some questions, please queue up at the microphone and I would ask that you identify yourself. And if you have a specific question for one of the speakers, to please direct it to that speaker. Or if it's a general comment that you'd like me to share across the board, I will do that too.

So no questions means you understood

everything exactly, 100 percent, and you agree completely with everything we said. Yes, sir?

DR. CONE: Ed Cone, Pinney Associates. One of the primary initial evaluations of all of these product starts with physical manipulation, and we've spent a lot of time talking about methods. One of the missing elements in defining, particularly for intranasal administration, is defining particle size distribution. And of course, that's very important and we do that routinely in evaluations.

But one of the missing elements that we add on when we evaluate a product is also look at uniformity, and uniformity across band sizes for particle size is very important to determine. And I say that because we've seen a number of products that differentially distribute the API into the finer segments. So I guess I ask, is this, in your opinion, something else that we should be doing because we certainly do it on a routine basis?

DR. LOSTRITTO: Yes, I think some of the discussions brought that out this morning, that particle size distribution into fines and coarse, or

some distribution definition that you want to have, D10,50,90 et cetera, could play a role in abuse deterrence. Also the different methods may give you different particle size distributions.

And I think somebody mentioned that it may be feasible, I think it was Elisabeth that said that in some cases maybe the active may be in the coarse particles and less in the fine, so you have to look at not only the distribution of particle size, but you have to look at the distribution of active in the particle size with the excipients.

I think you have also have to look at the liking potential of that. Other excipients or other ingredients that might be either innately aversive of their own nature, or added specifically for that purpose.

So I think, yes, I think looking at the distribution, size distribution is very important. You can't just look at a size number. So that's about as I think specific as I can get, other than saying that some of the ideas we pick up this morning will add to our thinking on that in terms of where the

active is and what other things may be in there that could decrease liking. It's not just about getting the particle size, remember, it's about whether it's going to be blank. And if anybody else wants to add to that.

DR. FLEMING: I think one of the kind of the way things were going yesterday, was we were reaching the conclusion that for the intranasal route in particular, evaluation of PK is going to be an important component, because particle size alone may not be sufficient to characterize that.

UNIDENTIFIED SPEAKER: If I could just -- I'm sorry, go ahead.

DR. KOVACS: Okay. If I can add to that and we are in agreement that the particle size on its own is not sufficient, however, there are technologies where you can assist the composition of the fractions and that can provide an understanding if it's uniform or the API is disputed preferentially in one of the fractions. So if your 10 percent or 15 percent of the fine, for example, it's preferentially excipient, or it's preferentially API, clearly it is going to lead

to two different options for conclusion. But there is that availability to look in vitro before you go into the PK studies.

UNIDENTIFIED SPEAKER: If I could just add one more comment, one of the big questions that we've asked for years now and have some feel for it, is what's a snortable particle range? And there's only one publication I know of that helps give a little bit of information and it does seem to be below 500 microns, which is the desirable particle range.

But we know in clinical studies where we had great difficulty getting things below 1,000 [microns], the majority were slightly below 1,000, but we still had to do clinical studies for intranasal abuse-deterrent labeling. So we presented that product that had very little particle size distribution below 500, and experienced snorters managed to snort the product. It was primarily 1,000 microns and slightly less.

So we may be over focusing on the ideal particle size range a bit. So that's a comment.

DR. LOSTRITTO: Thank you. That point's well taken. I appreciate it. Mr. Zach

MR. ZACH: Hi everyone. My name is Luke . I'm a pharmacy student so this question may seem trivial, so forgive me. So I guess this would be directed towards you, Rik. When I was listening to your presentation how one of the goals is to determine the aspects of an acceptable failure point, and I think that's kind of an oxymoron, an acceptable failure point.

DR. LOSTRITTO: Yeah.

MR. ZACH: And I was just wondering, how do you determine like these thresholds? I was just wondering if you could elaborate a little bit more on the acceptable failure points.

DR. LOSTRITTO: Yeah, I used the best nomenclature I could come up and we talked about that. It does sound like an oxymoron. By acceptable failure point, what I meant is something that is measurable, reproducible, and understood. A failure is not acceptable obviously, but we want to have a testing situation for that failure that is acceptable in terms of being reproducible, robust, and something that is feasible to do in the lab. And what was the second

part of your question?

MR. ZACH: That was basically it. Just to elaborate on like the thresholds and how the FDA is determining the acceptable failure point, like threshold, if that makes any sense.

DR. LOSTRITTO: Well, in terms of this guidance, going forward, we're still considering how to do that. As I mentioned, I think, at one point, it may depend in part on the properties, the pharmacological properties of the drug; what its potency is and what concentration, and what mass is going to be gleaned from a given operation and how likeable or abusable that is. So it may vary from drug to drug.

DR. HERTZ: Rik?

DR. LOSTRITTO: Yes, Sharon?

DR. HERTZ: So this is an important point and -- so I'm Sharon Hertz. I'm the division director for the Division of Anesthesia, Analgesia, and Addiction Products. We've been working with the folks here throughout the entire course of development of these products.

I want to just kind of refocus this a little bit on some of the things that we've been learning over time, and we can talk a little bit more about this after lunch as well, but at the end of the day, these products are intended to deliver the opioid in order to be analgesic.

So by definition they fail if the goal was to prevent release of the opioid. So we have to put this in the right context. The failure rate is to see how can the intended abuse-deterrent properties be thwarted? So in that context, we ask sponsors to manipulate the product -- and we're talking right now about products with physical, chemical barriers -- we ask companies to push the formulation to failure.

It's not failing as a product, but it's failing in terms of the extent to which it resists what can be very extreme methods well beyond what would be expected out in the community, because we are learning how to evaluate these products as these products are developed, as these technologies are developed.

And when we say, Push the product to

failure, it is a way for us to understand the full spectrum of the product's properties. Is it susceptible in one particular area? And this is part of the challenge that we have here in the context of both standardizing methods and applying methods to generic products, because the number of variables hasn't been defined yet. It's potentially infinite.

So when we think about standardization, it is not a limit on what should be applied to understanding the product's performance. It is the beginning of what should be applied. So standardization should never be a reason for failing to explore beyond, in order to characterize the product's behavior. It's a starting point, not an ending point.

So I think a lot of the concerns that we're hearing would be true if we were trying to say this is all one needs to do is these X number of steps. But what we're trying to do is provide the starting point for how one should approach these evaluations.

Similarly, even since the innovator guidance was published, we're learning constantly in response

to the creative approaches that we're seeing applied to this area. So I'm trying to sort of refocus the idea. We're not attempting to make everyone do a cookbook, but we're trying to create enough of a starting point where companies can see how their product is performing and then modify further evaluation based on the responses.

So the idea is, if you pick a hydro -- I'm going to come up with chemistry terms that are going to show that I'm not a chemist -- but if you pick a particular pH and show that your product immediately is susceptible to that pH range, you don't need to go further, but we want that pH explored.

And then you'll go to the other side of the pH range and you might have a product that's very robust in resisting manipulation there, and we want that explored a little bit more to see what the extent of that is.

So that's the idea of the standardization is to give us a common foundation upon which these products can be evaluated, and so that we're not having completely different approaches that don't

necessarily overlap applied, because without that overlap we can't fully compare. Does that help a little bit?

DR. LOSTRITTO: Yes, I think so. Yes, thank you very much.

MR. ZACH: Thank you.

DR. LOSTRITTO: Okay. If there are no other questions, it's now 11:30. I would propose that we take our hour break now and reconvene at 12:30. Is that okay? Thank you very much.

(Whereupon a lunch recess was taken at 11:30 a.m.)

DR. LOSTRITTO: Hi. We're going to start in a couple of minutes. Welcome back. For those who haven't signed in yet and registered, we notice that the registration --

All right. Good afternoon and welcome back. So we're going to have our second public comment period and we have nine folks scheduled to make public comment and they'll have -- is it eight or nine minutes, Michelle? Eight?

MS. AVEY: Nine.

DR. LOSTRITTO: Nine minutes each to make their comments. We're going to ask that the speakers please come up here, identify yourself and your affiliation and who you're representing and any potential conflicts of interest and so forth, associated with your affiliation, just to make it clear.

All right. First -- should I call off all nine names so everybody knows who they are? All right. We'll start with Pamela Osborne (ph). And not here, so we'll go down the list. Sebastian Schwier? Do you have anything submitted that needs to -- okay.

DR. SCHWIER: All right. Good afternoon. My name is Sebastian Schwier. I'm a pharmacist by training and I'm with Grunenthal, a privately-owned company and located in Aachen, Germany. I'm a full-time employee of Grunenthal, which has developed abuse deterrent technology for opiates, stimulants, and other scheduled drugs for abuse.

The technology and patents are licensed to manufacturers in the U.S. Though opinions expressed in this testimony are my own, and not necessarily

those of Grunenthal. Statements made are not by or on behalf of any partner or the direct manufacturer.

At Grunenthal I'm an international technical project leader and responsible for the development of usage and formulations within Grunenthal. I've eight years of expertise in developing abuse deterrent formulations including formulation and process development, developing in vitro tests, setting up small test (inaudible) for formulation screening, as well as larger tests set ups for complete characterization of new formulations.

With my testimony today, I want to touch two topics. One is a question, how in vitro tests can contribute to assure abuse deterrent properties at release and during shelf life. And the second one is, how similar in appearance compared with the reference listed drug, a generic ADF can or should be.

Concerning the first topic, it is, of course, very important that for each product, critical product attributes are defined and adequate process and product understanding exists. I certainly agree that standardized and validated in vitro tests, like

dissolution or assay tests have to ensure adequate product quality at the timepoint of release and during shelf life.

Part of each test method is also a specification where acceptance criteria and limits are defined. When we tried to set up specifications for ADF properties like extraction rate or particle size, we could consider a maximum allowed limit under one specific test condition. For shelf life specifications the limit can be identical, could be bind) or can be turned into a maximum allowed difference from the initial value.

The challenges we are currently facing are variable results in combination with or as a result of the methods that are currently not standardized. The high variability of the results might lead to autospecification results for products that are from a conventional point of view okay.

That means conventional release parameters like the dissolution profile assay and purity were met and provide adequate product quality for the intended use.

Concerning the standardization of ADF typical in vitro tests, I personally believe that the tests have to be adapted for each technology, composition, and API. Validation of a test method with regard to excipients and API use may not be an issue, however a test that is suitable for one technology might not be suitable for another technology, thinking on hard tablets or (inaudible) capsules. Furthermore, results could also depend strongly on test setup and the individuals that are performing the test.

Therefore, my personal opinion is that, as of today, ADF properties should not be part of the release specification or specification during stability testing. Nevertheless, ADF properties have to be investigated thoroughly during development and with a to be marketed product, including investigations concerning the impact of storage on the ADF properties of the drug product.

Concerning the second topic and the question, how similar in appearance an ADF can or should be compared with an non-ADF or another

reference product, I just want to make a brief statement.

Similar to the difference between formulation technologies for immediate release and extended release dosage forms, the different technologies lead to different sized and shaped formulations, I think there are two options. Either the generic has to be more or less a copy of the reference ADF product, or the FDA allows more flexibility for the generic companies.

In the first case, where the generic and the reference product are more or less identical, there should be product specific guidance. If the products are more different, there should be more extensive testing required. For example, iterative in vitro characterization, PK and PD studies. This would also allow switching from one to another technology, or from tablet to capsule. Thanks for the opportunity to testify today.

DR. LOSTRITTO: Next one is Edwin Thompson. And Edwin, you have a slide I believe? Okay, let's see if we can -- there you go.

MR. THOMPSON: Good afternoon. I am Edwin Thompson, president of Pharmaceutical Manufacturing Research Services located in Horsham, Pennsylvania.

The FDA in vitro testing for abuse deterrent opioids is fatally flawed, and has resulted in the misbranding of opioid products. Consequently, the general principles of evaluating the abuse deterrence of generic solid oral opioid drug products is flawed. An applicant could receive approval for a generic product with abuse deterrent labeling knowing, however, that the generic product has no abuse deterrent properties. To demonstrate the flaws in the FDA's in vitro abuse deterrent testing, I will use the testing and approval of abuse deterrent labeling for OxyContin.

Abuse deterrent labeled OxyContin provides no meaningful abuse deterrence to the primary known route of abuse, oral consumption. The FDA has stated that the vast majority of deaths associated with OC, original OxyContin, were related to oral consumption. The approved labeling for OxyContin that sales representatives are promoting to physicians states,

"Relative to original OxyContin, there is an increase in the ability of OxyContin to resist crushing, breaking, and dissolution using a variety of tools and solvents."

This statement may be generally true, however it is highly deceptive, clearly lacks full disclosure, and is misleading. OxyContin's label, in table 4 reports that both original OxyContin and reformulated OxyContin, are finely crushed, overcoming the resistance to crushing and breaking.

Also, it was reported by the FDA that reformulated OxyContin, when vigorously chewed, results in dose dumping. The FDA review reported, "Upon chewing vigorously, OFR and OC products are bioequivalent, bioequivalent with respect to oxycodone, Cmax and AUC. Reformulated OxyContin has no meaningful advantage in breaking or crushing over original OxyContin."

The summary of evidence and conclusion section of the FDA reformulated OxyContin clinical review included this statement. "The controlled release properties of ORF, reformulated OxyContin, can

be overcome with chewing and swallowing." Physicians should have been informed that the controlled release properties of OxyContin can be overcome when finely ground and swallowed, and chewed vigorously and swallowed.

This is more important information to a physician than the information in the labeling. This information would prohibit rather than approve abuse deterrent labeling for OxyContin. The FDA should stop using friability tablet testing to support abuse deterrent properties as it is not representative of breaking strength for abuse deterrence.

Also, the OxyContin labeling informs physicians that, quotes, "When subjected to an aqueous environment, OxyContin gradually forms a viscous hydrogel. For an example, a gelatinous mass that resists passage through a needle. The division director of DAIP at the time of the approval, Robert A. Rappaport, MD, in his summary review stated, "These features also render the product almost impossible to dissolve, syringe and inject."

Douglas Throckmorton, MD, in his summary

review stated, "OCR gradually forms a viscous hydrogel, i.e., for example a gelatinous mass that resists passage through a needle. The in vitro testing was sufficient to demonstrate that OCR reformulated OxyContin prevents, prevents oxycodone from being drawn into a syringe to any meaningful extent." These statements are incorrect and misleading.

The fact is that when OxyContin is subjected to an aqueous environment, it can easily, easily be extracted to high purity, and high label claim, by an unskilled person in minutes, with a viscosity similar to water, drawn into a syringe and prepared for injection.

OxyContin can also be easily extracted in alcohol to high purity and high label claim by an unskilled person, and converted into crystalline powder for distribution and sale. Reformulated OxyContin does not have any meaningful abuse deterrent properties to prevent extraction and injection. The FDA need to explain their choice of 40 percent alcohol rather than the readily available, inexpensive,

optimal alcohol options in conducting these studies.

The FDA for the last eight months has been unable and unwilling to refute this information. In response to my February 22nd, 2016 citizen petition, docket number 2016-P-0645, the FDA wrote, "The FDA has been unable to reach a decision on your petition because it raises complex issues requiring extensive review and analysis by Agency officials." The FDA in vitro testing for abuse deterrence, both for pre-FDA guidance and after FDA guidance, are flawed, and must be corrected. And product labeling resulting from these studies must be reversed. Thank you.

DR. LOSTRITTO: Thank you. Andrew Barrett, please? Do you have any information to post here? Okay.

DR. BARRETT: Good afternoon. I'm Andy Barrett. I'm a full-time employee of KemPharm. Thank you again for the opportunity to speak today. As described in the briefing materials for today's meeting, it is the FDA's intent to ultimately issue a general guidance describing recommendations for standardized in vitro testing to evaluate abuse

deterrent properties with the aim of informing potential applicants that are developing abuse deterrent formulations of opioid drug products.

In accordance, the FDA is hoping to implement common protocols that incorporate standard test conditions, specified performance standards, control formulations, and a tiered approach to determining when abuse deterrent properties have been defeated, and how that information may be used during drug development and for other relevant comparative situations.

As a proponent of the scientific method, I fully recognize the benefit of standardization, common protocols, and controls in determining the effectiveness of a technology. However, in the case of emerging technologies, such as prodrugs, and abuse deterrent formulations, there cannot be a one size fits all approach.

Rather, as acknowledged in the briefing materials for today's meeting and addressed in the presentation made by the Branded Industry Working Group, it is imperative that the FDA build flexibility

into standardized testing. Otherwise we run the risk of narrow casting that can stifle innovation and hamper the introduction of products that could have a positive impact on remedying the epidemic of prescription opioid abuse.

Illustrating this point, two formulation strategies have led to FDA approved abuse deterrent labeling for ER opioids. These are physical/chemical barriers, and agonist/antagonist combinations. A key reason for the success in getting such opioid products approved is that current FDA guidance is focused primarily on these two types of formulation approaches.

On the other hand, this situation is encouraging as companies clearly heeded the FDA guidance in developing new ADF products with current data suggesting that such products have made meaningful impact on certain forms of abuse. However, one potential consequence of advancing certain standards related to abuse deterrence of extended release opioids is that it will limit the impact of emerging technologies and abuse deterrent formulations

aiming to address the immediate release opioids, which account for greater than 90 percent of all opioid prescriptions.

As a result, while there has been great success in one area of abuse deterrence, opportunities to make additional advances have been confronted by challenges that may have been avoidable if greater flexibility were applied to the 2015 FDA guidance. The case in point is the requirement of all ADF to be subjected to crush resistance as a part of the evaluation process.

Crush resistance may be highly relevant when considering physical/chemical barriers, for instance, but has little practical application when testing emerging technologies, such as prodrugs. For a prodrug to be converted to the active moiety, the covalent bond must be broken between the opioid molecule and another ligand.

As such, testing the crush resistance of a prodrug offers minimal value in determining its abuse resistance because prodrugs require enzymatic conversion to an active opioid moiety to achieve

analgesia. Therefore crushing a pro drug offers no ability to access the active opioid, you simply get a finer and finer powder.

In speaking today, my hope, and the hope of others who have addressed the committee, is to encourage the FDA and OPQ to take into account emerging technologies that have yet to gain FDA approval as the new standards for testing and evaluation of ADFs are considered.

A breadth of new technologies, such as prodrugs, gastric acid depleting formulations, Depo injections, implantable devices and combinations of existing approaches are rapidly advancing through the clinic and towards regulatory review.

Many of these offer considerable promise to improve upon technologies that have already been approved and/or address specific currently underserved segments of the market.

Much like the nuances of existing abuse deterrent products, emerging technologies are likely to have unique considerations that make strict standardization difficult. We therefore advocate for

continued flexibility in such standards in order to allow room for incremental improvements in abuse deterrent technologies. Thank you again for your time and consideration.

DR. LOSTRITTO: Next please, Ravi Harapanhalli.

DR. HARAPANHALLI: Good afternoon. Thanks to the FDA for arranging this wonderful session to discuss all aspects of abuse deterrence. It seems that science of ADFs may seem relatively new for some people, but the science and perhaps the art of drug abuse itself predates us (inaudible). And it is incumbent upon us here to really come up with solutions to see what we can do creatively and meaningfully to solve this problem. How we can creatively use the ADF technology to better advance the cause of the public health.

So with that, I believe that the guidance, particularly the 2016 guidance, is a very good start and it has a lot of elements in it, and we should really hone onto what's good about it and see how we can build off from it. There was a lot of discussion

about the fact that the guidance focuses mostly on crushable and gellable type products, and it's not encompassing other technologies and so forth.

There was a discussion that pulverization is not included, 0.1 normal HCL may not be adequate for certain in vitro testing and so forth. So if we go like this pathway, there's no end to it. I'm sure there will be a lot of issues that we can come up with that are not meaningfully perhaps covered in the guidance. So it is upon us to understand the principles behind it and see what industry also can do to meet what FDA has been doing to advance the cause of this guidance.

With that said, obviously there are a few points that I would like to bring up. Totality of evidence, I think it was discussed in great detail yesterday. And to Rob's point that, clinical relevance and clinical significance need to be considered. I think that's a good point that FDA made.

But a few points I would like to also bring up here. In terms of totality of evidence, this

concept has been successfully utilized in other programs at FDA. Biosimilars, for one, where they have clearly laid out the whole pathway where you have the physical/chemical testing rigorously at the base of the pyramid, then you move on to PK, and then the PD, and then, if necessary, a clinical bridge.

So a similar kind of a pyramidal structure is something that I think we should strongly consider here with in vitro testing being at the base of the pyramid, and then you keep going up. Maybe PBPK and then the PK, and if necessary then the HAL (ph) studies.

Every time our decision should be based on what we have really exhausted in the lower category of testing, and what is the true residual risk that we could not address and therefore we need to go to the higher level. I believe it is helpful for both brand and the generic industry.

We also heard from some aspects that all three tiers of testing should be done for all products. I feel that that's one extreme view on this issue. As long as the chosen in vitro testing regimen

is adequately assessed, and it's reviewed, and it's meaningfully conveying what it is supposed to, then I think there should be good merit to what in vitro testing data is suggesting before we go to the next level of testing.

We heard good examples of high signal ER (ph) in yesterday's FDA talk where there was a good correlation between PK and VAS for drug liking (ph). And they're also looking at taking the drug again as another VAS criteria. If these kind of things suggest that there could be good correlation and that in vitro PK and then to HAL, if that sort of an access can be studied well with maybe more examples, that should set the stage for this kind of a hierarchal and risk-based approach to testing.

One thing I would like to bring up is the incremental improvements. I think there was some concern yesterday that it shouldn't become evergreening (ph) scenario for the brand companies. So what does incremental improvement really mean? I think we need more clarity from FDA on that. Is it that it is only for the brand companies that they can

have certain minimum level of assurance in their original formulation and then at what rate and what extent they can keep changing it, that how it will impact the generic approval process? I think that's another point that I'm sure FDA will look into.

And a few other points I would like to make is, yes, ICH Q8. This morning Rik's talk was very well presented. I feel that this whole concept of ADF formulation design and development should be not considered as a separate entity but rather as part of our overarching approach to formulation development. QBD approach with ICH Q8 principles, starting with target product profile, how they dive down into the CQAs and then to your attributes that are selected for release and stability testing, how all these fit into your ADF assurance properties. I think if we do that well in the PDR (ph) section, I hope that FDA won't necessarily require stability testing of these attributes on a regular basis.

And a couple more points. I thought that there is some information needed on the controls. To Rik's point, I think he asked in fact us to come up

with some suggestions. And the guidance says that you send a control correspondence if you want to choose a control that you are not sure of. Can we have a little bit more clarity in the guidance itself that if there is an immediate release non-ADF type formulation already available in the market, maybe that's a first choice. If not, then can we go to something outside the U.S., same API in an immediate release form that's in ICH approved countries, can we use it as a control?

Or, thirdly and most importantly, can we make our own immediate release version? In my mind it is no different than making placebos for placebo-controlled clinical trials where we put enough (inaudible) into making these kind of placebo tablets. So same way, can we make our own immediate release versions so that we can use them in our studies? So these are some of the points I think we need to discuss further.

And one more point, most importantly for ANDAs and review. I'm sure FDA is already currently reviewing a few ADF related ANDAs. So where they are? How long it's going to take for them to review? What

kind of information they are going to communicate to us? And how they think they can retrofit this current discussion on ADFs to those ANDAs that are already under review? More so whether they're really under review or they've just been shelved until this guidance becomes final.

So there are a lot of uncertainties and we hope to get some clarity on that. And I also suggest that because control correspondence or a pre-ANDA meeting are not appropriate for those ANDAs that are already under review, the FDA should seriously consider mid-cycle review type mechanism and invite all such ANDA applicants to come and discuss and see how we can retroactively apply this guidance, and how we can possibly bridge. Because most of the time, companies may have already submitted this ADF type assessment in one or the other form, so how to bridge that. I think that is something the FDA should creatively consider.

So I think with that, I have only 30 some seconds. I don't want to take too much time, but basically these were the points I wanted to discuss

here. And I thank again for this opportunity.

DR. LOSTRITTO: Thank you, Ravi. Candace Edwards?

MS. EDWARDS: Good afternoon. My name is Candace Edwards from Amneal Pharmaceuticals. And first I want to thank the Agency for allowing the stakeholders to participate in this policy making process by providing industry with the opportunity to present our positions in a public domain. I think that's very important to sort of move this straight forward so that we can get to our goal, which is to finally get some approved generic abuse deterrent formulation products on the market.

So it's an interesting journey. I look back over where we started, where we are today. It's an interesting journey we've traveled. Some of the key events being, let's say the first introduction of a long-acting opioid product to the market back in 2010, followed by market withdrawal of that non-abuse deterrent, long-acting opioid product counterpart. And then followed by, I think in 2014, we progressed to the first public meeting where we actually brought

the scientific issues to the table, and started to share information from both the generic and the innovative perspective, and move on to --

I'm sorry, before we go I want to -- before the meeting, I think there was the approval of a labeling for one of the products that actually gave some specific information on -- and some specific language in the drug abuse independence section, which described results of data from in vitro and in vivo abuse potential studies.

And then followed by that, we had the public meeting in 2014 where we were able to share different industry perspectives on where we felt we needed to go in order to sort of standardize the data requirements, or the body of data needed to approve these products.

2015, I think we saw the issuance of a final guidance from a branded perspective. 2016 we saw the issuance of a draft guidance for the generic industry to provide the Agency's current thinking on evaluation of abuse deterrent generic drug products. And so that brings us to where we are today, the second public meeting.

So, as you can see, I think we've made considerable progress toward achieving the goal of getting to the point where we have a generic product approved. We have some standards. We have some guidance. We have a better understanding of the body of data.

Yesterday we heard from payers that the introduction of a generic equivalent would have a very positive impact on the cost of these products that are needed to meet the medical needs with regard to pain alleviation in the relevant patient population. So this is something that's -- would have a positive impact when we're able to bring these products to the market.

So my perspective now is from the generic industry's perspective. We are at the gate with regard to the process of having these final discussions with regard to how we can achieve the goal. Our goal, again, is generic product approval for this category of products.

So as we consider the technical requirements that the Agency has identified for evaluation of

generic ADF products, I see the requirements in two separate and distinct product development phases. The first phase being where the generic manufacturer will collect data on characterization of the reference listed drug with the regard to the potential for abuse for all routes. And that's what the guidance kind of does for us, it gives us different ways to look, from a technical perspective, different methodologies to look at potential abuse of the product that we're developing with regard to all routes, regardless as to what's in the approved labeling. And that's appropriate from a development perspective.

The goal here is that we want to look at the RLD for all routes, and then we want to achieve the goal to confirm that the generic product does not present any opportunities for abuse outside of those potential routes that are identified in the labeling. So that's what directs the generic process, the generic development process, as we move toward that sameness criteria for equivalence.

And as the product development nears completion, data is generated that the generic product

will have the same abuse deterrent characteristics as RLD, and will not present any unintended consequences for abuse outside of the approved labeling. If we use the tools that we have that the Agency has provided, if we see that we are presenting, it's going to change the path of the product development. Again, we're generic. We want to be similar. We want to be comparable, okay.

So the next phase of development proceeds with the goal of actually achieving the design characteristics that will render the generic product equivalent with regard to the route of abuse identified in the actual labeling. We're actually now looking toward moving to product approval.

Non-inferiority in abuse deterrent characteristics can then be evaluated based on comparative analysis with regard to potential abuse in the specific routes again that are identified in the RLD labeling. The use of standardized testing during this second phase of product development would go a long way to providing the generic manufacturer with a definitive tool and goalpost to provide the

appropriate comparative analysis, or non-inferiority analysis, which will allow us to achieve FDA approval.

So I'm in support of the technologies and the standardization of the technologies, at least from a comparative perspective. And I've heard from a few brands, so they may not serve the same value because of new technologies and things that come about, but at least it serves for the generic industry as a basis for comparison, which is, you know that's the nature of our business.

That being said, I wish to support the position put forth by the generic industry working group and state that I hope the Agency can use this input to actually come to some final conclusions on this draft guidance, with the goal of actually being able to move forward with approval of products for, in this category for the generics.

I further support finalization of the draft guidance and standardization of testing modalities to this end. I believe that the guidance serves as a basis for development of generic ADF products, and that it should be further augmented by product

specific guidances so that the relevant information can be used to facilitate generic development. And this could possibly fill some of the gaps -- if we were able to use these product specific guidances, could potentially fill gaps that would be identified by progress that's made with various new technologies coming aboard.

So, for me, a wonderful ending to a wonderful story, a wonderful journey, would be to realize the approval of a generic abuse deterrent product. And that we know that, looking at this journey, it's been at least five years that applications have been pending, have been sitting. You know, the ability to move forward and actually get a product approved would be a wonderful ending to this story. Thank you.

DR. LOSTRITTO: Thank you, Candace. Edward Cone?

MR. CONE: Good afternoon. My name is Edward Cone, and I'd like to thank the FDA for allowing me to comment. I'm an employee of Pinney Associates, and Pinney Associates provides consulting

services to the pharmaceutical industry in a variety of areas, including evaluation of abuse deterrent formulations. And I hope Pinney Associates is going to pay for my time and expenses for attending the meeting.

The first of three issues I'd like to comment on. One of the questions is, how far can the FDA go in standardizing in vitro testing of a generic ADF? And my comment is that testing of a generic opioid ADF against an existing innovator ADF, referred to as the RLD, requires an intimate knowledge of the ADF features of the RLD. The primary information on the ADF properties of the RLD is contained in this label, 9.2 abuse section. And there may be some other sources about the RLD in public documents and literature on the abuse deterrence of the product.

While this information, taken together, identifies the route of abuse in which the RLD has demonstrated ADF properties, it does not specify the test necessary for distinguishing the RLD from a non-ADF product. Testing of the generic product begins with identification of those discriminatory

tests by which evaluation of the RLD compared to a control non-ADF product starts. Then only those discriminatory tests that specify by the generic guidance are applied to the test product.

This approach standardizes the conditions to be tested, but may overlook other ways of manipulation, and may cause failure of the test product. Certainly the number of tests on a generic product will be greatly reduced, but will this be at the risk of potentially allowing products to be approved that are vulnerable to conditions outside those specified?

The unique properties of current RLDs seem to belie standardization of test conditions for generic products. While I'm certainly in favor of standardization to some extent, I'm skeptical of Category 1 tests that do not include a discovery phase that incorporates test conditions outside those identified by the guidance. Without a comprehensive discovery phase, vulnerabilities may be overlooked. And I guess it's kind of like looking for the Loch Ness monster a little bit. If you don't look, you

don't know whether it's there or not.

A second issue I'd like to comment on is what are the performance criteria that demonstrate equivalency of a generic ADF to an existing ADF? Currently a statistical approach is proposed by the FDA as criteria of equivalency of a generic ADF to an existing ADF. This seemingly logical approach may allow inferior products to meet criteria and equivalent products to fail.

This is because there's inherent variability in physical and chemical manipulations that attempt to simulate abuse practices when tests are conducted with a small number of replicates. This inherent variability will be difficult to manage with rigid statistical criteria. And it may place an unusual burden on generic developers who may have to resort to use of considerable replicate tests to meet statistical criteria.

A third issue that we have spent a little bit of time talking about but haven't gotten too far in development, is the issue of assessing ease of manipulation. And secondly a question posed was, how

can performance attributes measured by in vitro testing be quantified and linked to their impact on abuse deterrence in the community?

This is a difficult question, and it involves both the development of instruments that measure a subjective concept, commonly referred to as ease of manipulation. And then linking those measures to the abuse deterrent outcomes in the real world. Such measures of ease of manipulation must be developed and standardized. And already there's been some progress made in that area.

Several instruments have been developed to measure work requirements. As my colleague, Dr. Jack Henningfield mentioned yesterday, we've tapped into the science of behavioral economics. An example is the ALERT instrument, which is a series of visual analogue scales. This instrument has been used to evaluate the degree of effort involved in physical manipulation of innovator opioid ADFs. These scales, applied by trained laboratory technicians under standardized conditions, identified major differences in the degree of effort needed to physically

manipulate hardened ADF products compared to non-ADF products.

And this type of instrument allows a great deal of flexibility. Typically in the design of it, we would take the test ADF product, which is an extended release product in this case, compare it to an existing ADF extending product, and add additional comparators, like an existing, if available, non-ADF extended release product, and an IR non-ADF product. And the beauty of it is, you can do the study in a week.

Thus far this approach has been promising, but additional scales are also needed for evaluation of chemical manipulations. However, linking the results of in vitro laboratory valuations will be the next challenge, and will take years, if ever, to accomplish.

In conclusion, I support the efforts of the FDA to transition from non-ADF opioids to ADF opioids. We've seen the success of these products in reducing abuse results and rates in the community, and in reducing adverse outcomes. There remains considerable

work to do in refining Category 1 methods, and we appreciate the commitment and cooperation of the FDA that they've shown in guiding this program further towards success. Thank you.

DR. LOSTRITTO: Thank you. Robert Bianci?

MR. BIANCI: Good afternoon, I'm Bob Bianci from the Prescription Drug Research Center. We also provide consulting services to the industry. I have no financial conflict of interest to disclose.

I retired from the Drug Enforcement Administration as a Director of the Special Testing and Research Laboratory, which where I believe the first in vitro testing was done more than 16 years ago on an amphetamine product that never made it to market.

So it's kind of been a topic of interest, and since I've retired I have an opportunity to explore this, and it's been a great experience working with the pharmaceutical industry and the FDA. And certainly I thank the FDA for giving us this opportunity to exchange ideas. We're not always in agreement, but at least they're listening.

The basis was to provide a completely transparent process, however things are changing. The technology is changing in developing these products, as well as the laboratory testing that's being utilized these days. You know, delivery platforms are different, but those differences must be considered in development of protocols, but there are also some similarities, which brings us to standardization.

And we all know that the abuse deterrent formulations will generally only discourage the casual abusers. There will always be somebody that is going to challenge, but the top of the bell curve are those casual users, and we're going to reach most of them with these abuse deterrent formulations. It's similar to putting a lock on your door at home. If a burglar wants to get in, he's going to get in. But for the casual criminal, he's going to go to your neighbor's house. So it's a part of the process that you go to something else.

There is no abuse proof product on the market. And I say with emphasis, yet I think it will be here, but it's not here yet. And one of the

concerns that has not been addressed is the consumption of multiple doses. There's nothing to stop anybody from taking several doses. But I think that's going to change as time goes by.

So, the FDA has tried to take an adaptive approach, which is very refreshing. But they're also trying to completely characterize these products. And this has involved a great deal of lab work, that in some cases may seem to be unnecessary. But they're collecting data and that data is going to be the foundation of what we do in the future.

All the modes of abuse need to be considered in developing these protocols. And I think that the amount of effort, as Ed Cone said, is something else that needs to be measured as well. We know that if it's too difficult, they're not going to do it.

And the FDA wants us to produce protocols that are both reproducible and statistically valid, but also represent the real world. I like to use the term kitchen chemistry, or what are they going to be doing at home, and we need to address them thoroughly. And of course, one of the ways to do that is research

on the Internet, and I'll talk about that later.

Dose dumping has become an issue that is something that we will need to be concerned about. And certainly the FDA has been pretty directive in suggesting that alcohol, varied concentrations be used. And finally, we don't want to provide a roadmap for abuse. And I think that's apparent from some of the labeling restrictions so that people can't pick it up. If it says don't be chewed, they're going to try chewing it because that's a way to defeat it.

The people we're dealing with are not, in most cases, very well educated in the area of chemistry, but they're very clever. Without any technical training, they can figure out ways that we never thought of in trying to abuse these substances. But in most cases they're following a recipe that came from a friend, off the Internet, and they follow it blindly.

They all have very limited resources and there's been no evidence that there's any organized crime family trying to do this. Most of them are doing it for their own use. And the concept of trying

to extract an opioid and concentrate it and sell it on the street is really not worthy of considerations.

In many cases, the abuser is desperate. So dropping a couple of tablets in a container of water and coming back the next day is not a practical option. And the hardened users, the trained chemists, look at abuse deterrent formulations as an intellectual challenge. And if you read some of the postings online, you will see they're trying to stick it to the establishment, to the DEA, the FDA, by trying to defeat whatever they've developed, and they've been doing this for decades with controlled substances where they just modify the molecule so that it's not controlled, but still has those abusable properties.

I mentioned briefly the Internet. If you're in this business and you haven't viewed the Internet, you need to do that. There are many, many sites, and as soon as you access one, you'll be turned on to many others. But Blue Light seems to be the one that is most popular and very current. And that's where we need to get some information about what's going on.

For the scientists in the laboratory, whether it's a development laboratory or a quality control laboratory, are really not into this kitchen chemistry stuff. So they need to get an education. They need to figure out what those people are doing. What are abusers willing to do? How much effort are they going to put into it? But still maintain the scientific principles of reproducibility and statistical validity.

And of course, one thing we haven't mentioned is developing these tests. It needs to be done in a safe manner. So you don't want to expose the lab staff to any procedures that an abuser might do that could be hazardous to the staff or the facility.

Over the past 13 years I've developed a number of protocols for a variety of products, with different abuse deterrent features. And I did that in conjunction with National Medical Services Laboratory where we tweaked the procedures to satisfy the requirements of the FDA.

So in conclusion, I have to say that the FDA

has collected a lot of data over the last 18 months. And I'd like to see them share that by way of some of the standardization that we've been talking about for the past two days, so that each project doesn't become a research project. And I'm talking about fundamental things, like you know the solvents that are going to be selected, the particle size reduction we've talked about over and over again. How many time points do you have to utilize to make an effective evaluation? So I think all of those things can come out of what the FDA already has in their file.

The criteria, once they're established, I think are going to make the FDA's job a little bit simpler. This is no simple task to compare these products and to determine if it does have any abuse resistant properties. But it's also going to make it clearer for the sponsors, whether it's RLD or people that are coming into the generic market, of what is expected. And it's difficult to work in an environment when somebody is saying, well, we'll know I when we see it, just give us everything you've got. And that's what we've been doing all along.

So FDA, I request that you do share the data and you do produce some level of standardization with the flexibility for the different platforms that are being created. Thank you.

DR. LOSTRITTO: Thank you. Beatrice Setnick?

MS. SETNIK: Thank you and good afternoon. My name is Beatrice Setnik. I'm the VP of Scientific Affairs at INC Research. In my role, I consult with various pharmaceutical and biotech companies. I would like to thank the FDA for the opportunity to share my thoughts this afternoon on this topic and also to commend them for putting together the guidance. It's a very good starting point for, as we can see over the past two days, a very complex and challenging conundrum in terms of establishing equivalency between generics and innovator products.

There are a few things that I wanted to share with you in terms of some comments to the guidance; some of them that have been raised over the past two days. And one of them is really the different in vitro approaches to different ADF

technologies and it's been said by several of the speakers that the different types of technologies, whether you have a physical barrier, an agonist/antagonist combination, a prodrug or some of the emerging technologies such as overdose, addressing overdose or excess consumption, all do require and have different objectives in terms of their in vitro testing.

That is one of the areas that I think would benefit the guidance in terms of delineating just the differences between the in vitro approaches to the different technologies. I think that would be a good ground work.

Doctor Edward Cone and I had published a communication piece that was written actually before the guidance came out, but published shortly thereafter, and we had put together a table that looks at the different types of technologies and the different in vitro approaches that one takes and the testing that one takes. That could be used as a good reference to start to further develop that schematic of how the in vitro tests can differ between different

technologies.

I think once we lay the groundwork for the innovators, it'll be that much easier then to lay the foundations for how to bridge the generics to the innovators.

Another theme that has really come across these past two days is just the level of variability that can be introduced by just simply the manufacturing process. And this really has resonated with me, because if there are differences in variations in the manufacturing processes that could lead to different behavioral characteristics of the ADF, we are facing a situation where it is likely that on the in vitro testing panels, the generic and the innovator may look quite different, depending on the extent of variability in the process and how those characteristics behave in the laboratory environment.

In which case, I think it would be appropriate for the guidance to position itself to the possibility that clinical testing may be needed if there is a considerable amount of variation between the in vitro testing of generic and reference listed

drug. In which case, it would help to describe efficiencies in clinical testing. Certainly combining clinical tests that evaluate pharmacodynamic and pharmacokinetic endpoints can certainly be combined, streamlining the amount of pharmacodynamic measures in the abuse liability or the pharmacodynamic component can be easily conceived as well in for a generic product.

And one of the other issues to also think about in the clinical paradigm is the statistical approaches that one might take between a generic and a reference listed drug. So do the regular statistics apply that are referenced in the innovator products or do we look at these more as bioequivalencing testing in terms of pharmacodynamic measures. So those are some of the things that we may want to think about if the products do advance into a clinical setting.

I also echoed some of the earlier speakers in terms of the comments around the particle size distribution and the 500 micrometer cutoff point. From a clinical perspective, we have seen insufflation of much higher particle sizes. So I think that

depending on if a particle size is reached greater than 500 microns, certainly there may be variability in how much product then becomes bioavailable from larger particle sizes, but that could be variable with the types of products. So I think rather than setting limits, these types of cutoffs need to be more data driven and they may end up being more product specific in the end.

And one last comment that I wanted to make, specifically refers to the agonist/antagonist combinations or generics thereof. When taken intact, there are situations in patients where the antagonist may be bioavailable in small amounts, even though it may be sequestered, and this outcome may be the same in the generics.

So testing not only the manipulation methods, but understanding in a clinical setting what level of exposure of a sequestered naltrexone or an antagonist may be, is also an important endpoint that's likely going to be more evident in a clinical setting, rather than in an in vitro setting, as that particular exposure may have an influence on the

ultimate efficacy of the product.

And those were essentially my points. So thank you very much for allowing me to share those.

DR. LOSTRITTO: Thank you. Has Pamela Osborne come into the room? Pamela? Okay, that was the last of the public comments. So the public comment period is now concluded, and we'll no longer take comments from the audience.

Panel Discussion: Future Directions that Will Enable the Efficient Development and Evaluation of Abuse Deterrence of Opioids

So before we move to the panelists, I want to just say a word or two about the folks who helped prepare this meeting that we've been involved with it seems like for months now, planning, preparing and so forth.

So I'm going to ask a few folks who are the unsung heroes who have worked very hard here to please stand up. And wait until I'm done calling all their names and we'll give them a round of applause. Michelle Eby. Trang Tran, if you're here. Trang. Gail Schmerfeld, in the back of the room there. Thank

you. Chris Andre (ph). Thank you, Chris. And Amina Russell (ph), you can stand if you want, even though you've got the boot on, you could stay seated. So I just want to say thank you very much for organizing a great meeting. Thank you.

Now we're going to turn our attention to the panelists. And before we go through the designated questions and comments in the booklet, all the speakers are here, and there's a few folks who hadn't spoken, so I'd just like them to give a 10 second introduction, starting with you, Karsten. And then we can skip the folks who already talked, because we heard your introductions and then we'll hit the discussion questions.

DR. LINDHARDT: I'm Karsten Lindhardt. I'm the head of R&D for Egalet and heading up our Category 1 work for Egalet.

DR. THROCKMORTON: Doug Throckmorton. I'm the Deputy Director for Regulatory Programs at the Center for Drugs, FDA.

MR. RAULERSON: Patrick Raulerson. I am Regulatory Counsel at CDER's Office of Regulatory

Policy, and I work on regulation policy issues surrounding abuse deterrent opioids.

DR. LIONBERGER: I'm Rob Lionberger. I'm the Director of the Office of Research and Standards in the Office of Generic Drugs at CDER.

DR. TOLLIVER: I'm James Tolliver. I'm a Pharmacologist with the Controlled Substance Staff at FDA's CDER.

DR. YARASANI: My name is Venkatarama Yarasani. I'm the Executive Director from Teva Pharmaceuticals (inaudible).

DR. HERTZ: Sharon Hertz.

DR. LOSTRITTO: Okay. So what I will do, is I will read the topic for discussion and then we'll just see what happens.

So the first topic is, what technical and quantitative issues should FDA consider as it develops guidance to recommend standardization of in vitro testing to evaluate the abuse deterrence of opioid drug product formulations through various routes of abuse, including: ingestion, insufflation, injection and smoking. For example, what should FDA consider

with respect to mechanical manipulations, equipment, amount of time, effort, chemical manipulations, EG solvent, solvent choice and availability, particle size distribution, and volume of solvent used for extraction? Go ahead. Please start.

DR. LINDHARDT: Yes, maybe I should say I'm here on behalf of the branded industry. So actually first would like to make some comments that relates into this topic. And we really have a common interest in improving standardization of Category 1 studies. And we also started in November of 2015 a Category 1 focus group with the entire industry and representatives from academia and FDA, to discuss standardization of Category 1 work.

So I think it's a very important topic, and I think it's great meeting here and discussing that. And especially I want to acknowledge the work that's been going on in the FDA of trying to build in-house understanding of Category 1 testing.

And as we heard yesterday, both from Steve Hoag and Xiaoming Xu, and also today with Rik Lostritto and Cindy Buhse, that the material

properties, it's really how it interacts with both the manufacturing and the formulation of the process, really showing the complexity of the Cat 1 work. And that small changes in material can really make a big difference to what we see.

So I've been working with this area and trying to work with standardization in about nine years , and I almost feel sorry for Bob Bianchi and Ed Cone, who's been working for 30 years with this area. Because it's really tough, and it's really complex, that may -- and obviously I'm not really answering the question here.

And I think the answer is really that the FDA should really consider the complexity, should get some in-house understanding of what is needed, and have a product specific, material specific, or really understanding of the properties. Because that's really the only way to really get that full understanding that would enable us to really do proper standardization.

DR. LOSTRITTO: Thank you. I think I'll exercise some moderator privilege here. And as we go

down the line, folks who didn't have the opportunity to make a formal presentation, I'll give some deference to. So, Doug, Patrick, do you have something you want to add? Or anybody else who hasn't --

DR. THROCKMORTON: Can I ask what you meant, product specific guidance I understand; material specific, can you just sort of give an example of what you're thinking there?

DR. LINDHARDT: Yes. No, I was more relating to what we heard about, the kind of material properties and how manufacturing, or changes in manufacturing process has -- I think a good example of that was really we asked the FDA, you know, what do you actually mean when you say final (inaudible) formulation, or final to be (inaudible) [marketed] product.

And what do we need to test in our Category 1? And the answer to that was really quite appropriate, that we needed to use final to be (inaudible) product. And the reason for that, which I find evenly appropriate, was that there could be

differences in manufacturing process that could potentially impact the properties in Cat 1. And that's of course what we have done and followed. And I think that makes a whole lot of sense, but it's actually also supported by a lot of the evidence that we have now that that's really an appropriate approach.

DR. LOSTRITTO: Anybody else?

DR. YARASANI: Yes.

DR. LOSTRITTO: Please.

DR. YARASANI: Okay. The generic industry believes that FDA has a lot of information about abuse deterrent products from several NDAs that were approved so far and those that are under review with the Agency. The generic industry needs help from the agency with respect to the acceptable requirements for (inaudible) products that are relevant and reasonable for a given technology or product. And they should consider providing some standards that are reasonable across different technologies or platforms for a given route of abuse.

The generic industry appreciates if the FDA

could communicate the information through some product specific or technology specific guidance. I think that is the theme that is resonating through since yesterday.

With respect to mechanical manipulations that were mentioned in the question 1. I think FDA should consider the tools that are used to manipulate the product because I think we saw one slide this morning, Elisabeth was presenting, with variation in the make and model of the coffee mill and the time of exposure and all those things would result in different particle size. That particle size difference would result in different outcomes of the individuals tests that are going to conduct.

And then another factor that should be considered for mechanical manipulation is the, as (inaudible) FDA talking about the time and energy and also the knowledge, I think also another aspect that was brought up today, but time and energy is definitely a variable that also could impact the outcome of these studies. And the sample weight, I think that is another important parameter also to be

considered for the mechanical manipulations.

For chemical manipulations, the solubility of the API is one of the important parameters that should be considered. Because this in turn defines the selection of the solvent, as well as the volume of solvent that requires to do these studies.

Other parameters of importance are the particle size, as we mentioned before, of the samples that are used for these manipulations, or for testing, chemical testing. Time of exposure, temperature, or the agitation, there is a component of agitation conduct in these studies. These are some of the parameters that would impact the outcome of these studies.

FDA should also consider setting up a pre-ANDA meeting with sponsors of generic products to discuss about our understanding of the RLD and agree upon acceptable (ph) data package for generic products. We were happy to hear yesterday that (inaudible) is having the (inaudible) for a pre-ANDA meetings. But I'm not sure when this is going to be effective, but I'm guessing it will be at least a year

before we see the (inaudible).

And some (inaudible) mentioned about the existing ANDAs that are there. Probably FDA should consider having those kind of pre-ANDA meetings with the sponsors in the interim to discuss about where they are with respect to their submission and what is expected for further progress with the review of those applications pending with the Agency.

DR. LOSTRITTO: So, in terms of -- just a couple things real quick. In terms of pre-NDA, or NDA, that could happen any time. It's already an existing path of discussion. There's always controlled correspondence for ANDAs as well.

But in terms of sticking to the question, I also think the approach we take is going to have involve some of these basic manipulations that we were talking about that the household abuser is going to have at their disposal.

But I also think some more rigorous scientific study behind the scenes is needed to understand using things like instrument analysis and different types of viscoelastic analyses to point the

way to which form of manipulation, shear or compression and so forth, is going to likely be the most fruitful for a given type of product.

So I think to blindly do it empirically, and just have a laundry list of things from wire cutters, to mortar and pestles, to coffee mills, is not going to be a satisfactory scientific approach in the long run. You have to understand the fundamental physical/chemical mechanisms that are involved if you're going to have any effect.

Towards chemical manipulation, we have to remember that unless it's a prodrug, if it's a salt, salt forms can be defeated by simple manipulation of pH, and a simple biphasic extraction. So we have to again think holistically about the whole physical/chemical milieu, and then distill that down, pardon the pun, into something that can be put into categories appropriate for various types of approaches. And I think, Rob, you wanted to add something?

DR. LIONBERGER: Like this is a question to the industry representatives on the panel about the

question 1 here in terms of what we should standardize. So let me just put out this in a way to talk about it. Should we standardize a coffee grinder? Or, I mean, should we move toward saying how you should do something like milling. And maybe you can discuss the tension between going to a standardized condition and then being more relevant to what someone who's abusing this product with things they might find at home, you know what's the balance between those two in terms of the standardization?

Also from your experience, I mean do you run through -- did you buy coffee grinders in bulk and run them out? Like what do you -- if you're involved in significant development activities in this, what do you do to ensure the reproducibility of some of these tests or manipulations?

DR. LINDHARDT: Yes, we definitely buy several coffee grinders. And we also buy different coffee grinders and work with that and optimize that part. So yes, I think it's a really good question. It's a really tough question because one of the things that was (inaudible) in the Category 1 focus group

meeting last time was standardizing a hammer. Because a simple thing as a hammer, how hard do you blow or what's the surface you're hitting on? So there is a lot of elements to it.

And what you would probably end up with, even if you tried to standardize a coffee grinder, is that each material would behave differently, and one coffee grinder may not be the optimal one for one tablet, whereas it would be better for another tablet. So even if you did optimize, then it may not be kind of the most appropriate test of that particular drug.

DR. LOSTRITTO: That's the point I was trying to make.

DR. LINDHARDT: Yes.

DR. LOSTRITTO: And by the way, there is a standardization for a hammer. Other industries have this. The auto industry and other industries that are worried about product robustness.

DR. LINDHARDT: Yes.

DR. LOSTRITTO: And it's as simple as using a pendulum approach. The physics are extremely reproducible. But that aside, before everyone runs

out and gets all kinds of coffee mills going, understanding the fundamental rheological behavior in terms of stress and strength, and relaxation, and plastic and elastic deformation, this is going to point to the way of what types of approaches are going to work best. Then from there it could be a matter of fine tuning which type of mill is going to optimize the destruction of the system.

DR. LINDHARDT: No, I totally agree. And therefore I would also like to acknowledge what Sharon said before the meeting that, you know, this is not about abandoning kind of the iterative approach, it's about to have a set of studies and then we can kind of work from there. And I think that's also what you're discussing, is that we're getting some basic knowledge from these standard tests, but then we may need to go into a second iteration. Right.

DR. YARASANI: Yes, again the different mills gives different outcomes of a test that is performed. And what we are saying is that the generic industry, we do realize that when you're conducting these studies, manipulation, mechanical manipulation,

if you use one particular make and model of the mill, or the design of the blade, (inaudible) the blade design itself has different outcomes.

So if you just leave it open, and the time that is required to manipulate these products, it results in different way of interpretations. And when you have ANDA products, you will see data that is not generated the way the Agency wanted to and expect consistent performance among generic products. There should be (inaudible) again. I think somebody mentioned most (inaudible) about five out of seven products approval are physical/chemical barrier based.

So there should be a lot of information out there with the Agency, as well as applications that are under review. Probably combining that data probably gives some kind of a general standards, or acceptable tools and time so that the generic industry could explore around that area rather than just keeping it open, quite (ph) open and everybody tries their own way and comes back with their own justification and would never go where it wanted to go.

DR. LOSTRITTO: If there's any further input on this discussion topic.

DR. LINDHARDT: Maybe one small point. I think the guidance that we already have from the FDA has been very helpful, right. The volumes that we already have with the 2, 5, 10 milliliter, and that type of guidance is extremely helpful and we could definitely, you know more of that is great, as long as it's justified. But so, that's been very helpful. There's not been a lot of that in the branded guidance, and you know that could be something that could be improved there.

DR. LOSTRITTO: Yes, please. Go ahead, James.

DR. TOLLIVER: Yes, I certainly see a point for trying to standardize, for example, the physical/chemical tools. But I think it's already been said, but I can think of it from experience because I put a lot of these applications, and so I have a good idea of what standard tools would be.

But what catches my mind is that on at least two occasions, possibly more, I looked at applications

and sure enough they did the standard tools, but then they went a step further, and what they actually used, because keep in mind that for innovator products, we're really interested in trying to get those tools that provide the best computation of the product. And what surprised me is that they came up with tools that I'd never heard of, okay. So I was familiar with all these regular tools that were used, but when it came to doing or preparing to do the human abuse potential study, they used a tool that I never thought of.

But take it a step further, not only did they use that tool, but they were able to show that it was on the Internet. That it was on the Internet. So it's kind of like, yes, you can standardize the tools and it would be good to look at those and see what they do, but you always have to keep open the possibility that there may be others that might be particularly effective. Because these two tools that were used, when you look at the particle distribution, they were better than the standard tools that were used. And at the same time they were on the Internet.

So you think of standardization, but you

also have to keep that door open and realize that sometimes you may have to go outside of that, where it would be good to look at other outside of the standardized.

DR. LOSTRITTO: Part of the conundrum, and it's probably obvious to everybody here, maybe it doesn't even need to be stated, is that we're trying to write guidance in sort of the opposite point of view from when we usually write a guidance. We write a guidance because there's an expectation. The industry or whoever the audience is, is intending to follow the guidance to try and get some sort of regulatory pathway towards success.

Here it's the opposite. We're trying to write a guidance, and we know as soon as it hits the public view, that they're going to try to obviate it and get around it. And that every attempt will be made to circumvent it from those who -- from that certain sector of the audience who is going to be reading it to try and figure out what to do next. So it's a very difficult conundrum, but that's what we're stuck with.

All right, the second question. How can FDA standardize in vitro testing to help substantiate appropriate and consistent product manufacture that assures abuse deterrence at release and through a product shelf life?

And I'll just kick this off by saying we heard some very good comments today from public comments, and from Q&A session and so forth. And some of the things that came out would be something like a surrogate, or a sentinel I believe somebody used, a sentinel surrogate test, that could serve as an indicator that your abuse deterrent formulations are still abuse deterrent. And as Dr. Throckmorton put out, you know had me clarify, we're not talking about an exhaustive battery every time you need a stability time point.

So with that backdrop, I'll open it up to folks on the panel. Please, Karsten?

DR. LINDHARDT: So I think first of all, and I think that was also mentioned earlier today is really understanding your technology and understanding your formulation. And also understand your critical

quality attributes and being able to justify that. So I think it's not much different than anything else we do when we kind of characterize our product and shelf life, is that we of course need to provide the justification for the critical quality attributes of the product.

So that's really, you would say, a job for the industry to provide that evidence to the FDA in your review. And you know, that will be really product specific what that means. But I think that's the only way.

DR. THROCKMORTON: Yes, I get to ask questions, I don't get to -- absolutely out of my league, the technical stuff. It's been suggested that people form groups, industry, FDA, groups of various kinds. And I'm looking at you but anybody, are we thinking ICH, PQRI? Give me -- I'm trying to think of what format that kind of group might take.

DR. LOSTRITTO: There is a precedent. I mean I was thinking about the same thing too. So in another area of the industry where I worked, in aerosols, that industry got together and formed their

own International Pharmaceutical Aerosol Consortium for research and for discussion of topics of common chemical and manufacturing interests.

So and it's not PQR or ICH, but it's possible for the industry to do that among themselves and to create a forum where they can share their data in various ways so that you can expand a knowledge base, protect your proprietary interests, and so forth. I've seen that happen before in other sectors of just regular industry, and the (inaudible) too. Yes, yes. Anyone else have any -- please go ahead.

DR. YARSANI: For sure. Thank you. I think the generic industry working group kind of are in the same line as the FDA, some of the FDA speakers' point of view and also the brand working group point of view, with respect to conducting these studies, and the release and the shelf life of the product. That means by having a connection between, that we generate good development (ph) and identifying some tests that could be used as surrogates for ensuring the abuse deterrent characteristics of the product, the release and as well with the shelf life of the product.

So in a former way, what we want to present, respond to this question is, the generic product sponsor demonstrated a significant formulation and process understanding of their (inaudible) product during development. And that data is submitted in the ANDA to the Agency. This knowledge would enable us to identify some of the standard tests that could be used to ensure abuse deterrent characteristics during release and shelf life of the product.

This includes, for example, drug release from your polymer-based AD product, low volume viscosity of product in bio comparable solvents for gelling type AD product. For the technology of the AD product also provides for some standardized testing that could be used to ensure consistent manufacture of AD products. For example, SAF (ph) antagonist for agonist to antagonist type products, ISL (ph) for the (inaudible) agent, the hardness of a (inaudible) product.

That data demonstrating any characteristics of the generic product and some of the standard tests that are adequate, some standards are adequate to

ensure consistent manufacture of AD products. So the generic industry is of the opinion that there is no need to include in the QC testing the extensive battery of AD tests that are conducted during development.

DR. LOSTRITTO: Any other discussion or comment? Okay, we could go to the next -- I have to go to the next. All right. Topic 3. How can performance attributes measured by in vitro testing be quantified and linked to their impact on abuse deterrents? For example, discuss what amount of time delay in defeating an abuse deterrent property should be considered significant and the basis for the recommendation?

I'm going to let somebody else kick this one off if they want to.

DR. LINDHARDT: I actually have a question back on this one because I was not 100% clear, with abuse deterrence, does it mean real world abuse deterrence or does it mean abuse deterrence as it relates to the Category 1, 2 and 3 testing?

DR. LOSTRITTO: I think when we use the

phrase "impact on abuse deterrence", we're talking about in the field. And Sharon, I think that's the term we pretty much use when we discuss it.

DR. LINDHARDT: Real world, right?

DR. LOSTRITTO: Yes.

DR. LINDHARDT: So there's been some studies that are showing how much time an abuser would typically use to -- or there's been a study I think of (inaudible) and made some studies on that. And I think the outcome of that was about 15 minutes. But I think looking at that, this is a dynamic space. This will not be a static kind of number. As more abuse deterrent products comes to the market, that may change.

And so I think that kind of gives a challenge to all of us to kind of be dynamic in our relation to this entire area. And also when we do our studies, that at this point we should probably not just limit our testing to what is just -- what an abuser would do to kind of go through the 15 minutes, but really try to really -- and I actually see abuse deterrent studies as more characterizing the abuse

deterrent properties as it's really showing how abuse deterrent it is.

So to say from a real world perspective, because you don't know how it's going to be abused in the end, real world, so it's really to provide as much data to characterize the formulation from an abuse deterrence perspective.

DR. LOSTRITTO: I think the -- and I'm just musing so I'll probably get in trouble with both ends of the table here, Sharon and Doug. But this really is kind of an inside out sort of human factors analysis, if you think about it. Again, like a guidance is meant to elicit compliance, human factors usually involves people trying to use the thing properly. But this seems like it could be a subset of a human factors approach towards that by linking the in vitro testing to how that might relate to abuse, might involve the human factors expertise.

DR. THROCKMORTON: It's a great question. I agree, it's quite fluid in the way you said it. Look, human abuse potential study, and you know others can correct me when I get this wrong, but it's close to

human pharmacology. It's asking, does the pharmacology predict a measurable surrogate of risk for abuse? In this case it's human liking, visual analogue scale of human liking. It's just that's the test, right.

We're making an inference based on that outcome, that liking scale result about whether or not the product under the conditions that it was tested under is liked by, in this case, a set of individuals recovering from substance use disorder. And making a link between that to risks in the real world about, for abuse, understanding that there are a million other things in addition to that pharmacology that would influence the choices that those abusers make in the real world. Other things related to, you know, where they are in terms of their socioeconomic structure, their choices that their cohort makes, all of those things.

But using the visual analogue scale liking is our way of deciding whether or not the product, under those conditions as tested, has this pharmacology, has the properties. Other things may

mitigate that, and that's what you're talking about. You're talking about I think in those more real world social preferences or something like that. That's where human factors, I would typically put it. So it's after the pharmacology has been understood through human abuse liability, tested through what we would call human factors or preference testing, or you know whatever the right grouping is.

So you're right, they're linked but they're I think looking at slightly different things.

DR. HERTZ: So, just for the record. It's the recreational, the non-dependent recreational abusers that we enroll for some of these studies. And we're continuing to learn as we have more and more experience coming through with these products. Even since the publication of the innovator guidance, we're continuing to learn.

We've borrowed a lot of what we use for this type of assessment from other fields. So we're looking at understanding product performance, and we start off with how we characterize the performance of the product based on non-abuse deterrent products.

And then we're borrowing from that to see how we can stress and strain these formulations to look at these other considerations for trying to defeat the product for the purpose of a particular route of abuse.

Similarly we've learned from our products that even in the clinical studies, while it's important to know whether or not the drug will be liked, what we're really finding out is how much do they want, how important is it, or how likely is it for that person to want to use that drug again. The take [the] drug again outcome is one that seems to be distinguishing itself as particularly important. Because once you're able to get the opioid out, there's going to be a degree of liking. So how do we give that liking context? So we're learning more in borrowing these human abuse liability studies from the original use, which was in establishing abuse potential.

And I'm just -- so going back to the physical/chemical, which a lot of this manipulation discussion pertains to. We continue to learn, and that's why it's so challenging. That's why we need to

have as much input as we can. That's where the need for research is, to a large extent, to understand how these different relationships can be identified. For instance, is the relationship between particle size and positive pharmacodynamic outcomes linear? We actually have some data that suggests in some situations it may not be, because particle size and the other properties of the product may create a different performance characteristic.

How much does the delay factor count in terms of willingness to take the drug again? You know, so these are all things that we're learning constantly. And we're trying to get as much input as we can, with these meetings, we're going to advisory committee where we discuss these as much as we can.

So I think for the physical/chemical type of deterrence, it's going to be very challenging for a little while longer for us to learn enough to be able to potentially streamline the amount of testing necessary. So right now the concepts of stressing the formulation, seeing what it takes to defeat it, seeing how that's going to compare between the new generic

and the existing innovator, is going to be a bit of a learning process. And I think that the degree to which the excipients in the generic differ from the innovator is going to be a very interesting part of that learning process.

And when we get to some of the other areas though, I think it will be a little bit potentially different areas to learn from. So for instance, with the antagonists, is in vitro enough? What is the performance of the product after it's been manipulated for abuse in terms of the availability, the bioavailability of the antagonist?

Are excipients that are, in that context, intended to provide extended-release characteristics relevant for understanding if there's an effect on the pharmacodynamic outcomes?

So there's pieces to learn here, and I think that as we get more and more information about these different products, about the different behavior characteristics, about the results of different types of testing, we'll be able to develop more and more guidance and require potentially less extensive

testing.

For the aversive products, we're still waiting for some advances there, because it's a challenge, it seems, to be aversive only to the unintended population. So once we get some more information there, we'll be able to, again, increase our learning with that group.

The prodrugs, as discussed, you've heard a little bit, are going to be another area of learning as we grow in understanding of what it takes to potentially defeat that type of product. And then we are going to be even more -- have another opportunity for learning, another level, when we start to see these different methods and technologies combined, right?

So there's layer upon layer here where we are going to have to follow the innovation and the creativity there, and then learn enough to be able to translate and understand how to facilitate, to the extent we can, other product development, other product -- generic products, or just understand how to reduce the burden overall of the development of these

products with regard to the amount of testing.

DR. TOLLIVER: I think question 3 is one that's been around for a very long time, and I'm thinking of it from the standpoint of how much time for manipulation of a product and so forth. To me, it's a question that I don't know how to get around it or anything, because I keep thinking that is has to do -- we have to think in terms of who are we impacting? Who are these individuals who are trying to manipulate it?

And I find it difficult to say that the only population that we might be trying to impact is the -- what one speaker has called "the desperate population". In other words, that you picture them trembling to prepare that next dose and so forth. I understand that that can happen with heroin abuse and so forth, but how about the teenager that on a Friday night is rumbling through the cabinet and finding some pharmaceutical pills. He only does it on a -- you only do it on a Friday night or on a weekend or something. It's not continuous abuse. The casual abuser in other words.

How might that be different and how much time would they be willing to spend to manipulate a product versus someone who is really, I mean, very much dependent and is trying desperately to starve off withdrawal and so forth, and so they need to fix that next dose as quickly as possible.

I don't know where that difference stands and to what extent. And so I don't like to always think of us having to look at our in vitro studies from the standpoint of trying to get them done as quickly as possible and negating the fact that there might be a group of people who are actually willing and have the time and so forth, to spend more time to try to manipulate the product. I don't know where -- how that -- what the impact of that is.

DR. LINDHARDT: Yeah, I think that's a really good question. I think there will be a difference. I think there's still a lot of need for research in that area to really understand that. But there's definitely also a clear difference, you know, if a young person have found some tablets and put it in the coffee grinder, and then their mommy's coffee

grinder is then broke, because you have a very hard tablet as compared to other tablets out there.

So there's a lot of elements to that, that goes beyond just the time. There's the -- what's the impact on the tooling and so I think a more sort of complex research on the behavior of these different types of abuser population would be extremely helpful.

DR. YARASANI: Yeah, I, as the generic industry, I think as rightly pointed out by one of the panel members, it's (inaudible) got a straight answer. And we just got into this kind of development. So we, as a generic industry, we understand that the generic products should be no less abused different than the (inaudible) product. This includes the time and effort in defeating (ph) the products. And believe that, we also know that if we do the testing with the same rigor, the generic part should be no less abused than the brand product.

Of course, again, as Sharon mentioned, that the agency is also in the process of getting more data, more information, and coming up with some kind of guidance (inaudible) this kind of (inaudible). But

as generic industry, we need help from the agency by outlining testing required and the acceptable criteria with the reasonable ranges for different testing outcomes. I think at this point as well, we are with respect to this particular question.

DR. LOSTRITTO: I just want to respond quickly to something James said; it's a very interesting point. But I'm not so sure that the casual abuser is really at low risk, because if they're opiate naïve and they manage to defeat two or three MR tablets, or if they're taking it with alcohol, doing something other than a more experienced abuser might know not to do, I'm not so sure they're at less risk necessarily.

DR. TOLLIVER: Less risk of what?

DR. LOSTRITTO: Compared to the dedicated or serious abuser. I'm not sure that they're at less risk.

DR. TOLLIVER: Yeah, I'm not necessarily talking about at risk. I'm talking about their willingness to still go forward with additional time, whatever it takes, in order to prepare the drug if

they want to use it. That's what I'm really getting at.

MR. RAULERSON: Yeah, I think Dr. Tolliver raised a really interesting point. The way I'm thinking about it is that we potentially get a bigger bang for our buck if we can stop that sort of gateway abuse, the teenager stealing pills.

An earlier presentation today about Safe Lock, of course any desperate abuser would just deal with the entire container and break it open. But the policy benefit of stopping a hardcore abuser from abusing a pharmaceutical is very -- look, because they are going to find an illegal alternative. Whereas the policy benefit of stopping a recreational casual abuser who has not initiated, is potentially much more significant. I think that we should definitely keep that in mind, that we really want the market to, at the very least, stop -- make that form of abuse much more difficult.

DR. LOSTRITTO: All right. If there's no more comment, we'll move on to the next question. How can FDA build flexibility into standardized testing so

that it may be suitable for application to emerging technologies? Are there any specific emerging technologies that might require new types of testing?

I'll just kick that off by saying you know we -- it's part of our responsibility to search out and learn about new technologies. Some of it comes to us, some of it we seek out and learn through our own reading. And one way to address that in the guidance is that as new technology emerges, that its evaluation has to be pointed at its mechanism, whatever that particular new mechanism might be.

And that sounds overwhelming general, but that statement, in and of itself, starts pointing the way for new technologies, some of which we know about, like I said through our own public domain information and some we can't comment on, but I'll kick it off with that and see what others want to say.

DR. YARASANI: Yeah, as the term emerging technology indicates, they are emerging, they're not there yet. Some of them are maybe proprietary to some of the brand companies and the agency may have some of those emerging technologies with them.

And as the generic industry, we are willing to do whatever it takes to comply with the public safety expectations of how this will be (inaudible). As you know, as such the (inaudible) products are complex and that (inaudible) for the industry and these technologies are evolving within the last few years, and it is natural to expect that new area technologies would emerge in the near future.

But the generic industry will use good science to develop these emerging technologies best to any products, but we need, of course, we need help from FDA. With priorities and clarity around expectations for these products, the generic industry will be able to more successful in making affordable quality generic area products available to the patients.

This calls for an ongoing collaborative interactions among FDA, generic industry, and other potential stakeholders. Any potential gaps we would see between the new technology and the current guidance, could be addressed through, probably as you mentioned, maybe a technology specific guidance or a

platform specific guidance, part (ph) specific guidance. I think that is the generic industry's kind of approach to this question.

DR. LINDHARDT: Yeah, no, I agree to the collaboration. I agree to product specific guidance of some of these, but I think there's need for flexibility also in a non-emerging technology. I think the flexibility is really in the way we are testing these products, because the material properties are so different that we would need to have room for flexibility whether it's emerging or not. Emerging technologies, also technologies we don't know yet, right, so it should cover all of that, but I think that also means that we should build in -- there should be flexibility in all the test protocols that we make, or at least the second iteration stuff.

DR. LOSTRITTO: Any other comments to this particular question? All right. I think that's all the specific questions that we have, and I guess we should move towards closing it out, but I have a few comments I'd like to make before we close it out.

I want to thank everybody for their

participation, not just on the speakers and the panel. You want to say something, Doug? Okay. Not just the folks who spoke, we're very grateful for, but also the public comments and the Q&A session, and just your active participation in the audience and some of the hallway questions and so forth.

You know as I said earlier today, we -- I came to this meeting with a clean sheet of paper about moving to the next guidance, and I really appreciate some of the feedback I got in some of the areas on controls and stability and what sorts of information we might look at for correlation, flexibility, new technologies, and so forth. Seeing your concern and interest in how to do that was very useful.

So I want to thank you all for that very much, and Doug if you have a few comments now. Thank you for letting me finish.

DR. THROCKMORTON: Yeah, thanks Rik, and thanks to Rob and thanks to everybody that worked so hard to organize this. Thanks to everyone that came over these last two days. So I've been collecting descriptions of what you guys are all about.

Let's see. Everyone agrees it's important. And there's no humor in that. Everyone agrees this is an important issue. Interesting journey. Challenging conundrum. Conundrum actually shows up in more than one person's description.

And someone called it a Loch Ness monster. I'm not exactly sure who that was or under what circumstances. Anyway, that was -- so lots of interesting descriptions of the task that you have before you, which is obviously to sort of balance the need for scientific assessment to support appropriate decision making, and the interest in supporting predictable product development, both generic and innovator.

I'd say the meta-theme I'm hearing is the sort of tension between standardization and individualization, and it played out in one way or the other in pretty much all of the discussions that have occurred in the last two days.

The other tension, I'll just acknowledge, because I think it's pretty evident, is the differences between the brand name and generics

industry here. And I recognize those are not polar or diametric or anything like that, but there is this -- that is another tension that we're all going to have to acknowledge in trying to find a way to work through and so I feel like it's worthwhile saying.

People have said many things. One size cannot fit all. Essential to provide a roadmap to the development. But we all recognize there are challenges. So we all recognize the challenge of this being in an early stage of scientific assessment. This is a manufacturing science that's new, and so there's a lot we don't know yet.

Observations have been made that small changes in apparently the same formulations, can apparently have large effects in terms of product performance. Well, those are the sorts of things that you'd like to understand better if you're going to try to provide standardized information and recommendations.

Observations that there are a lot of important things we'd like to know and understand better and one of the things we just talked about.

This relationship between pharmacokinetics, between exposure to drug, and risk for abuse, whether it's risk in the form of assessed as a liking study or risk in the form of real world impact. We need to know that relationship better than we do at present.

We needed to know it -- we signaled that when we put out the brand name draft guidance, now whatever four or five years ago, and it's still something that we need to know better. Dr. Dayno talked about the organoleptic nature of abuse deterrent formulations testing, by which he meant that there are other sensory things that impact the assessment of these products that make them particularly challenging. It isn't a matter of simply measuring an exposure, an amount of something. I did have to look up organoleptic. Maybe others knew what that meant.

Assessing the effort used to abuse a product has come up in several contexts and people have pointed out that that's not a thing that we've typically tried to measure when we assess or compare products, and identifying what's an acceptable failure

rate. We all know that products, by their nature of being manufactured, fail at some rate. The question is what's an acceptable rate from a social or scientific perspective.

Solutions have been pretty varied, I would say. Many of them reinforced the value of the guidance, but then go on to make some suggested amendments to us that we'll take into account. People talk about the need to broaden it beyond the crush resistant and extraction resistant technologies. The need to talk about the impact on manipulated products as well.

And the one unanimity, you all called for product specific guidances, both industries I should say. Although it wasn't exactly clear you were talking about the same content in those documents. That's at least a place to start, and I would say is the one suggestion that I think we should all leave with, which is you should be working together, to the extent that you can. To the extent this meeting that -- this group that people have suggested can be put together and found a way to be constituted

appropriately in all of that. Finding a way to talk past the challenges and finding proposals to give to us.

You know obviously if you all came up with a single approach that you thought would suit the best purposes of product development here, we'd be absolutely delighted to see that and take it very seriously. It would move the field a great deal. That requires sort of careful collaboration and things, but those are the kinds of things that have been materially successful in other settings. I'm thinking of drug-eluting stents and other places that I've seen where similar challenges have come up and industry's been able to pull together and come up with suggestions that we've really been able to make use of.

So I'll close just by thanking you all for being as open as you have been. I hope nothing that I -- you take nothing that I said as being critical, because saying what you think, making the suggestions to the extent you have, is absolutely essential for us to decide what needs to happen next. Really

appreciate that. Appreciate the groups that came together and answered the questions that we posed. That's really helpful for us, even if those answers are not in sync with one another, it's really useful for us to understand where you all are coming from.

Look forward to having additional conversations. Appreciate all of your help in everything, everyone's participated. And I hope everyone has a safe trip home.

DR. LOSTRITTO: A couple of very quick housekeeping points. Please remember to take all your personal stuff with you, because it all goes up on sale to eBay after you leave, if you leave it here. And remember that the docket to receive comments relating to the issues discussed at this meeting will be open until December 1st of this year. Thank you very much.

(Whereupon, the meeting was adjourned.)

CERTIFICATE OF NOTARY PUBLIC

I, SAMUEL HONIG, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

SAMUEL HONIG
Notary Public in and for the
State of Maryland

CERTIFICATE OF TRANSCRIBER

I, CINDY MCALLISTER, do hereby certify that this transcript was prepared from audio to the best of my ability.

I am neither counsel for, related to, nor employed by any of the parties to this action, nor financially or otherwise interested in the outcome of this action.

November 11, 2016 _____

DATE Cindy McAllister