FOOD AND DRUG ADMINISTRATION

DEVELOPMENT AND REGULATION OF
ABUSE-DETERRENT OPIOID MEDICATIONS

Public Meeting

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Opening Remarks – Douglas Throckmorton

DR. THROCKMORTON: Good morning, everyone. Happy Halloween, question mark. Welcome to the second day of the meeting. We are going to be starting. I am going to make a few opening remarks, and then we'll be having some speakers, and then an open public hearing in this first session.

We understand everyone's interest in getting back to your homes for Halloween and things like that. And so, we are working to keep time close to make certain that we respect your time, and we get you out early this afternoon.

I am going to begin by making just a few framing remarks, remind you what we talked about yesterday. So yesterday, I talked about two public goals that framed everything that the FDA was doing around abuse-deterrent formulations as well as opioids and their safe use writ large.

Those two public health goals I think I just
want to remind you of because I think they're going to help inform the conversation we're going to have today. They are, first and foremost, providing appropriate access to pain medicines for patients who need them, including opioid drugs, and second reducing the misuse and abuse of prescription opioids. So that's the first set of goals to keep in mind as we think about the things we're going to talk about today.

The second set of goals that I also went through yesterday were the goals that we have laid out for the FDA that Dr. Hamburg -- that Dr. Woodcock have laid out for us around the development of abuse-deterrent formulations specifically, a twin set of goals there, too.

Incentivize the development of opioid medications with progressively better abuse-deterrent properties, and support their widespread use, and assure the appropriate development and availability of generics, reflecting their importance in the marketplace. I'm saying them again just so that, as we go forward, we remember
that that's the framework that we're working within at the FDA, and then, obviously, many other important questions come from that.

So for today, we are going to be focusing on the overarching policies that underlie the actions the FDA looks to take in the future, so how to support appropriate development and use of abuse-deterrent formulations, starting with a framework of potential actions that the FDA could take.

I am not going to walk through this slide in great detail, but if you remember yesterday, Dr. Woodcock in her talk laid out a possible framework for action, beginning with a level of evidence required to get something into a label, put information into a labeling about a product and its abuse-deterrent formulation characteristics, ending with actions that the FDA might take on a much broader scale against classes of products.

This is the framework that we're going to be interested in having conversation with you about today. We're interested in your comments on the
kinds of things we would need to do before thinking about taking some of these actions, the incentives that we might want to put in place before thinking about these actions, the unintended consequences that we need to avoid as we look to think about these actions.

We are going to be talking first. Dr. Hertz is going to be talking, and she is going to be reviewing some of the actions that we've taken to date. Yesterday, when I talked, I pointed out, I think appropriately, that, for the FDA, those are opportunities for us.

Actions that we are given to take are opportunities to clarify our thoughts, make policy decisions, and then make them public, help others understand the road that we're walking, if you will. She's going to be talking through those and try to tie those actions to some of the questions that we're interested in having you talk about this afternoon.

Then the second set of questions, questions about prioritizing these future FDA actions and
incentivizing them, how to do it appropriately, how to do it without unintended consequences that would harm one or more of those goals that I talked about at the beginning.

So with that, I'm going to turn the podium over to Dr. Sharon Hertz. Dr. Hertz is the new director of the Division of Anesthesia, Analgesia, and Addiction Products at the FDA. And, Sharon, thank you for coming.

(Applause.)

**Presentation – Sharon Hertz**

DR. HERTZ: Thanks, Doug. So this is a sketch of what I'm going to discuss today. But I think what you'll see now is a theme of repeated slides. And that's important because these are areas of emphasis for focusing what we're going to discuss today, but also important areas for us that we're developing internally as well.

So I'm going to go over some of the important background items just to help frame the conversation. I'm going to discuss some of the premarketing data challenges we have, some
questions concerning postmarketing data, which we're not discussing today, but I think it's important to have the picture in general when we're thinking about these things.

Then I'm going to go through what our experience has been so far. And I can tell you, we are learning along with industry how this is going to all fall out. It's really been an interesting journey. Then back to that possible regulatory actions piece and some future challenges that we are going to have to work out.

You just saw this slide, so I will not spend a lot of time on it. But, it's very important for us to incentivize further incremental change over time, and that's going to be a lot of hopefully our discussion today, but also recognizing the importance of having the availability of generic products and understanding their importance in our healthcare system.

So we posted a draft guidance for the development of abuse-deterrent formulations back in January of 2013, and we got a lot of input in that
docket. And we are still working on it and editing the guidance. So we hope to have that out in the not-too-distant future, and we've got a lot of good feedback and really clarifying quite a bit.

So what sometimes seems to be misunderstood in the public discussion here is what does abuse deterrent mean. And it means -- a product with abuse-deterrent properties is intended to reduce abuse. It's not synonymous with abuse proof or entirely preventing abuse. And that would be a desirable goal, but in order to support labeling, what we're looking for are incremental improvements over time. I feel like you folks are going to -- I'm not ignoring you. I just have to see the screen over here.

The reason why abuse proof is an unlikely ultimate goal is the fact that opioid analgesics have to be able to deliver an opioid. And inherent in the pharmacologic effects of opioid, of course, are the possibility of euphoria and the development of physical tolerance. So that's why a lot of times, when we're talking about the future of
analgesic development, we are also really interested in new classes of drugs. But opioids having the prominence they do in our current healthcare for pain, these efforts are going to be incredibly important to try and make them safer.

Generally, we see three routes of abuse. Oral is the most common, period. And that could be oral attacked, oral manipulated. Nasal and intravenous routes of abuse vary in frequency depending on what the drug substance is, what challenges may or may not be present in the formulation, and whether the product is in combination with a non-opioid.

I'm not going to talk about smoking or inhalation. It's a little bit different, and most of the efforts we're seeing right now are focused on these three routes.

It's still very early. I mentioned that we're learning. And we're learning based on the work that industry is doing as well as some of the academic work. And not only are the technologies early, but our understanding of the clinical
impact, the epidemiologic impact, and the statistical methods for evaluating those, they're all new. We're not entirely sure how we're going to assess this over time. We're still developing those methods.

So we're taking a product-by-product approach. I can tell you that, in the docket comments, a frequent comment was the request for a bar, an absolute bar to call something abuse deterrent. And I can tell you unequivocally, I doubt there will ever be, an absolute bar, because it's going to change over time based on what's out there. We're going to evaluate each product based on the setting in which that product emerges.

Ultimately, that's also, in part, to incentivize continued improvement. If we set a bar, everyone will reach the bar, and then we have to refigure the bar. We want this to frequently -- we want to see change over time as the technology improves.

It would be great if ultimately all opioid products had features that would reduce abuse. I'm
not entirely sure if this is possible for all of
the IR products, but perhaps for the ER.

So again, the bar issue. Some of the
important principles when we are evaluating
programs, the known routes of abuse -- and some of
you will be cringing because we have had these
conversations over and over. But it's important
for us to understand what's done with the product
now and what we can anticipate based on
intervention. So we'll question the value of a
barrier for intravenous route of abuse for a
product that has little intravenous abuse.

So for instance, some of the combination
products with non-opioids or the relative safety of
the different routes of abuse. If a product is
very good at preventing nasal abuse and that shifts
behavior to intravenous abuse, that's not
necessarily serving the public health even though
it's a demonstration of an abuse-deterrent
property.

Then the next step is we will look at what
the actual data show and how that reflects what was
intended and what the studies actually were capable of showing. So part of that evaluation is, was the in vitro manipulation adequately evaluated so that the test conditions for human abuse liability studies were appropriate? Again, the routes, and then of course the magnitude of effect.

What's ideal is if we have a comparator, not just an API or IR product, but other similar products that are on the market, either the existing non-abuse-deterrent product or ultimately any approved abuse-deterrent formulations. And we are looking at whether there are viable ways for doing cross-study comparisons, perhaps when there's a common comparator, but we are not entirely sure how much weight these cross-study comparisons should hold, given that these tend to be small studies and we all, I think, know the risk in cross-study comparisons with small studies in particular.

Then we need to weigh the different effects on the different routes of abuse. So the premarketing data are an attempt to predict future
behavior. We get a sense of what a product is capable of doing, but we also know that the community in which this is targeted, the abuse community, is very creative. And we also know that any intervention may result in a shift in behaviors that is not always predictable.

So that's why postmarketing evaluation is so important and all these products, as was mentioned yesterday, have a postmarketing requirement to continue to evaluate the effects of the abuse-deterrent formulation on abuse once they are marketed.

This is some of the language from the standard PMR that we issue. It basically says, "Go out and study this." And it doesn't necessarily say how because that's part of what we're trying to work out, spending a lot of time and resource trying to figure how to create these studies, how to evaluate these studies, and, again, it's an ongoing learning process for us, got a lot of good people working on this.

So I'm going to go over now the experience
that we've had with some of our labeling, based on
the results of abuse-deterrent products, studies
that have come in. So I'm going to talk about
these three, OxyContin, Targiniq ER, and Embeda in
particular.

OxyContin, an extended-release formulation
of oxycodone, was reformulated in 2010. But there
was no abuse-deterrent language in the labeling at
that time. And it's a much more extensive
discussion than I am going to go into now as to how
that came about. But the common theme here is that
in spite of having in vitro and human abuse
liability study results that had some reasonably
good results, we had no context back then for what
to do with this.

So we took a very conservative approach.
Language reflecting this type of data was included
in 2013, in part because we had some postmarketing
data, although -- and I have to emphasize -- this
was very early postmarketing data. And any of the
postmarketing data that I discuss referable to
these actions we've taken has been not conclusive,
but very early.

But it was suggestive that it supported the relevance of the premarketing data. And we went ahead and labeled the product with language for the nasal and intravenous routes of administration. Then at about the same time, the original formulation was withdrawn, the NDA, and we made a determination that it was due to safety relative to the new formulation.

This wasn't on the last slide, but it's on -- or two slides ago, but it's on this slide, just because many of you may be aware that this product has also been reformulated to have abuse-deterrent properties. And again, very similarly, we had some data at the time it came in, but we felt we didn't have adequate context, and even earlier postmarketing data than I had mentioned before.

So the earliest postmarketing data did not tend to support the premarketing study results. And out of an abundance of caution, we felt we needed to really watch this type of situation, that
if we have some type of discordance, that's really
going to influence our thinking about what we know
about how to interpret premarketing data. This
original formulation was withdrawn, but there has
not been any determination that it was due to
safety.

Targiniq is a fairly recent product to reach
the U.S. market. And it was approved with abuse-
deterrent language based on premarketing
evaluation. This is, I think, in part reflective
of the increased experience we are starting to have
with the premarketing data. And you'll see there
are no comparative data in the label for this
extended-release oxycodone compared to the existing
one.

I said a few slides ago that we thought that
was extremely important, but we felt that the
results here were fairly robust. And we felt that
it was suitable for being included in labeling.

This is the part, I think, that gets very
frustrating for those of you in industry because,
how can you predict how we'll interpret the data.
And it's a little frustrating for us as well, but because this process is a continuum of building on experience, the best I can say is, we will try to have these conversations as early as we can with you, based on data that you share, and try and make sure that we have cleared the way for your expectations to be based on our thinking at the time.

This product just is a little different than some of the others. There may be some questions about regulatory actions that we are discussing. I will say this product has some limitations. Based on the fact that it's a combination with naloxone, it's got an upper limit of a total daily dose of 80 milligrams on the oxycodone side. That's important as we think about the place of this product and others on the market.

Embeda was approved in 2009, and this is a combination product in which the naltrexone is sequestered. The naloxone and Targiniq is not. In this case, it is. And we put something in the label. Now, of course, 2009 is before 2010 if
you're watching my slides closely. I don't want you to think I'm not aware of some of these contradictory statements I am making.

But what you will see is that, for this one, we put some data in Section 12, under pharmacodynamic in the Clin Pharm section, because we thought it was very interesting data. But it came with a big disclaimer. So we didn't actually allow any abuse-deterrent claims at this time, again because of the lack of context.

I mean, we tried to be very clear, so the statement that there is no evidence that the naltrexone in Embeda reduces the abuse liability of Embeda, I think is pretty clear.

We have updated the language, and we don't spontaneously go into -- well, sometimes, we do. But in this case and some of the others, we didn't spontaneously update these labels. These were based on discussions with the company.

But we did recently approve language that was consistent with the current draft guidance, so it's been reorganized and reconfigured. Everything
is now in Section 9, which is where this is all landing, and the disclaimer was removed. I'll show you in a bit what has replaced that as some of our standard language.

So there's been this sort of progression of thinking based on our experience. First, we didn't have any language based on premarketing data. Then we had some postmarketing data. Then we had a strong disclaimer, and then we updated. And here is some of the language now that goes into these package inserts, that abuse of the product by these routes, meaning reflective of what the labeling has, oral, nasal, or intravenous, as well as by whatever hasn't been demonstrated.

So for instance, if you have a product that has an effect against the nasal and intravenous routes, we'll say that abuse by those routes are still possible as well as by the oral route because, obviously, we don't want any misunderstanding of the data. And then additional data, including postmarketing epi studies when available may provide further information on the
impact. And that's reflective of what we hope to get from those PMRs and that there may be further updating of the section.

I'm going to talk about this first bullet a little bit more later, but part of our thinking of products that have been coming in is we're starting to get this idea that an abuse-deterrent effect in one route may shift behavior to a riskier route.

So if you have a good nasal effect, but not so much on the intravenous, is that a public health benefit since intravenous carries additional risks, not just risk of overdose, but transmission of infectious disease? So that's part of our thinking. And then of course, most recently, we went ahead and labeled a product that had nothing postmarketing, but some data that we felt we had confidence putting in.

Looking for cringes around the room, immediate-release opioids offer their own set of challenges in the abuse-deterrent market. In particular, with an extended-release product, generally, an approach to abuse is going to focus
on defeating the extended-release properties, trying to get that drug out in a hurry.

For oral abuse, there's really no need to manipulate an IR product. Right? It's designed to deliver the product without a delay, most of them. However, for nasal and intravenous routes, there's still a need for manipulation. So that's one issue.

Also, IR strengths tend to be lower. I know there's overlap with the ERs, but they tend to run lower, particularly when they're in combination with a non-opioid. And that has an effect on understanding abuse patterns and routes of abuse.

So for instance, when it's in combination with acetaminophen, acetaminophen may provide something of a deterrent effect based on the route of abuse. So we take that into account, and that has to be taken into account when the human abuse-deterrent studies are designed.

Then we have a whole group of oral solutions here, which have some very important clinical settings where they are used, not the least of
which is hospice. But so far, this isn't something we've seen much exploration in, in abuse-deterrent oral formulation. And I am not entirely sure that's ultimately going to be suitable. We'll see what comes up.

So this should look familiar. This is the possible framework of abuse-deterrent claims, some of the regulatory conclusions that we are hoping to achieve over time. First is the data sufficient to support a claim. And we are starting to get there now. We have labeling out there with clear abuse-deterrent claims.

Then we have data that's sufficient to block approval of other drugs with the same opioid that lack the same abuse-deterrent property. Well, I know that's going to have an impact on people who have been engaged in developing the product over a number of years, but if we're going to be able to conclude that abuse deterrence is a safety feature, then we don't want less-safe products coming out.

Then what level of data is sufficient for FDA to take actions against existing products with
the same active ingredient? And there is this asterisk of what those actions could be, including withdrawal of the non-AD formulation or imposition of a REMS, with methods to improve the safety, given that that product lacks the AD properties.

Then what about the standard for when we say it's time for the whole group to have abuse-deterrent characteristics? Will we get to a point where there is data that says the benefit from these formulations is sufficient to now impose it on the class? And what that class consists of hasn't been defined. So is that going to be the whole group of extended-release products or is it going to be opioids in toto?

How are we going to ultimately communicate this? This is a completely made up possible example of one type of thing that could happen in the future. So I hopefully will not get questions next week about where the guidance is for developing this.

(Laughter.)

DR. HERTZ: But obviously, we're here to see
products that have different characteristics. This scale is meaningless, by the way. I just couldn't figure out how to get rid of the numbers.

(Laughter.)

DR. HERTZ: But what we're going to see are products that have more or less abuse-deterrent properties for different routes. And here's the question. If Product 1 has these relative proportions based on their internal studies, does the size of that blue box in product 1 have any relevance for the size of the blue box in study 2?

We don't even have an absolute way of comparing. So the boxes here look the same size. In fact, they are, but we wouldn't know without a clear standard if they actually meant the same thing. It's just proportional within the drug.

Also, the first two products look to have the same amount of abuse deterrence. Right? But again, that's meaningless. There's no way of relating right now those two columns.

So we ultimately do want to have some sort of framework for a couple of reasons. Abuse
deterrence is a big concept. There are many ways of demonstrating different abuse-deterrent effects, but how do we convey this to a field of healthcare professionals who really are not as enmeshed in this as we all are?

If you have something that has a tremendous effect in one route relative to something that has a tremendous effect in another route, how do we weigh that? So these are some really big and interesting questions that we're going to have to tackle over time.

So we have some basic idea now of how to approach an evaluation of abuse deterrents and how to include some of this in labeling. In some cases, we have postmarketing data that supports the premarketing findings, and that is very helpful. But it's clear that the decision-making is going to remain very complex, as this is an evolving field.

I know you thought conclusions would be the last slide, but I have more questions for you. So premarketing methods, we still need an understanding of how to figure out when those blue
boxes are comparable.

So what are the standard methods that we can start to use? I know there was a lot of discussion yesterday about whether we could have standardized testing for in vitro. But think about it in this context of how we have multiple products out there and how we're going to know how they compare, and that might be one of the values to developing some standardized testing in that arena as well as for the clinical studies.

There's a lot of work that needs to be done to figure out how to do the postmarketing evaluation. So as different groups and people out there continue to think about this, we are always interested in hearing any thoughts or developments on how this can be approached. And then, of course, how we're going to ultimately communicate this to prescribers and the public is something that needs development.

So we're going to have a series of topics for discussion today, and I am just going to paraphrase them quickly here. What is meaningful
abuse? It sort of relates to how big does that blue box have to be to have some meaning?

We have to always think about that in the context of the route of abuse, the product strength, IR versus ER. And what we ultimately hope to do is develop a weight-of-evidence approach for products with different effects on the different routes.

How do we support and incentivize improvements over time? And just as importantly, how do we avoid actions that could inadvertently hamper development? We are thinking about that as well.

It's very important that we try not to cause harm as we try to improve the safety of this class of drugs. And we heard, I think pretty eloquently yesterday, from some patients and patient groups about the importance of minimizing possible negative impacts of transitioning to abuse-deterrent opioids, patient access, the effect on products that are under development, and others that we may not yet have anticipated yet.
So I will turn it back over to Doug. Thank you.

(Applause.)

DR. THROCKMORTON: Thank you, Sharon, very much. I am looking across the room for our next speaker. Bernie, you are here. Excellent.

So now we are going to have three presentations, one from Dr. Good from the VA -- and I'll introduce him in just a moment -- and then a presentation from the group representing branded industry, and a presentation from the group representing the generics industry, beginning with someone I've had the good pleasure to work with for many years.

Dr. Good comes to us from the VA. He is a professor of medicine in pharmacy at the University of Pittsburgh. He is also on the medical advisory panel for the Pharmacy Benefits Management program in the Department of Veterans Affairs and is their co-director for the Center for Medication Safety.

He is a member of the Drug Safety Board at the Food and Drug Administration also and a member
of the Therapeutics Information and Formulary Support Expert Committee -- that needs an acronym of some sort -- at the USP. Bernie, thank you for coming.

Presentation – Bernie Good

DR. GOOD: Thanks so much, Doug. And I appreciate the invitation to speak. I can't state enough how much we appreciate the collegial relationship that we have between the VA and the FDA, and it's really been terrific. And so thanks for asking to hear our opinion here.

So I wanted to start with disclosure. I have no conflicts of interest with pharmaceutical industry. However, I do chair the Medical Advisory Panel for Pharmacy Benefits Management for the Department of Veterans Affairs. So take that into consideration with my comments.

I wanted to give a few words about the VA. I am sure most of you are familiar with us. We are a staff model HMO-type organization. It's a comprehensive healthcare system. We have direct providers of care. Providers are employees. We
own and operate our infrastructure. And importantly, our prescription drug benefit is integrated, not added on or contracted out.

As of the end of fiscal year 2013, we had 152 hospitals, 990 clinics, including 821 community-based outpatient clinics. There are 22.7 million total veterans, 10 percent of which are women. We have 8.8 million enrollees, 6.3 million patients treated, and 4.8 million pharmacy users each year.

Looking at the pharmacy numbers, we have 267 million outpatient prescriptions. That's 30-day equivalent, most of which are provided through our mail order and some through our local facility pharmacies. And our outpatient drug expenditures are 3.3 billion.

So we have quite a bit of opioid use in the VA. In fiscal year 2013, we had 7.1 million opioid outpatient prescriptions. Those are 30-day supplies, most of which were generic, 1.1 million unique VA patients who received at least one prescription of an opioid during that year, and we
spent $89.4 million on outpatient drug expenditures.

I give this number just to give you a magnitude. We're one organization, and using mostly generics, we're still spending $89.4 million a year. If we were to go to abuse-deterrent opioids with an all-in policy, it would cost the VA hundreds of millions of dollars, more than likely. So a consideration for us has been the cost, and that hasn't been discussed much heretofore about the cost implications.

The VA is very interested in safe and effective use of opioids. We have an opioid safety initiative. In August of 2012, the VA Undersecretary for Health charged a task force to develop a short- and long-term plan to deploy an opioid safety monitoring system and to ensure opioid pain medications are used safely, effectively, and judiciously.

In May of 2013, we developed and implemented regional opioid safety initiative pilots. And then as of August 2013, this OSI, this safety
initiative, was expanded to all VAs. In 2014, we added naloxone kits for opioid overdose reversal to our national formulary to be provided to at-risk veterans.

This opioid safety initiative provides report, which give national-, regional-, facility-, provider-, and patient-level reports. We look at average dose per day of selected opioids. We look at concomitant use of opioids and benzodiazepines since that greatly increases the risk. We look at overall opioid utilization. We look at patients receiving long-term opioids and the presence of urine drug screens, and we look at the dose based on morphine equivalence.

These are some of the results that we've seen since we began this opioid safety initiative. And you can see that, over time, we've had 50,000 fewer veterans from the end of fiscal year 2012 to the third quarter of fiscal year 2014, 50,000 fewer veterans who were receiving opioids during that time.

If we looked at morphine equivalence,
Dr. Amy Bohnert from the VA published some papers looking at safety of opioids and looking at the average morphine-equivalent dose, and as expected, found that unintentional overdose and death greatly increased as daily dose of opioids went up. And a cut point was around 100 morphine equivalents.

So we've looked at that, and we've tried to evaluate those veterans who are on 100 morphine equivalents or more and to encourage providers to work towards safe and appropriate use. We're not saying that it's inappropriate that patients be on high dose, but this should cause us to step back, and take an additional look at those patients, and make sure we're doing it.

So you can see here, looking at the veterans, we had 59,000 veterans that were on greater than 100 morphine equivalents. And over a couple years' time, it's dropped down to 52,000.

So thoughts about abuse-deterrent formulations for opioids, we do support the development of abuse-deterrent opioid formulations for all products, including generic formulations.
And we're extremely interested in supporting safe, effective, and responsible use of opioids.

I have already mentioned our opioid safety initiative and then the naloxone rescue kits for at-risk. We already have reports of where these naloxone rescue kits have been used successfully within our system, so we are very encouraged by that.

I would also point out that the great majority of veterans receiving opioids are not at risk for diversion or misuse by crushing, smoking, snorting, or shooting up. I tried to find, of all these opioids, what percentage are felt to be diverted for these illicit uses. And that number, at least I was unable to find it. But we know that the number of patients that actually abuse drugs this way is a very small percentage, both within VA and outside the VA.

The point is that converting all opioids to an abuse-deterrent formulation would be quite costly to the VA. Now, it may be the right thing to do, but we would like to have adequate evidence
to support great expenditures to us. And if it's going to cost us a lot, it will cost every health system quite a bit of money.

We do favor widespread availability for both product formulations, that is, abuse-deterrent products as well as current products, but -- and I am speaking for pharmacy benefits management at this point -- providers should be able to prescribe either product formulation, current products, or abuse-deterrent formulation products based on clinical assessment for risk, for abuse, or diversion.

I have here, "more research is needed," in quotes because it seems like every paper you ever read or presentation, they end up, "more research is needed." I think it's quite important that we have more outcomes research.

So there's been a lot of talk about looking at whether these products decrease abuse, but the focus so far has been on individual products. So if you take OxyContin's abuse-deterrent formulation, yes, it looks like that product is
being abused less frequently.

So you can look at the evidence for an individual product, and I think that's quite useful. But I would also say we need to understand better what the evidence is, that by making these products to have abuse deterrence, whether that will decrease for society, at a societal level, whether you decrease abuse, and more importantly overdose, unintentional overdose or intentional overdose, and death. At the end of the day, these are things that are most important.

I realize that the second type of research is not easy, and so I would encourage the FDA to engage substance-abuse experts. I'm not sure if substance-abuse experts are part of this group today, but engage the substance abuse expert community in trying to develop appropriate studies to come to this, to get better information.

For me, it's encouraging that I think we have time to do the appropriate research. I heard yesterday, projecting to 2020. So hopefully, by the time there would be legislation that might
mandate that all products, talking about all in or not all in, hopefully that there will be time for us to do he appropriate types of study to get this answer so that we know, as a society, it is worth investing all the money that this policy will take.

Thank you very much.

(Applause.)

DR. THROCKMORTON: Thank you very much, Dr. Good.

The next speaker is Dr. Marina Brodsky, who comes to us from Pfizer. She has a PhD in neurosciences and pharmacology from Cornell University Medical School and has worked in a variety of different areas of the pharmaceutical industry. Thank you for coming.

Presentation – Marina Brodsky

DR. BRODSKY: Thank you very much.

Hello. My name is Marina Brodsky. I work at Pfizer, but today, I represent the Branded Industry Working Group, including 14 companies listed here involved in the development and/or marketing of innovative abuse-deterrent opioid
analgesics.

On behalf of that group, I would like to thank the agency for the opportunity to share our recommendations on the actions needed to advance the development and adoption of abuse-deterrent opioids.

This audience certainly is well aware of the prescription opioid abuse reaching epidemic proportions in this country. And there is an urgent need to develop new, efficacious, non-opioid options to treat pain. However, until these new treatments become available, and possibly even after these treatments become available, opioid analgesics are likely to remain an indispensable component of pain therapy.

The Branded Industry Working Group shares the FDA's vision of the future in which most or all opioid analgesics are available to patients who need them in formulations that are less susceptible to abuse. And the sheer magnitude of the crisis of opioid abuse, misuse, diversion, overdose, and death is now. We really don't have the luxury of
waiting for this future to come around.

The FDA has been unquestionably in the forefront of efforts to advance the development and adoption of abuse-deterrent opioids, and we want to thank the agency for their leadership. This is a phenomenally complicated field, and I think it's very clear, based on the discussions yesterday, if you were here, it's very complicated. And significant progress has been made, but more can and should be done.

Importantly, continued innovation in this area requires concerted action by numerous stakeholders in addition to the FDA. And some of these stakeholders were indeed identified in Dr. Woodcock's remarks yesterday morning.

The Branded Industry Working Group prepared seven recommendations in response to the questions posted by the agency approximately five weeks ago. Now, these are complex issues, and I think I could probably spend a day talking about it, just trying to convey the conversations that the Branded Industry Working Group had.
What we will do is really just list the
action and address them in some detail. Some of
these actions can be put in place now. Some will
require more time. Some clearly are within the
FDA's purview, and some will require the agency to
work with other stakeholders. All of them are very
important. And I will come back to this slide to
look over it in greater detail once I have
discussed the actions on the subsequent slides.

But first, it is the high prevalence and the
complexity of chronic pain combined with the need
to provide pain relief to patients with pain, that
have contributed to the increased use and
availability of opioid analgesics and the
associated rise in prescription opioid abuse,
overdose, and death.

The 2011 Institute of Medicine Report on
Pain, followed by several other publications,
clearly stated that healthcare professionals,
especially in the primary care setting, need more
training in clinical management of chronic pain and
appropriate opioid prescribing.
In addition, we know that it is difficult to identify those perhaps relatively low numbers of people who take opioids who actually abuse or misuse opioid analgesics, and it is challenging to a practicing clinician to identify them.

Abuse-deterrent formulations of extended-release opioids are indeed designed to provide patients with the same pain relief as opioids without such properties while helping to reduce abuse via tampering, which in fact has been shown to be the more deadly form of abuse.

It is therefore imperative that universal adoption of abuse-deterrent opioids be considered an integral part of a comprehensive approach to responsible opioid prescribing.

The first question posed by the agency was on the role of labeling in fostering the development and use of abuse-deterrent opioids. Branded Industry Working Group believes that labeling is essential. In fact, we recommend that the FDA implement prominent labeling visible at a glance to distinguish between abuse-deterrent and
non-abuse-deterrent products.

Such labeling should include the medication
guides, the packaging, and it has to be easily
recognizable. It could be something like an
abbreviation or a symbol, perhaps a boxed
statement, something that would catch an eye,
perhaps akin to the USDA-certified stamp on the
food products in the grocery store.

This would go a long way to address the low
awareness of the availability and the low
recognition of abuse-deterrent opioid analgesics on
the part of clinicians, payers, and especially
patients.

In addition, labeling can help encourage the
use of abuse-deterrent opioid analgesics by
discouraging the use of non-abuse-deterrent
products, of course provided that the patient needs
are met. Therefore, additional labeling amendments
may be required to direct clinicians to use
abuse-deterrent products preferentially.

Precedent has been established with the
latest update to extended-release opioid labeling,
which provides the guidance to the clinicians not
only on the kind of pain that should be treated
with extended-release opioids, but even on when to
treat it, that is, when alternative treatment
options are inadequate.

   Such additional labeling that directs
clinicians toward abuse-deterrent products, again
where appropriate, would address the tendency of
many clinicians to underestimate the risks of abuse
and misuse, and their reluctance, perhaps, to
switch a patient to a product that doesn't offer an
efficacy advantage. It could also inform payers.

The second question posed by the agency had
to do with the definition of meaningful abuse-
deterrent properties. After considerable
deliberation, the working group agreed that
ultimately meaningful abuse-deterrent properties
should be defined in general as those supporting a
claim that a product is expected to result in a
meaningful reduction in abuse, tier 3 labeling for
a given route of abuse.

   We spent a lot of time discussing this, and
it is not surprising that we were able to come up
with examples where this definition could be
challenging. For example, one could envision that,
with some future product, the conduct of, let's
say, human abuse liability studies may be
associated with challenges in the area of safety or
may generate ethical concerns. How would that
affect the definition?

It is working through these challenges that
will require continued commitment on the part of
the sponsors, on the part of the agency, in order
to advance this new and rapidly evolving field of
abuse deterrents.

While highly desirable to the agency, to the
sponsors, to many other stakeholders, the goal of
acquiring the postmarketing observational claims
and data is in reality inaccessible for newly-
approved opioid analgesics with meaningful
abuse-deterrent properties, as defined above, but
for two reasons.

Firstly, the time needed to obtain such data
is uncertain and could be years, if not decades, in
view of the current barriers to sufficient new drug
utilization, which is required to get any
real-world data. Secondly, as the FDA is well
aware, the sources of postmarketing data have
critical limitations, some of them listed here.

The next question posed by the FDA had to do
with the circumstances that would support refusal
to approve a new opioid lacking meaningful
abuse-deterrent properties and other complex
questions. But the working group certainly agreed
that the FDA should not approve new opioids or
opioid formulations that lack meaningful
abuse-deterrent properties unless they fulfill a
specific unmet need or provide a unique therapeutic
benefit.

Again, as discussed on several occasions
yesterday and today, FDA, we believe, should
encourage and support, including the development of
guidance documents, a transition of all opioids,
both immediate- and extended-release towards abuse
deterrence. And some of the work that has been
done in the area of extended-release opioid
analgesics should pave the way.

Now, it is very important that we continue to keep our eyes on the development of novel opioid analgesics or formulations, which deter abuse via oral over-consumption, again, as brought out by earlier speakers today and yesterday.

This is a very complicated area for a number of reasons, and it is in fact the focus of multiple ongoing efforts, which haven't yet yielded a product. We believe that a product that has the ability to deter abuse by multiple routes, including oral over-consumption, would merit fast-track designation.

A related question again posed by the agency is on the circumstances for withdrawal of currently-marketed opioid analgesics lacking meaningful abuse-deterrent properties. The working group agreed that, upon approval of new opioid analgesics -- and the multiple here is intentional -- with meaningful abuse-deterrent properties, the FDA should reassess the risk/benefit of previously-marketed non-abuse-
deterrent versions, with the term "versions" here defined as products containing a particular opioid molecule with the same or similar timed-release profile and duration, same route of administration, and the same indication.

Now, if the benefits of the old marketed non-abuse-deterrent opioids no longer outweigh their risks, the FDA should require the sponsors, perhaps within two to three years, to withdraw for safety reasons both branded and generic versions of such products.

The sponsors can submit new data to support abuse-deterrent labeling following a reformulation and/or additional abuse liability testing. Very importantly, the withdrawal should be contingent on the performance and availability of the new product with meaningful abuse-deterrent properties. That product must meet the efficacy and safety needs of the pain patient and must maintain the overall risk/benefit profile.

Now, as mentioned earlier, this is likely to precede the acquisition of the postmarketing data
by the new product for the reasons I've described earlier. However, given the nature and the extent of the public health crisis, we believe that the robust pre-market category 1 through 3 data should be sufficient to support benefit over risk, and even a moderate incremental benefit could have a big impact in saving lives. Of course, the sponsor of the new product will have to work with the agency and with the DEA to ensure against drug shortages.

Where the FDA has the authority to act, they should do so. And where they do not, the FDA should work with stakeholders to obtain the requisite authority.

The working group generated several other recommendations for actions to encourage investment and development of new and better opioids with meaningful abuse-deterrent properties. They include providing clear guidance, requiring and ensuring the preservation of meaningful abuse-deterrent properties by generic manufacturers.
We also believe that, in anticipation of new and better opioids -- and more is better in this area -- the FDA should provide guidance on demonstrating superiority and/or non-inferiority, and how to have human abuse liability studies, and on how to communicate the data in the label. It may not directly address the hypothetical graph that Dr. Hertz put up, but it will at least give some initial assessment of how these products compare, at least on specific routes of abuse.

We believe that the FDA should also work with Congress to provide extended data exclusivity for products with meaningful abuse-deterrent properties in recognition of a significant amount of work and data that needs to be generated to support this labeling.

The FDA has used exclusivity and vouchers to foster development in other medication categories, and some of the examples are listed on the slide. In some cases, it is appropriate under the circumstances of epidemics, and we are certainly dealing with an epidemic here.
Finally and very importantly, the issue of patient access has been raised several times throughout this presentation. The agency and the industry may be doing everything we can to advance the development and adoption of abuse-deterrent opioids, but all our efforts can be for naught if other important stakeholders stay on the sidelines, especially in the area of reimbursement.

We realize that reimbursement is outside of the FDA's purview. However, we ask the agency to take a leadership role in working within the Department of Health and Human Services, with the Centers for Medicare and Medicaid services, to create stronger mandates and policies to support patient access to opioid analgesics with meaningful abuse-deterrent properties, as well as to other important and appropriate pain therapies.

Existing payment structures help illustrate system-wide barriers both at the prescriber and formulary levels to the adoption of new pain therapies, and more importantly to appropriate management of patients with pain.
For example, non-opioid analgesics are uniformly recommended as first-line treatments for many chronic pain conditions. However, patient access to the branded first-line non-opioid analgesics is often restricted with prior authorizations and step edits.

In contrast, patient access to currently available, largely generic, non-abuse-deterrent opioid analgesics is completely unrestricted. Furthermore, patient access to proven approaches, such as the multi-disciplinary chronic care pain management team, is very rarely reimbursed.

These policies, which disadvantage appropriate first-line therapies and provide preferential patient access to the currently available, largely generic, and non-abuse-deterrent opioids, contribute to opioid over-prescribing today and are likely to delay, if not prevent, the adoption of abuse-deterrent opioids.

In summary, let me take you through our recommendations, albeit at a high level. The FDA should implement prominent labeling to clearly
distinguish and identify abuse-deterrent products with and without abuse-deterrent labeling. Meaningful abuse-deterrent properties should be defined as those supporting a claim and supporting tier 3 labeling.

The third item is that FDA should not approve new opioids or opioid formulations lacking meaningful abuse-deterrent properties, provided that unless the new opioid fulfills an unmet clinical need or provides a unique therapeutic benefit.

Four, upon approval of new product with meaningful abuse-deterrent properties, the FDA should reassess the risk/benefit of previously marketed non-abuse-deterrent versions. And if the benefit no longer outweighs the risk, the FDA should require the sponsors to withdraw for safety reasons, both branded and generic versions, perhaps within two to three years, or reformulate.

Tier 3 abuse-deterrent labeling is minimum and sufficient to trigger the withdrawal. The FDA should clarify the development path, however
challenging this may be -- we certainly recognize this both for branded and generic products -- and work with Congress to address the limited and uncertain intellectual property protection.

It is extremely important that all relevant stakeholders engage in this, and the role of HHS and CMS working with the FDA cannot be underestimated. There is a need for stronger mandates and policies to support patient access to these formulations.

In conclusion, developing opioid analgesics with meaningful abuse-deterrent properties is in fact an enormous challenge from a pharmaceutical perspective. It requires a sophisticated approach to both the development and manufacturing of these products.

In order to deliver on what is essentially two opposite goals, and as stated earlier on several occasions already, the fact that the drug has to release the opioid molecule to deliver analgesia means that we may never be able to design an abuse-proof formulation. However, no one should
underestimate the role of abuse-deterrent formulations as part of the comprehensive approach to appropriate opioid prescribing.

Individual companies would welcome an opportunity to participate in continued discussions regarding these complex, scientific, regulatory, medical, and policy issues associated with abuse-deterrent opioids.

Finally, given the crisis opioid abuse, all stakeholders need to act, need to take action, need to engage in order to do what they can to advance the shared vision of a future in which most or all opioid analgesics are available to patients who need them in formulations that are less susceptible to abuse. Thank you.

(Applause.)

DR. THROCKMORTON: Thank you very much, Dr. Brodsky.

Our third set of comments is going to come from Dr. Jason Gross, representing the Generics Working Group. He has a doctorate in pharmacy from the University of Arizona, has spent 21 years in a
variety of different jobs in the pharmaceuticals area, most recently with working for Cipher Pharmaceuticals, and I look forward to his remarks.

Presentation – Jason Gross

DR. GROSS: So my name is Jason Gross, and recently, I became an industry consultant. It's a pleasure to be here in front of the FDA, presenting the Generics Working Group's opinions and thoughts on abuse-deterrent formulation, regulations, and guidances affecting the approval of abuse-deterrent formulations. I'd like to thank the Generic Industry Working Group for inviting me to present on their behalf. It's both an honor and a pleasure.

On the dawn of the 30th anniversary of Hatch-Waxman, the Generic Industry Working Group recognizes the significance of this meeting and the challenges the FDA will face in propagating new regulations and guidances that will ultimately shape the future of AB-rated generic pharmaceuticals with abuse-deterrent pharmaceutical properties.
The working group would like to thank the FDA for permitting the group to participate in this forum and provide their thoughts and opinions in this very complex space. It's a pleasure for me to be back in Washington, in Maryland, where I started my career at NIH and moved on to the FDA and industry.

Over the last meeting from yesterday and today, the complexities and challenges that the abuse-deterrent space faces reminds me of many of the other obstacles and challenges that have faced my industry and that I've been part of in the last 20 years.

Over the last 20 years, there have been various milestones in the generic industry, all which also have various complexities. These complexities were resolved with various sound science in the best interests of public health.

The group has a standard disclaimer, which has been on almost all of the slides. And my disclaimer is that I don't have any -- I'm representing the group, and the group has only paid
for my travel to attend the meeting.

So with regard to the executive summary and with regard to abuse-deterrent technology in the Generics Working Group, I am pleased to see that it almost is like our slides got mixed up. And Marina and the Generics Working Group and the Branded Working Group have a lot of similar and poignant points to make, but very similar. And it's one of the first forums where I participated, where there are a lot of similarities in the concerns and interests of public health.

So as with the Branded Industry Working Group, both the branded and generic working groups agree that the FDA should implement prominent labeling to distinguish between non-ADF and ADF products. In addition to motivating adoption of abuse-deterrent formulations, this will also help mitigate marketplace confusion among prescribers and enhance consistency for patients.

Once a true abuse-deterrent formulation alternative becomes available, the non-ADF manufacturers should initiate work to reformulate
their product or withdraw the non-ADF application
with certain provisions to mitigate any drug
shortages or patient access issues during the
transition, and we'll expand upon that a little
bit.

In addition, the Generic Working Industry
Group is proposing the following. FDA should
develop abuse-deterrent formulation requirements
within each specific bioequivalency guidance with
products that are affected by abuse deterents.
Guidance should clarify when generics should submit
an ANDA or a 505(b)(2). Yesterday, we heard there
is some clarity coming and, hopefully, that will
continue.

Consideration of fee reduction for 505(b)(2)
applications for generic manufacturers, in special
cases -- we'll talk about that, but special cases
where an application was meant to be filed as a
505(j) and it has to be filed under a different
regulatory pathway, the generics would like to have
some relief of the fees associated with that.

Of course, we'd like to have a special
abuse-deterrent category in the Orange Book to properly label these products and categorize these products. And as an enhancement to the GDUFA, an expedited review pathway should be available for abuse-deterrent formulation generics.

As has been stated many times yesterday and today, this is just one piece of a very large puzzle. And it's a very important piece, but it's not the only piece.

Therefore, we would encourage the FDA to take part in influencing the various constituents and process federal agencies at the state level to encourage prescription drug-monitoring programs and require prescribers to participate in training and education to help them understand, just as Dr. Woodcock said yesterday, the development and prescribing of medications in the opioid space to treat pain is still evolving, and the philosophies have changed over time.

So a quick perspective -- I mean, there's different perspectives that can be presented, but some things are working. The latest survey data
found the number of people, 12 years or older, currently abusing prescription drugs decreased from 7 million in 2010 to 6.1 million in 2011, a 12 percent decline. Prescription drug-monitoring programs in 49 states, these are things that weren't in place several years ago and help alleviate some of these issues that we're facing.

Medical provider education laws. Less than half of the states have laws requiring recommendations, educational prescribers, or other healthcare providers who prescribe prescription pain medication. We need to improve the education.

While we see a decline, we still have a public health crisis where non-medical use of prescription painkillers impose a cost of approximately $53.4 billion in the U.S. economy. Emergency department visits for prescription drug misuse -- now, this is a term, misuse versus abuse, but sometimes misuse incorporates the abuse -- more than doubled between 2004 and 2011.

The Branded Industry Working Group and the Generic Industry Group are here today to
collaborate with the FDA and other stakeholders to
develop regulatory policy for abuse-deterrent
technologies as a tool that may be incorporated to
reduce this public risk, but it's only a tool. The
Generic Industry Working Group is here to help
initiate development of the regulatory policy for
generic abuse-deterrent formulations.

One of the aspects that we were asked to
comment on is the labeling claims for abuse-
deterrent properties. Labeling is a tool. It's a
tool to incentivize development and use of
abuse-deterrent formulations. The generic and
branded groups agree the FDA should implement
prominent labeling to distinguish between the
products.

This labeling can also help distinguish
between not only the administration, the storage,
but also the disposal of these products. As we
have abuse-deterrent technologies, these products
may become more difficult to dispose and
environmental concerns of those natures.

Approved abuse-deterrent formulation
generics should have the same labeling as the reference listed drug. The Generic Industry Working Group recommends the FDA create an algorithm with respect to labeling by route of administration.

Degree of abuse and technology employed, that would apply standard consistent warning corresponding to the categories of studies fulfilled and equating to the tiers as opposed to being assessed fully on a case-by-case basis.

As part of GDUFA, FDA should consider offering exclusivity also to generic manufacturers and incentive to develop abuse-deterrent formulation technologies. The Generic Industry Working Group recommends revisiting the use of the word "tier."

This is a minor point, but tier is used in a different area of reimbursement. So one of the aspects of using tier could be confused with the aspect of reimbursement and how tiers are used outside in third parties and other stakeholders are affected in this space.
Development of generic opioids with abuse-deterrent formulations has been a complex issue, and it's going to require a lot of guidances and require a lot of thought. But the FDA should develop abuse-deterrent formulations within each product-specific guidance. And different mechanisms of abuse-deterrent formulations are very, very analogous to extended-release delivery. Various extended-release deliveries produce the same effect, the same safety, the same efficacy of products, but they incorporate different technologies.

There are different ADF technologies that may be deemed to be equivalent. You don't have to have the exact same technology to achieve the final goal of reducing insufflation or reducing injectability. So there are various technologies that will be available, and generics should be permitted to use different technologies and mechanisms to fulfill the end result.

FDA needs to provide clear guidance indicating which circumstances in abuse-deterrent
formulation would be required to be filed under a regulatory pathway, such as a 505(b)(2) or a 505(j).

Currently, we heard yesterday that this seems to be moving in the right direction and there is more clarity being shown on this space. But currently, without the development of standardized abuse-deterrent formulations and propagation of specific ADF requirements for specific bioequivalency guidances, proposed 505(j) applications might have to be submitted under 505(b)(2).

For those scenarios in which a 505(b)(2) is warranted, for which would normally be a 505(j), we recommend the FDA invoke a reduced fee for generic manufacturers in par with the GDUFA fee structures proposed in GDUFA fee of 505(b)(2) with clinical data.

We hope there's not that shift, but there's some complexities that create ambiguity, and companies that have developed formulations would like to get those formulations approved. Sometimes
it's very difficult for them to put it in queue, wait several years through the generic process, only to be found that technology and the regulatory approval process aren't dovetailed to the approval, and they have to move to a different regulatory path.

Category 1 requirements should be standardized for generics against abuse-deterrent formulation, reference listed drug. And on a case-by-case basis, category 2 and category 3 data may be required, but may not always be required.

With GDUFA, FDA should implement an expedited review pathway for generic abuse-deterrent formulations, not in every situation, and it doesn't need to cover all of the situations, but there's a few just for a thought-provoking aspect.

For abuse-deterrent formulations, generics under a new definition of a first generic; for scenarios when generics were part of a withdrawal process and had to be formulated, thus leaving a gap and need for medicines for patients; and for those abuse-deterrent formulation products for
which the brand was given an expedited review.

There may be more. We just put these up as producing some thoughts.

Review processes. The Generic Industry Working Group requests clarity with respect to how the FDA plans to conduct reviews for abuse-deterrent formulations. We heard yesterday that this process is already underway. The FDA spent a fair amount of time bringing equipment manufacturing formulations and developing test methodologies, but we still now have to translate that into a regulatory context.

The Generic Industry Working Group requests clarity with respect to how FDA plans to conduct reviews for ADF. I've mentioned that.

Under GDUFA's assurance that reviewers within OPQ, new drug division, life cycle management will have the appropriate skill set to conduct consistent reviews for ADF products in a timely process. And that's both for the branded as well as generic reviews, so there's a sense of uniformity. If a generic meets the requirements of
an abuse-deterrent formulation, the generic would have a special ADF rating in the Orange Book along with the branded product.

So meaningful abuse-deterrent properties, what data should be provided to support this? This is going to be evolving. We're not sure today. I think it's becoming more clear than it was a few years ago, but it's still evolving. And as we heard, the FDA has made a fair amount of progress in defining what they think will be critical parameters.

So these four bullet points pretty much say the same thing, but in a different context. But as was pointed out today, all dosage forms are subject to abuse, not just extended release. So the FDA should provide regulatory pathways for the approval of all, for different dosage forms, and consider this in a larger picture.

The workgroup shared the view that testing and acceptance criteria will provide clarity and ultimately define meaningful abuse-deterrent properties. Category 4 studies, we heard, there is
some complexity there. And yesterday and today, we've heard that category 4 studies still carry a fair amount of complexity.

The Generics Working Group believes that they should not be required at this time. They are currently flawed with regard to the design and analysis and will provide limited value in this short time frame.

FDA should create standards for required abuse-deterrent formulation testing that assures the uniformity of claims.

Yesterday, we heard from the University of Maryland, where they tested a range of products, one that they thought had mostly immediate-release products. And when they tested some, they had actually injectability resistance or different products had different dissolution characteristics.

These differences have a significant meaning, particularly with the example they provided with the injectability of a product, where a small manipulation actually created a product that was not injectable and became injectable.
Benefit and risk assessments. As with the branded group, the Generic Industry Working Group agrees that there may be exceptions where a new non-ADF opiate is medically needed. I apologize, but we agree with the fact that new formulations, new opiates, should not be approved without abuse-deterrent formulation and technology. But that's a broad statement. There are going to be exceptions to that policy, and that's going to be based on medical need. It's going to be based on a category. It's going to be based on a product.

So we can't just whitewash that and just make a broad standing claim. But there will be many exceptions for the new ADF opiate, such as medically needed opiates. In such instances, the FDA should have an exemption procedure in place with a sponsor to complete and demonstrate appropriate rationale for why abuse-deterrent technology may not be required for that space.

The Generic Industry Working Group agrees with the branded group that the FDA should not approve new opiates or opiate formulations without
meaningful abuse-deterrent properties unless they address an unmet need or have a unique benefit.

However, those requirements need to be standardized to achieve abuse-deterrent labeling that all products are evaluated on a level playing field. Whether they're branded or generic, it has to be well-known that if we say something is non-injectable or difficult to inject, a physician knows what that means, whether it's a branded or generic product.

Generic Industry agrees that the FDA should require non-ADF sponsors to reformulate products within a reasonable time of launch of the matching abuse-deterrent formulation or withdraw the ADF product. But this is a very careful and complex issue also, and it can be a slippery slope.

As an example, what may be perceived as an abuse-deterrent formulation at the time of approval may not remain as an abuse-deterrent formulation during marketing. It was already commented about how creative abusers can be, and the University of Maryland in that example I cited earlier had a
technology that was not very syringeable, and they did a slight manipulation, and it became very easily syringeable. So there is a technology that now no longer is it in the marketplace or that's in the marketplace, could be theoretically, and lose its ADF properties.

Generics should not be removed until adequate postmarketing data has been obtained and reviewed by FDA for the innovator to ensure that the ADF properties truly deter abuse in the public setting.

Can you imagine a situation where we removed a category of products because there was an abuse-deterrent technology that displaced them, and then a few months or maybe a year into the process, we've realized that abuse technology isn't quite as abuse deterrent as we thought? And we now have a product in the marketplace that is no different than the products that it displaced.

During a transition period, the sponsor and ADF should require to work with the FDA and DEA to mitigate any drug shortage or patient access
issues.

So while the group supports the concept of the withdrawal of non-ADF products when the ADF products are approved and marketed, there are complexities that require attention. FDA should use this with great discretion to ensure monopolies are not created and Hatch-Waxman is not circumvented.

As I stated before, what may be perceived as an ADF at the time of approval may not remain as an ADF during marketing. In situations where the branded ADF product is shown to be defeated by an abuser but the generic ADF product has not been compromised, should the generic ADF be able to remain on the market and the branded product be removed from the market?

As we have seen over the past, there's different technologies for delivering extended-release dosage forms. This example actually is a recent example in the sense that with extended-release dosage forms, there's a new requirement to do alcohol testing, alcohol dissolution studies to
look at extractability because it was realized that
under certain circumstances, when people drank
large amounts of alcohol, there could be some
dose-dumping of extended-release dosage forms.

So in a case where a generic might be
superior to a branded product after time in the
marketplace, how does that look in a regulatory
environment?

Policies need to be a balanced approach,
allowing generic competition while giving incentive
to branded companies, as an example, expedited
review for generic abuse-deterrent formulations in
scenarios where the innovator changed or had
incremental improvement, resulting in improved
revised labeling.

So another question that was asked and was
requested dealt with abuse-deterrent development of
ER opiates versus IR products. The Generic
Industry Working Group believes that abuse-
deterrent formulations should be applied to all
opiates.

As appropriate, we recognize that there's
more dosage forms than the extended-release forms that are the main subject today. There are solutions. There are the injectables. There are patches. And there are going to be other dosage forms that may yet be developed. So the abuse-deterrent properties and concerns need to be applied across the board.

This is fairly important also when you decide about withdrawing a market class. It's almost like -- what's that fish, the sea cucumber? When you squeeze the cucumber, you get this balloon and you can't quite catch it. And as was eloquently expressed, when you elucidate a withdrawal from the marketplace in a particular space and you're left with a branded product, you have a few things that are going to go on.

You're going to have a few patients that are going to be able to go on to the new branded product with the abuse-deterrent properties, but you're going to have another set of patients that might not be able to afford that particular product. And they're going to be displaced into
the space of having to redefine their algorithm for
their pain management and have to develop new
products, new treatment paradigms.

Then you also potentially may create another
public health hazard because these patients that
might have been abusing that technology go to a
different technology that has more potency, and
they have more adverse events.

So when you make these switches and you make
these environmental changes, you have to think of
the epidemiology effect and maybe make them in a
broader category when there is more categories out
there, and abuse-deterrent technology is more
prevalent to prevent that secondary abuse.

The generic industry recommends that FDA use
marketed-derived data and set up mechanisms to
assess the data with regular periodicity. This was
also expressed by colleagues. Prespecified
thresholds that correspond with action or no action
to be taken, independent assessments, and
transparency to the public and stakeholders would
require regular reporting. And how are these
So a few additional recommendations to enhance abuse-deterrent formulations were provided by the working group, and we'll review just a few slides on that.

The FDA should provide clear guidance to generic manufacturers, abuse-deterrent formulation requirements included within product-specific bioequivalency guidances.

We eventually believe that what will happen with the abuse-deterrent space is there will be broad categories of what is abuse deterrence when it comes to insufflation.

What is abuse-deterrent technology when it comes to injection? And what is abuse-deterrent technology when it comes to vaporization or the ability to smoke a product? These then will be translated into each of the bioequivalency guidances, and generics will have to meet those criteria.

The FDA should commit and identify the data sources that will be used to gather postmarketing
surveillance and conduct external boards to assess adequacy of the abuse-deterrent formulations.

For a 505(b)(2) application, the generic manufacturers should have reduced fees analogous to the fee structure associated with GDUFA versus that of PDUFA. And generics would like to have an AB rating within the Orange Book to clearly identify that their product, too, has abuse-deterrent technology.

An expedited review pathway should be available for abuse-deterrent technology for the generics, and various circumstances may permit that over others, but for ADF generics potentially under the new definition of a first generic that's being proposed for GDUFA, that may be another pathway.

For scenarios when generics were part of a withdrawal process and had to be formulated, thus leaving a gap and a need for medicines for patients, as was pointed out this afternoon or this morning with the VA, these products, the generics, represent a very large percentage of the products being dispensed, almost over 80 percent. So that's
going to cause a very large public health crisis
with regard to fees and costs associated with that
particular withdrawal.

For those ADF products for which the brand
was given an expedited review, it may be another
indication of the need and, therefore, generics'
need for an expedited review.

Some additional comments for consideration,
patients' safe use and patient access. We have to
recognize that 97 percent of patients use their
medicines properly. So every time we do a market
shift or we do a change, it's affecting 97 percent
of the patients that would have taken that
medication and are well-maintained on their pain
therapy.

We have a responsibility to assure that
those patients are not adversely impacted by his
change, including increased patient cost that may
translate to patient access issues.

Exclusivities for abuse-deterrent
formulations need to be balanced against potential
patents listed in the Orange Book and the
likelihood for increased patent litigation in this space.

The Generic Industry Working Group asked the FDA to influence the process within the government to require all states to require their medical providers to participate in prescription drug monitoring programs, and this will help industry's ability to monitor abuse-deterrent formulations and actually understand whether they are actually working or whether this initiative is having an impact.

The Generics Working Group asked the FDA to influence the process within federal agencies to mandate healthcare prescriber actions and training. And speed of development versus regulatory and legislative speed, it's moving faster. I can tell you when I first started, we were looking at changes in inhalation as far for asthma, for aerosolization.

Those regulations for generics took years, many more years than we are looking at in this condensed space for propagating new regulations in
the abuse-deterrent technology. So we recognize that the FDA is accelerating the development and trying to keep up the alignment with scientific advancements in this area, but we still need to recognize that advancements are moving fairly quickly now.

So in summary, we have one slide to summarize some of the points of the Generic Industry Working Group. The recommendations, as previously iterated, the first two bullet points are in full agreement with many of the parties that presented yesterday and today.

The FDA should implement prominent labeling to distinguish between non-ADF and ADF products. Once a true ADF alternative becomes available, the non-ADF manufacturers should be required to reformulate their product or withdraw their non-ADF product with certain provisions to mitigate any drug shortage or patient access issues.

In addition, the following recommendations. Marked withdrawal of non-ADF formulations must be carefully considered, as perceived, ADF
formulations may be compromised postmarketing, creating new monopolies. And not only that, we have to really be concerned at patient access and what that does to the 90-plus percent of patients that are using the drug properly and rely on the cost-effective products.

Standards for ADF properties are required for uniformity. Guidance should clarify when generics are required to submit an ANDA or a 505(b)(2). And FDA should develop ADF requirements with each product-specific B guidance.

Consideration of fee reductions in cases where a 505(b)(2) may be required; an expedited review pathway available for ADF generics, particularly where there's been a market withdrawal or a displacement.

FDA should influence the process. That is redundant among all of the speakers yesterday and today, but the FDA really needs to take part in this. This is not just one piece. This is a part of a larger puzzle. It's part of a larger picture. And the FDA, as well as the DEA, as well as local
health authorities, need to take part in new
initiatives to train and to educate physicians as
well as patients. These are the larger initiatives
that will actually prevent some of the abuse and
misuse of the product.

So with that, the Generic Industry Working
Group would like to thank the FDA for their time
and we thank you.

(Applause.)

Clarifying Questions and Answers

DR. THROCKMORTON: Thanks very much.

We have just a few minutes, and if there are
clarifying questions that people have that they
would like to ask, if they could just come to the
microphones, and then we'll move on to the public
speaking.

Jason, I might start out by just asking you
to clarify something that you said in your remarks.
You emphasized the importance of data in the
postmarketing space, and you seem to be concerned
about how the FDA -- you recommended we be very
transparent about the data we used or something.
Could you say a little more at what your concern was behind that recommendation?

DR. GROSS: Yes. There is the aspect of the data is going to be coming in from different modalities. And the modalities that are derived from this data are going to be generated, some by the branded products, some by company or by government agents such as the VA.

Yet, there is also the epidemiology aspect that there are other circumstances that change. So recently there were some data trends that looked like the abuse-deterrent technology was -- or I shouldn't say abuse-deterrent technology, but there was a shift in the use and misuse of drugs.

When you look at epidemiology around that, most of that data came from Florida, when the DA stepped in and shut down some of the drug mills and prescribing that was going on in Florida, and that created a big dip.

There is also some other things going on in the industry, such as a change in medical marijuana. There's some data coming out early that
seems to shift -- some of the misuse or abusive 
opiates are shifting now with the availability of 
medical marijuana.

So when we look at datasets to make a 
determination of the effectiveness of 
abuse-deterrent technology, we need to make sure 
that what we're making assumptions on are valid, 
and that the shift -- or that we are making an 
impact because in the end game, we can look back. 
Some of the best deeds that we've ever accomplished 
sometimes are achieved -- don't really result in 
the best expectations.

An interesting example of that, I guess, 
would go back a few years, where the FDA 
recognized, with sound solid scientific data, that 
the antidepressants were causing some suicidal 
disease or increase within pediatric patients, and 
labeling was adequately propagated to affect that. 

As it turned out, suicidality increased, and 
what we realized was that suicidal tendency was 
always there. The labeling provided additional 
warning, but we realized that we just needed to
continue to prescribing antidepressants to those patients, but watch them closely. The answer wasn't withdrawing the medication.

So these same kind of attributes and thought processes in epidemiology surveys will need to take place in the abuse-deterrent space. And what we perceive as a change, we need to show proper documentation and show that these changes have had a meaningful impact. If not, there's no reason to be withdrawing these products and making this kind of shift.

DR. THROCKMORTON: Great. Thank you.

A question back in the back there?

DR. WOODS: My name is Jim Woods from the University of Michigan, and I would like to address the question to Dr. Good. I used to give lectures on pharmacology of opiates to medical students when I was a little boy, and you dropped a bomb on me because you said there were something like 60,000 prescriptions for narcotics that were the equivalent, if I understood you correctly, of 100 times morphine equivalent, daily equivalents.
Is that true or did I misunderstand?

DR. GOOD: Yep, that's correct, 100 morphine equivalents per day.

DR. WOODS: Okay. Then I have a recommendation for you. Give naloxone kits to everyone who has that prescription.

DR. GOOD: We have them freely available to all those veterans.

DR. THROCKMORTON: Question over here?

DR. COPLAN: Good morning, Paul Coplan from Purdue Pharma, a question to Dr. Good. Dr. Good, you mentioned in your talk that about 4 percent of the opioid use in the VA system are brand and that 96 percent are generic. And the cost implications of converting to abuse-deterrent formulations would, hence, be very expensive.

Could you comment whether that 4 percent is 4 percent of extended-release opioids or 4 percent of all opioids? And since a lot of the discussion, as Dr. Hertz mentioned in her talk, is focused on extended-release opioids, how that would potentially change the impact of the formulary?
DR. GOOD: So I don't know the breakdown of branded products and looking at extended-release and short-acting. I suspect or would be pretty certain that most of those branded products are long-acting.

So I think if this is an iterative process where FDA focuses first on long-acting and then brings in the short-acting, regardless of whether they are generic or not, I think that will still have a significant impact on cost. Whether it's the right thing to do or whether it's not indicated, I think, remains to be seen.

Open Public Hearing

DR. THROCKMORTON: Why don't we transition, then, to the public speaking part, and I'm going to transition to another microphone. The public speaking, we have the same arrangements that we had yesterday, and I hope that people are mostly towards the front of the room. I'll call your names.

I think, Mary, we have roughly the same number, so around three minutes per speaker, and I
will begin with Stefan Aigner.

DR. AIGNER: Good morning, everybody. My name is Stefan Aigner. I'm with Inspirion Delivery Technologies. Inspirion is a start-up company solely dedicated to the development of abuse-deterrent opioids through multiple innovative technologies.

We actually believe, after listening to the presentation yesterday, that our approach might be the next innovation some people might be looking for, a physical chemical abuse deterrent, which addresses many of the issues pointed out during the presentations yesterday. We have multiple abuse-deterrent formulations in development, and hopefully will be filing with FDA soon.

We would like to thank FDA for arranging this very instrumental meeting. Actually, it's quite remarkable how a meeting like this can really set the juice free, and it's very good interaction.

Especially for a company the size of IDT, the clarity and direction the FDA has provided in the abuse-deterrent guidance and also in our FDA
interactions has been very helpful. If that weren't as well oiled, it would be very difficult for us to quickly advance programs.

A number of comments. As a follow-up to yesterday's panel discussion, there was a question about nasal absorption. And I would just like to share, we seem to have a unique data set, which indicates there is unique nasal absorption in intranasal liking studies and absorbed, which we will gladly share going forward.

Overall, regarding the development of generic versions of abuse-deterrent brands, IDT would like to suggest that FDA ensures, as I'm sure you will, that the AB-rated interchangeable products are as safe and as efficacious as the brands.

As we think about the different methods of manipulation, extraction, different routes of administration, and this very interested abuser base that are determined to learn quickly and share all their findings over the internet, I think it's very important to robustly characterize products so
you don't create a problem where we might have had a good start in the beginning to get a handle on it.

Second, on a higher level, as new abuse-deterrent formulations become available, I think we all agree the maximum impact is, if all the opioids would be abuse deterrent, that's something we could implement today. But if you see an opportunity for a specific molecule and moiety, and we have abuse-deterrent formulations we are convinced could have an impact, I would encourage all the working groups to FDA to quickly say yes. It might be time to discontinue the non-abuse-deterrent forms.

Thirdly, the cost of developing ADF products, I know Marina called it costly for Pfizer. Certainly, IDT would actually echo that, and also the development as well as educating prescribers to shift their behavior. As you know, Pfizer has got hundreds of reps out there. That's very needed work because prescribers today don't really have a good handle on what to do with those
abuseable opioids today.

We applaud FDA for the significant steps FDA has taken to incentivize and support their development. Without that, a company like IDT wouldn't even exist. Certainly, balancing the incentives for meaningful innovation with the interest of the public health to have affordable generics, we entirely agree.

But we do support this request by the ADF coalition to establish a five-year market exclusivity period for 505(b)s. And to me, it appears that it might be in the interest of the generic companies that a brand first innovates, gets a fraction of the doctors, gets the volume up, and then at some point, clearly, the generics would follow. But the first two pieces, traditionally, brand companies have done.

Again, thanks for the opportunity for being here and sharing our views. And we are looking forward to the next hopefully very similar meeting in the not-too-far future.

DR. THROCKMORTON: Thank you very much. The
next speaker is Albert Brzeczko.

DR. BRZECZKO: Good morning and Happy Halloween. My name is Al Brzeczko, and I am lead scientist at Acura Pharmaceutical Technologies. Acura currently has an approved product for an IR opioid and also has on the market a product called Nexafed, which has anti-meth-resistant properties in the field geared towards reducing conversion of meth in pseudoephedrine products.

Today, I would like to focus on two areas of discussion, incentives to industry and what are meaningful abuse-deterrent properties. Acura believes that differentiated labeling is sufficient incentive to develop abuse-deterrent formulations. However, to date, the success of abuse-deterrent formulations in the market against the non-abuse-deterrent generic counterparts has proved less than robust.

As pointed out yesterday, there is resistance from the insurance industry from supporting these new formulations, primarily based on a lack of understanding of the benefits of abuse.
liability, liking studies, and their endpoints.

The long-term potential of withdrawal of non-abuse-deterrent products, including generics, from the market adds to the incentives for the industry. However, the new FDA concept of prematurely removing older abuse-deterrent formulations from the market, perhaps not based solely on safety assessment but on a subjective assessment of incremental improvement, provides disincentive. Investors want a clear understanding of duration of marketing, which would be clouded by this new concept.

Perhaps the greatest disincentive for innovation stems from the FDA's lack of clarity on meaningful abuse-deterrent properties. Under the current draft guidance, the new formulations' meaningfulness against current marketed products is quantified by category 1 through 3 testing. However, the guidance further identifies a relevant or known route of abuse. We now understand that relevance includes other factors such as consequences of abuse, namely addiction, overdose,
and death.

   It was supported in yesterday's open hearing that our most-abused products are immediate-release opioids. However, FDA states in the Federal Register notice, "As more extended-release long-acting opioid products are reformulated with abuse-deterrent technologies, individuals who abuse opioids may shift their attention to opioid drugs lacking abuse-deterrent properties, including IR products."

   This seems to suggest that FDA does not consider immediate-release products relevant for abuse-deterrent formulations. The current approach in which companies spend millions developing new technologies, only to find FDA does not see any abuse in the market, is at best inefficient. It certainly does not support innovation in this field.

   As such, Acura recommends, first, withdrawal of products from the market, be they abuse-deterrent or non-abuse-deterrent formulations, should be based on a clear finding of safety.
deficiency; that is, the product is definitively more abused than the equivalent product on the market and, after consideration, whether the remaining products satisfies the needs of the patients and the communities.

Second, FDA should, at pre-NDA stage, provide sponsor companies timely and definitive feedback that the proposed abuse-deterrent properties or formulation, if proven robust through testing, would qualify for abuse-deterrent labeling. Otherwise, FDA will stifle innovation and limit participation in this market to only the large pharma companies that can afford the entry fee and assume the risk. Thank you.

DR. THROCKMORTON: Thank you. Penny Levin?

MS. LEVIN: Hi. I'm Penny Levin. I'm representing Teva Pharmaceuticals. Thank you. As my colleague Yatindra noted yesterday, Teva is a manufacturer of both branded and generic products and strives for a balanced regulatory policy that appropriately incentivizes innovation while also facilitating the development and timely approval of
affordable generic products for the American public. Teva is committed to ensuring the highest standards of safety and quality for our pain therapies.

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

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

We also believe that for a generic to be considered interchangeable to an abuse-deterrent
branded product, the generic must meet the
traditional standard of bioequivalence and also
that the abuse-deterrent properties of the generic
product first qualify for the same tiers of abuse-
deterrence labeling as the branded product; possess
the same abuse-deterrent mechanisms as the branded
products, such as physical/chemical barrier,
agonist/antagonist combination, et cetera; and have
an equivalent abuse-deterrent effect as determined
by FDA.

The technology of abuse deterrence is
everevolving rapidly. Teva recognizes that just as ADF
products and technologies vary, assuming FDA's
recommendations for both the safety and
effectiveness of the branded products and the
equivalence of the generic versions, in this
context, Teva envisions that, depending on the
mechanism of abuse deterrence, the closer the
formulation, the nature, and grade of excipience
and the manufacturing process of the generic or to
the branded product, the more heavily weighted
FDA's recommendations may be toward in vitro
Conversely, depending on the mechanism of abuse deterrence, the greater the degree of significance of difference between the branded and generic products, the more likely that additional in vitro pharmacokinetic and human abuse liability studies may be warranted.

Perhaps most importantly, Teva welcomes the opportunity to discuss this important issue with FDA and share with you the technologies and data we are developing to help the FDA further the development of guidance for both the branded and generic products. Thank you.

DR. THROCKMORTON: Thank you. The next speaker is Carlo Di Fonzo.

DR. DI FONZO: Good morning. My name is Carlo Di Fonzo, and I'm the head of regulatory affairs at Nektar Therapeutics. Nektar is developing novel therapeutics based on our advanced polymer conjugation technology.

Nektar has designed new molecular entity, new agonists having unique properties such as a
reduced rate of CNS entry with the goal of reducing
euphoric CNS side effects and limiting abuse.
These new agonists have abuse-deterrent
features that are part of the molecular structure
and are not reformulations or prodrugs of currently
available opioids.

We applaud the FDA efforts to encourage the
development of abuse-deterrent formulations.
However, as the FDA has acknowledged, while the
currently available abuse-deterrent formulations
are expected to provide some improvements, their
impact on the abuse epidemic may be limited since
all of them are subject to being capable of being
defeated.

We believe that the new molecular base, the
abuse-deterrent approach offers great promise to be
the next generation of abuse-deterrent opiate
products, which could have a marked impact on the
abuse epidemic. Nektar's most advanced new
agonist, Nektar 181, is being developed for
treating chronic pain conditions and has completed
phase 2 clinical testing.
The results of the studies completed to date have shown a profile suggestive of less abuse potential of Nektar 181 versus the standard opiates such as oxycodone and morphine. Human data reveal that the plasma to CNS equilibration for Nektar 181 took 1.7 hours, which is significantly longer, approximately nine times longer than the published value of only 11 minutes for oxycodone.

This is an important result, as previous studies have established that the rate of opiate delivery into the CNS is an important predictor of its reinforcing strength. Furthermore, an initial human abuse liability study of Nektar 181 resulted in significantly lower drug liking and drug high scores versus oxycodone.

The encouraging abuse-deterrent safety profile of Nektar 181 was recognized by the FDA with their granting of fast-track development status. We are in the process of finalizing our phase 3 clinical trial design in close consultation with the FDA, and we plan to start the phase 3 clinical program in the first quarter of 2015.
FDA's issuance of the January 2013 draft guidance on abuse-deterrent opiates was an important step to help guide the development of abuse-deterrent products as well as to provide meaningful incentives for companies to generate data to obtain differentiating label claims.

However, the draft FDA guidance has focused exclusively on abuse-deterrent formulations and does not include NMEs that have reduced abuse potential designed into their chemical structures. We believe it is important to recognize the molecular-based approach in the FDA guidance document by having a separate section on NMEs.

The current-tier labeling is also specifically directed at label claims for abuse-deterrent formulations. We recommend that a separate tier label be added for abuse-deterrent NMEs as well as addressing criteria for these products, potentially qualifying for less restrictive scheduling, and thereby making them more readily accessible for treating patients with pain.
As we heard from patient advocates yesterday, millions of people are suffering from pain. I also personally suffer from sciatica. I urge the FDA to make patients front of mind. Making safer opiates available and accessible to the patients should be a priority of all of us. Thank you for the opportunity to speak today and thank you for organizing this public hearing.

Happy Halloween and good trick-or-treat-ing.

DR. THROCKMORTON: Thank you, sir.

Jody Green?

DR. GREEN: Good morning. I am Jody Green, the director of research at Denver Health, Rocky Mountain Poison and Drug Center, and the RADARS system. I am here today to respond to FDA's inquiry of what does it mean for a product to have meaningful abuse-deterrent properties.

This is a critical component, considering tier 3 labeling currently requires the product is expected to result in a meaningful reduction in abuse, and tier 4 requires that the product has demonstrated reduced abuse in the community. The
word "meaningful" is difficult, considering there is no one standardized measure or set of measures by which all drugs are evaluated.

The FDA has identified the outcomes of interest, such as addiction, overdose, and death, but not yet the specific measurement of these outcomes. Clearly, this is not easy to do. Proper assessment requires multiple data sources, adequate coverage of the study population, timely information, and most importantly, the ability to monitor product-specific information by dosage form, as well as immediate-release and extended-release.

We also heard today the importance of monitoring the route of abuse, although as my colleague, Dr. Iwanicki, presented yesterday, we would argue that chewing should be considered as well in the assessment of the routes of abuse.

Proper evaluation of the effectiveness of a product with an ADF platform cannot be done without product-specific surveillance. We would never expect efficacy of a single product to be evaluated
on the basis of data collected from a class of
drugs, nor can we expect abuse-deterrent labeling
to be evaluated in that manner.

Next, the word "reduction" is used
throughout the draft guidance. What about products
with purported abuse-deterrent technology that
enter the market at a low rate of abuse like
tapentadol? Demonstrable reduction is unlikely, as
the rates are already very low and there are no
other marketed products with the same active
ingredient. How would such a product meet labeling
requirements?

Of course, it was also mentioned, the
difficulty in evaluating products with low market
penetration. This complexity scores the need for
standardized data sources, key measures, and
established abuse thresholds by which all products
should be evaluated rather than explicit reduction
of abuse for that specific drug.

Tier 4 draft language requires the
postmarketing data from a variety of data sources
can demonstrate that a product's abuse-deterrent
properties cause persistent and relevant reduction in its abuse.

First, we commend the FDA's call for data from a variety of data sources. This is very important in evaluating abuse-deterrent formulations. Timeliness of these data sources, ideally no more than six to nine months' lag, is also important to ensure that we understand effectiveness sooner rather than later and can take immediate action in light of a critical abuse-deterrent failure.

Tier 4 requirement also suggests that the formulation has withstood a test of time on the market and continues to offer tamper-resistant properties, resulting in relevant reduction in abuse that is not just statistically significant by some outcome measures, but a meaningful relevant improvement of patient safety has been achieved and sustained.

The balance between patient benefit and acceptable risk is incredibly complex. Therefore, we can expect the measurement to be complex.
So in conclusion, we ask FDA to consider specifying the fundamental factors required to determine a meaningful impact, one, that formulations make a difference and, therefore, product-specific data are essential; that timely surveillance data allow for timely evaluations of meaningful impact and patient safety; and that three years of product-specific monitoring with multiple systems be deemed adequate to establish tier 4 claims. Thank you very much.

DR. THROCKMORTON: Thank you very much.

Jack Henningfield?

DR. HENNINGFIELD: Good morning. I am Jack Henningfield. I am vice president of research, and health policy, and abuse liability at Pinney Associates and professor of behavioral biology at the Johns Hopkins University School of Medicine.

Yesterday, you heard from my colleague, Ed Cone, focusing more on tier 1 or category 1 testing. And what I'd like to do is briefly bridge to some implications for category 2 and 3 in generics.
AD testing, of course, begins with category 1, and, frankly, unless a new drug substance is involved, category 3 testing probably doesn't make much sense in most cases. First, you need to understand how the drug performs in vitro in detail.

Category 1 data, in turn, can guide the design, and implementation, and what kinds of studies need to be done in category 2 and 3. In some cases, a thorough in vitro categorization, I think, can expedite category 2 and 3 testing.

If you are working with a new molecule, that might be a case where it makes sense to do some category 3 at the same time that you're doing in vitro, just as you're doing some animal work undoubtedly. For example, category 1 data may inform category 2 and 3, in part, by telling you which kinds of studies need to be done. Do you need to do nasal in smoking? Is it ethical to do some studies in humans?

I believe our science will evolve to the point that category 1 testing may substantially
reduce the need for certain category 3 testing, but
we're not there yet. And in fact, it was discussed
yesterday quite a bit. We really aren't to the
point that we can go from category 1 and predict
category 2 accurately, and predict category 3
accurately. And I think that has a lot of
implications.

There are certain cases where there is a
delayed onset that is substantial. In such cases,
that may predict outcomes in category 3.

Certainly, a drug that onsets in a couple of hours
is going to be less likely to be abused in general
than a drug that onsets very quickly.

Of relevance to generics, we just, as I
mentioned, are not at the point of being confident
that in vitro data are sufficient to predict key
attributes that could be determined by category 2
and 3 testing.

The good news is that the science is
advancing rapidly. And I think we are at the point
that on the basis of thorough in vitro
characterization in standard PK studies, category 2
and category 3 testing may be streamlined, especially where the technology is the same as the innovator product.

I think this is going to have to be discussed on a case-by-case basis with FDA, taking the step-by-step kind of approach that's been discussed. I really don't see any way around that at this point. There's a lot of call for standardization. I think we can only go so far from standardization at this point. That's the reality of the diversity of the products that we're facing.

Finally, for approval and labeling, I think FDA still must be confident that the studies have met what my colleague, Ed Cone, calls the rigorous and relevant standard. And we have to constantly keep looking at what's happening in the real world or community for approval.

Finally, what is enough for approval of a generic, I think, will have to be determined on a case-by-case with FDA, in particular because they're not going to be all using the same
technologies. So in some cases, I think there will be cases where we can really streamline the category 2 and 3, and in other cases, it may not be possible. Thank you very much.

I really have to commend you guys for what you're doing. This is so exciting for those of us that have been in the field for decades. This is just remarkable progress. Thank you.

DR. THROCKMORTON: Thank you. Next speaker is Eli Briggs.

MS. BRIGGS: Good morning. My name is Eli Briggs. I am the director of government affairs at the National Association of County and City Health Officials. We represent the 2,800 local health departments across the country, and we applaud the FDA for its consideration today of the development and regulation of abuse-deterrent formulations of opioid medications.

Prescription drug misuse and abuse is the fastest-growing drug problem in the United States and is a grave public health concern that many local health departments are tackling head on.
Each year, 15,000 lives are cut short due to this problem and, put simply, the development of abuse-deterrent opioid medications will save lives.

Harm reduction strategies such as providing naloxone to third-party recipients and first responders have already begun to save lives, and many of the largest local health departments, including Boston, New York City, and Chicago, are on the front lines of this work.

There are also other strategies such as patient review and restriction programs that help curb the prescription drug abuse and overdose epidemic. And public health professionals also work to educate the medical field about safe prescribing practices that will prevent drug abuse.

We also applaud the discussion today of the prescription drug-monitoring programs that we certainly feel need to be more widespread and more used across the country.

A powerful and logical next step is the development of abuse-deterrent medications. And we urge the FDA to utilize robust surveillance to
measure the lives saved once these new medications are available and also doctor and patient education about the benefits and potential risks of the new formulations will go a long way.

Local health departments are partners in this work and look forward to continuing to work with FDA on this important issue.

DR. THROCKMORTON: Thank you very much.

Shekhar Mehta.

DR. MEHTA: Thanks and good morning. I just wanted to thank the FDA for holding this public meeting on a very important topic and also the moderators and panelists for providing great information and insight. I'm Shek Mehta and I'm with the American Society of Health System Pharmacists or ASHP.

ASHP is a national professional organization whose over 40,000 members include pharmacists, pharmacy technicians, and pharmacy students who provide patient care services in acute and ambulatory care settings, including hospitals, and health systems, and clinics.
For 70 years, this society has been on the forefront of efforts to improve medication use and enhance patient safety. ASHP believes pharmacists have the unique knowledge, skills, and responsibilities for assuming an important role in substance-abuse prevention, education, and assistance, and appreciates and commends the FDA and stakeholders for undertaking work thus far in attempts to curb abuse from opioids.

In 2012, ASHP actively advocated in support of rescheduling hydrocodone because our members believed that the resulting increases in safety outweighed the risks to patient access and administrative burden.

We know that death rates from drug overdose have tripled since 1999. And Dr. Gross, you also mentioned that ER visits from inappropriate use doubled since 2004. Three agents, oxycodone, hydrocodone, and methadone, account for almost 80 percent of these ER visits.

ASHP supports measures such as the formulation and development of abuse-deterrent
opioids as one in a collection of strategies to
address this national issue. However, ASHP
cautions the FDA to recognize the unintended
consequences of implementing preferential programs
for abuse-deterrent formulations and weigh those
consequences against the realistic benefits of such
formulations.

These unintended consequences can include
things such as costs and the social stigma to
patients that legitimately require higher doses of
narcotics or opioids, for example cancer patients.
In addition, the introduction of new formulations
with variable bioavailability to the market can add
complexity to therapy.

The society recognizes that, from a
population health perspective, abuse-resistant
formulations may not reduce the overall level of
abuse. Although some evidence suggests that, for
specific agents, abuse diversion in medication
areas decline after introduction of the
reformulated ADF product, existing data indicates
that the introduction of the ADF product causes
abusers to simply switch to alternative and often illicit agents such as heroin.

ASHP urges the FDA to further investigate the efficacy of these resistant formulations of opioids in preventing drug abuse prior to taking regulatory action to incentivize the development.

The society recognizes and advocates for a collaborative and multi-faceted solution to the opioid abuse problem in the nation. And this solution might include strategies such as a national prescription drug or prescription opioid monitoring system. The organization strongly recommends an assessment of current and future research, necessary to ensure that the most effective combination of tactics are being used to deter abuse.

I thank you very much for your time, and we look forward to working with other stakeholders to address this issue and providing written comments in January.

DR. THROCKMORTON: Thank you very much.

Next speaker is Julian Phillips.
MR. PHILLIPS: I guess we are a little ahead of time, so I guess I can take a bit extra. Thank you very much, everybody else, for being so fast.

First, my name is Julian Phillips, and today I am actually representing myself and not just Paul Gileno. I am from the U.S. Pain Foundation, and I am an ambassador in Pennsylvania.

I was going to throw out some various statistics, and numbers, and things, but I was reminded from yesterday, with all the numbers and statistics that were thrown out, of a statement made by an American named Mark Twain, who is attributed this saying to British Prime Minister Benjamin Disraeli, although that's not necessarily true. And the statement that came out was that there are lies, damn lies, and then the statistics.

So today, I have decided to completely rip out what I was going to say about pain, et cetera, and just tell you a 32-year story in as short time as I can. That story is my story.

Some 32 years ago, I was playing a game of water polo, dislocated my right ring finger. After
that dislocation and not doing much about it for a few weeks, I eventually went to a hospital in Britain. They threw me out because they said it was two weeks, so you don't need to see anybody. You need to go to your own doctor.

Long, long story really short, after many, many sorts of treatments from splinting to shots to medications, I had surgery. That surgery led to, in the 12-year period, approximately 19 more surgeries, culminating in the amputation, moving nerves around, and being decided that I had a thing called RSD, which I had never heard of, and told, "You better get used to it, pal, because you're going to live with it for the rest of your life. Oh. And by the way, it may get worse."

Well, the "may" turned into reality. It did. I came over here in 1991. I was not using that many medications because I recognize that, every time I took a powerful narcotic, I was exchanging a little bit less pain for a lot less brain.

As a job of running businesses, and to come
over here -- incidentally, I had to have my own business, I had to employ Americans, and I had to spend in the excess of $150,000 to stay legal, which I had to do for my family. I needed my brain. And so I tried as hard as I could to take as little medication as I possibly could.

I ultimately ended up, in 2003 I think it was, having a spinal column stimulator. Now, incidentally, during this period of time, I had tried every type of treatment that was, whether it was conventional or non-conventional, from the pins -- can't think what they're called right now, I'm sorry -- to many, many other treatments, including a cannula being thrown into my stump and left there for a week, which was probably one of the most painful things I've ever experienced in one 10-minute time while they were trying to get this thing into the nerve, without anesthesia, of course.

I want you people to understand something, please. You've got to put a face on this thing called pain. It's human. There's 100 billion
people suffering with pain today in the United States. We're real. And yes, you can come up with all sorts of things. You can come up with statistics. You can come up with anything you want to say of the abuse, et cetera.

You can come up with abilities to change the medications so that they are not abused, can't be abused so easily. But you know one thing that will happen and will happen with surety? And that is, the people that want to abuse it will change something and will abuse it.

You'll spend millions and millions of dollars. And you'll cost people like me the inability to get the medication that he needs for being able to change it for the space of perhaps two, three weeks, maybe months, maybe a year, even, but they will change it and they will abuse it. That's a fact of life. You know it. I know it. Everybody knows it.

So please, please, yes, I am really grateful for you doing this because I do believe, passionately, that one life lost is one life too
many. I don't care whether it's from abuse of medication, whether it's from alcohol issues, which believe you-me cost the country a lot more than abuse of the medications. So please put the human face to what you are discussing.

I appreciate you doing this. I think it's very important, and I will always advocate for things and methods that will help reduce the possibility of abuse because, ultimately, that does mean that I might not get the medication, which right now, my insurance company have changed their formularies, so I have got two medications I can't use next year.

My health professionals don't like prescribing, and they have got me on contracts and goodness knows what. Just put a human face to it, please. Thank you very much for listening to me.

(Applause.)

DR. THROCKMORTON: Thank you, sir. And the last speaker, Daniel Cohen?

MR. COHEN: There's a saying in Congress that you get to the point in every debate where
everything's been said, but not everybody has had a chance to say it, so I'll take my turn at it.

   My name is Dan Cohen, and I serve as the head of North American Government Relations for Grunenthal USA. I also lead the Abuse Deterrent Coalition. It's an informal communication group of over 20 abuse-deterrent manufacturers and patient advocacy groups who seek to expand the use of abuse-deterrent technology. And a majority of our members have participated here in these last couple of days.

   In the short time that I have, I am going to take a simple point. Drs. Woodcock and Throckmorton opened our session yesterday, and again today, with observations about abuse deterrence that is very much aligned with our goals and ideals as abuse-deterrent technology suppliers.

   However, the public sector's and the private sector's understanding of the meanings of the terms real world, real incentives, and iterative approach to improvement, we differ on those. As used by the agency, perhaps the unintended effects are not the
same as those used by real-world manufacturers.

The product-by-product approach, the open-ended aspect of abuse-deterrent approvals, is somewhat akin to Oliver Twist asking for more. More what? It's not enough to ask for more ADF because we don't know how much is more when a standard has been met, or even if there is equitable treatment between and among products.

As a regulated industry, we're asking for greater surety, because without surety, companies that have other diverse product lines are under pressure to divert resources from abuse-deterrent research to those that do have a clearer pathway to success.

More importantly, for my coalition, the early stage, the aspirational, the entrepreneurial members, the ones who live on investor funding for their very survival, are seeing those funds drying up as the capital markets conclude that abuse deterrence is not a priority.

The approach to abuse deterrence should be less Oliver Twist and more John F. Kennedy. This
nation should commit itself to achieving the goal
before the decade is out of ensuring that every
solid form Schedule II opioid and stimulant has a
current state-of-the-art abuse-deterrent technology
embedded within for branded and generic alike.

Tell us as industry to deliver abuse
deterrent on a date certain, and we, together,
through our innovation and your approvals, can
jointly deliver a solution.

The terms and incentives means to industry
that we have to balance time and money. FDA has
the power to appropriately incentivize industry,
but does not yet offer the correct formulation. We
really just need two incentives for us both to
succeed.

So as not to waste it, incentivize our time.
Finalize the draft guidance for abuse deterrence to
set out specific, appropriate, and consistent
testing standards for all opiate and stimulant
Schedule II products, branded and generic.

We need the surety of a testing regime to
know if our research will likely result to product
approval. To ensure continued investment, incentivize our financial resources. We don't ask for public money, public monies you don't have. We simply need a date certain when the entire Schedule II opioid and stimulant market must convert to abuse deterrent. We can then scale our investments of time and money to meet those challenges.

Give us these twin incentives, and our industry will give patients and parents effective pain relief and stimulant products that contain real abuse deterrence as we are discussing today. With the surety of your commitment to require abuse deterrent, current and aspirational abuse-deterrent manufacturers will be able to maintain and increase investment in current and future technologies.

Lastly, we need to do this to build on the product such as the new formulation of abuse-deterrent OxyContin. There has been a marked improvement in its abuse profile. In the first three years since its introduction and ultimately, FDA approval of the new label, there has been an
86 percent decrease in the deaths due to overdose.

While not a silver bullet to solve all forms of abuse, this abuse-deterrent product has reduced the diversion based on the abuse of this needed painkiller. Yet, back to the word "more" again, as current abuse-deterrent products cover only about one-half of 1 percent of all product sales, we need a clear pathway for more approvals.

As many have stated, no abuse deterrent is 100 percent effective, but they are a significant safety improvement over drugs without any abuse deterrents. Do not let the pursuit of the perfect become the enemy of the good.

The only thing abuse-deterrent manufacturers need to undertake the risk to develop new technologies is for FDA and manufacturers to provide real-world assurances, assurance that a decision to invest in developing abuse-deterrent technology will be rewarded if we meet your specific metrics and timelines, and our assurances to our families that we will protect and support patients as we take every reasonable step to
include abuse deterrence in the most abused drugs society has today at the earliest feasible date.

While I was planning to end here, I can't help but just respond to one point about those that have raised questions about abuse deterrence. John Adams and Gerald Wilde posited a concern in a similar format some time ago, that these products need more research; that there's no proof that the expense will outweigh the cost; that it may work in individual products but won't work across the industry, the consumers should decide if they really need it; that the benefit of protecting someone from risky behavior means that the propensity to take greater risk will continue.

Adams and Wilde were professionals at the Institute for Economic Effects. Those were the arguments they used to lead the campaign 50 years ago against seat belts. Thank you.

DR. THROCKMORTON: Thank you very much.

That concludes the open public hearing. I think we're going to take a 15-minute break now. Actually, I guess it is a 16-minute break. I'll
see you back here at 11:15. Thank you.

(Whereupon, a recess was taken.)

Panel Discussion

DR. THROCKMORTON: If I could get everybody to sit back down, please, that would be terrific. I'm going to go ahead and get started as people find their seats again so that we can be respectful of lunch. I know that's important for everyone.

This next session is going to be a panel discussion with a set of individuals -- individuals with a broad set of backgrounds and expertise -- how's that -- that have seen the Federal Register notice, have seen the questions, and we're basically asking them to comment and then discuss them. The hope is that, in that discussion, we're going to be getting a lot of help that we're needing in those specific areas.

So what I'm going to do is, I'm going to ask each one of them to give their own brief bio, just basically who they are and a little bit about their background, what they're bringing to the discussion. And then either myself or Carol
Bennett, who is from our Office of Regulatory Policy here at the FDA, will be going back and forth asking the individual questions.

Then as individuals on the panel have a comment about that question, I'd ask you to raise your hand, or we'll go down the line, or something like that. And then once that's done, basically I would ask you to discuss amongst yourselves.

If you were here yesterday, you saw how that worked. It worked exceptionally well yesterday. We got a lot of valuable information in that back and forth. The FDA individuals are here to clarify questions and things; otherwise, we plan on taking notes and admiring the depth of your comments and thoughts.

So with that, why don't we start? Bernie, you've already introduced yourself, so we'll go to the next individual.

DR. BAUMGARTNER: Hi. I'm Todd Baumgartner. I'm chief medical officer and head of R&D at Purdue Pharma. I'm a physician. My clinical training is in family medicine, and preventive medicine, and
public health. I have a master's in public health
as well. I've been in the industry for about
22 years, formerly at Bristol-Myers and
AstraZeneca, and have been at Purdue for five
years.

I think, as you saw earlier today, Purdue is
very interested in this space of abuse-deterrent
formulation technology. We have two approved
products with labeling, and we have a big pipeline
in this area.

MS. EDWARDS: Candis Edwards, senior VP of
clinical regulatory affairs at Amneal
Pharmaceuticals. I'm here to speak on behalf of
the generic industry and our interest to move
forward with policy and strategy for approval of
generic abuse-deterrent formulations. I've got
35 years in the industry. I am also associate
professor at Saint Johns University in the graduate
regulatory program.

DR. KREBS: Hi. I'm Erin Krebs, and I am an
internal medicine physician. I have been asked to
be here today to represent the perspectives of
practicing physicians on behalf of the American College of Physicians. I have a primary care practice myself. I work for the Minneapolis VA, and I am also an associate professor medicine at the University of Minnesota. It's important to note I am not representing the perspective of the VA today, so my opinions today are mine and with the goal of, again, representing practicing physician perspectives.

MS. KRIVACIC: My name is Susan Krivacic, and I am an independent patient advocate or patient representative, mainly in the area of oncology. I'm a 25-year non-Hodgkin's lymphoma survivor, somebody that has used opioids in the past for chronic pain when I was diagnosed with cancer back in the late '80s.

I also have my own consulting practice as well, PBG Consulting, which is a management consulting firm working mostly with clinical research organizations, other life sciences companies. And I have been doing that for over 10 years, but also previous to that was in the
clinical research industry for about almost
20 years, so I've got probably about 30 years,
nearly 30 years' experience in the industry as well
as over 25 years, I guess, as a patient advocate
for various organizations. So I have kind of got a
dual role.

I have also been on a number of these FDA
advisory committees for the opioid abuse-deterrent
formulations going back, I believe, almost to 2007
or 2008, when the initial one with oxycodone
started, so thank you.

DR. MICHNA: Hi. I'm Ed Michna. I'm an
academic pain physician at Brigham and Women's
Hospital in Boston. In my past life, I was also a
lawyer and a pharmacist. Because of that, I have
done a lot of public policy work in this area. I'm
on the board of the American Pain Society, and I'm
involved in the public policy committee for them
also.

DR. RICH: Good morning, everyone.
Dr. Robert Chuck Rich. I am a practicing family
physician from rural southeastern North Carolina,
so you can understand the accent. I am representing the American Academy of Family Physicians again. I am their incoming chair of the Commission of Health and Public and Science and their former chair of the Opioids and Pain Management Workgroup, which is responsible for doing a fair amount of the work for AFP in terms of setting policies and procedures for management of opioids.

I am also a regional medical director for Community Care of North Carolina, which is the nonprofit organization administering the Medicaid program. And one of the facets of that program is that it is education to the Medicaid providers about opioids and pain management through Project Lazarus, in which I have actually been going out to practices and actually doing provider education actually in the practice just about opioids and safe prescribing.

DR. SKOLNICK: My name is Phil Skolnick. I'm the director of the Division of Pharmacotherapies at NIDA. I've been there about
four years. Prior to that, I was the president and chief scientific officer of Dove Pharmaceuticals. Prior to that, I was a Lilly fellow in neuroscience. I am here, says NIDA, but whatever views I express today are my own. They don't represent those of the NIH or NIDA.

DR. WOODS: My name is Jim Woods. I am an academician. I'm at the University of Michigan, Department of Pharmacology. I already confessed to you this morning that I used to give lectures on narcotics to medical students, which I no longer do.

I was, for about 30 or so years, in charge of a program, a preclinical pharmacology program, for abuse liability of narcotics that was run under the aegis of the College of Problems of Drug Dependence. So I have a lot of experience with preclinical abuse liability assessment, which I will probably express my opinion about later on.

DR. KLEIN: This is the little FDA table. I am Michael Klein for the controlled substance staff.
DR. HERTZ: Sharon Hertz.

DR. LIONBERGER: Rob Lionberger, Office of Generic Drugs.

DR. RAULERSON: Patrick Raulerson, Office of Regulatory Policy.

DR. BAUMGARTNER: My apologies. I forgot a very important aspect of my presence here today. I am representing the Branded Industry Working Group. It's a pretty important feature. And Dr. Brodsky made a presentation from that group this morning as well.

MS. BENNETT: Thank you all so much for agreeing to be on our panel today and bringing your very diverse experiences to this important issue. The first question we want to discuss involves labeling, which you have heard a lot of discussion about over the last day and this morning as well.

Does labeling incentivize the use of abuse-deterrent labeling? Does that incentivize the use of opioids? Does it incentivize the manufacturer creation of abuse-deterrent opioids? Does it make these products more likely to be used, less likely
to be used? And what impact would the labeling
have on the creation of generics?

So I open it up to you all. You can go in
order or jump in as you feel moved.

DR. MICHNA: I'll start off. I guess
everybody else is shy. My theory has always been
on the labeling, is that clinicians make false
assumptions based on the labeling.

OxyContin had a tremendous problem, and
after reformulation, that problem was largely
addressed. But that being said, it wouldn't be a
drug that I would recommend to give to a patient at
risk or is demonstrating risky behaviors, based on
its pharmacokinetics, its pharmacodynamics. So I
think we have to be careful with the labeling.

I wanted to hop on what was said earlier by
some of the patients out in the audience. I think
these drugs are meant for patients. And we have to
be sure that there is some benefit to patients.
And right now, we really don't have the data on
what type of opioids or what formulations and what
percentage of patients go from using it for
legitimate medical purposes to then misusing them and abusing them.

Dr. Woodcock, initially when she came out, she talked a lot about misuse. And in a clinical realm, it's misuse that's our major problem.

So I think, if you could direct some of the research that's going to be done on these products to focus in on patient effects -- for example, you take a patient that is now misusing, overusing for anxiety for whatever reasons, and then you expose them to your product. Does that behavior change? Do you normalize it? Does your overall dose improve?

That's one creative way of looking at it. The other way is the flip side. When patients are exposed to your drugs, is the incidence of evolving into a bad pattern of misuse and eventually abuse going to occur?

A lot of these factors are unknown. I equate it to, say, fine wine. If you're going to have wine and you're drinking cheap wine, you're not going to want to drink enough of it to really
make a difference if you're not doing it to abuse it. But if you get a good bottle, you're going to drink a lot of it, and maybe you're going to drink more than a lot of it. And that might drive an overuse pattern that gets you into an abuse kind of criteria.

So these are just my iterations here, but I think it's really important to really focus on individual products, and individual drugs, and pharmacodynamics, and pharmacokinetics of these drugs.

Is a flat kinetic profile, even of a drug that is high-reinforcing, is that better than one that dumps a lot of the drug up front? I don't know, but could be an interesting question to ask. And as these drugs are developed, maybe some of the research could be focused on that area.

I have taken enough time. I'll let somebody else speak.

DR. KREBS: So I really agree that I am concerned about how labeling could be misinterpreted or mislead. I think this is a
problem that we've seen over the last couple of decades, as I was taught in medical school and residency that patients with pain were relatively protected from developing addictive disorders and that that was not something we needed to be concerned about.

I was also taught that the long-acting drugs may be less likely to induce addictive disorders because they didn't have those habit-forming properties. People didn't get a quick high. Well, I think we can recognize right now that those things were myths, and that we've been too comfortable and too casual in our prescribing of these medications. And now we are trying to reel it back and understand how we can more safely and appropriately use them.

I am concerned that especially a prominent and strong label that says abuse deterrent will be confusing, that people will not understand that, in fact, what it deters is tampering with a product rather than actual development of abuse or addictive disorders.
As someone who practices in primary care, I can tell you that my patients who struggle with chronic pain, many of whom have a vulnerability to an addictive disorder, who maybe have experience or struggled with addictive disorders, don't really sound like the abuser we've heard so much about the last day or two.

So they are not crushing their drugs. They're not smoking them. They're not shooting them up. They are not trying to get high. Their goal is to get relief and to get their life back. And sometimes, they have very high expectations that their medications might help them do that.

Sometimes, those expectations can lead people astray, and then there are all these gray zones of misuse that occur in practice, again, not by people intending to abuse the drug. No one wants to become addicted, but we know that, in practice, this stuff happens. And so I just wonder, can these new formulations prevent that kind of patient harm?

Without seeing the evidence for that, I
would be very hesitant to endorse a strong abuse-
deterrent label. And for my patient, when I am
sitting there, I'm not concerned that my patient is
going to crush and inject the drug. I'm concerned
that they'll become habituated, have physiologic
effects from the drug, and maybe develop an abusive
disorder over time, or that perhaps the medication
will be accessed by a child in the house, someone
else, and usually just taken orally.

That's the big concern. I think that's
what's driving the epidemic. So there's my concern
about strong labeling and this focus on really
tamper-deterrent products.

DR. RICH: I would add to that the question
in terms of provider education about the purpose of
the labeling. Again, my concern is, as a
practicing physician, many primary care physicians
that give it are not necessarily with proper
education by the FDA and our professional
associations as to what labeling actually
represents and what, actually, abuse-deterrent
formulations represent.
I'm sure practicing physicians want to do the right thing and will try to prescribe appropriately again, but without a full understanding of what the terminology means, what abuse-deterrent formulations actually get you, I am not sure, again, how well labeling will be received by the rank-and-file primary care physician.

MS. EDWARDS: So from a generic perspective, I would think that the labeling is important for a manufacturer because it's important for us from a safety perspective to identify any particular properties that one of our products may have. When you think about, from the perspective of the patient, the drugs or the class of drugs that we're talking about with regard to the long-acting drugs are covered by REMS programs.

I think the appropriate place to address the education component of the information in the labeling and what that means to the practitioner should be more appropriately addressed through a REMS program.

However, the information, I believe, does
need to be on the labeling, and from a purely generic perspective, it doesn't necessarily impact us because what we're doing is we're copying the brand. But I still see it as important information because it identifies an important criteria or characteristic of a particular drug product.

    Again, the REMS should be designed appropriately such to educate the practitioner, the patient, and to govern that whole process around the usage of the drug.

    DR. BAUMGARTNER: So from a branded industry perspective, as Dr. Brodsky presented this morning, we do think clear labeling to describe the abuse-deterrent features is an incentive for development. And the steps that FDA has taken thus far, I believe, have accomplished that to some degree.

    As Dr. Hertz said this morning, these drugs are not abuse proof. That's not the intent. And I think the labeling that's come out has had many caveats around that to make sure that, that impression is not conveyed.
While labeling is important from an incentive perspective, as was mentioned this morning, there are other incentives that would help further incentivize such as adding additional exclusivity related to the work that's gone in, particularly the clinical work that's gone in, as well as very important messages that were conveyed this morning about FDA playing a role in ensuring that reimbursement for this innovation is rewarded by the payers. But we think the labeling is a very important step and a very useful step.

MS. BENNETT: Can I ask a payer to comment on whether the labeling is important for that side of the equation?

DR. GOOD: So labeling is important, generically speaking. Labeling is very important because our assumption -- if a drug carries a labeled indication, our assumption is that the FDA has reviewed the evidence supporting that claim and that the evidence is robust and trustworthy.

So I think labeling is important, and I would agree with Dr. Krebs that our concern would
be, then, if it says abuse-deterrent formulation, there could be the misperception that, then, this is going to deter the abuse that we most likely see, which is not crushing, snorting, shooting up of these drugs, but it's misusing intentionally or unintentionally by an oral route.

MS. BENNETT: Can I ask about the patient perspective? Does the labeling make a difference to the patient?

MS. KRIVACIC: I'm sorry. I didn't mention before, all my comments are my own independent views, representing patients. From a patient perspective, I would think that the labeling would also need to include information that this is equal to the original formulation so that it's providing the clinical benefit just like it would without the abuse-deterrent properties and is also safe.

I know one of the things I always do -- and I hear this from a number of patients, too -- is they will ask their doctors, "This is a new medication. Is this safe? And is this as effective?" And that's a very important piece of
this entire puzzle, and it speaks to that first goal that Dr. Woodcock talked about yesterday.

MS. BENNETT: Any other comments on labeling?

DR. KREBS: Yes. I guess, towards just that point of safety and effectiveness, I think it's important to recognize that we really lack the kind of information we should have about these drugs, using them, especially for chronic pain long term. There was a NIDA conference just last month and the task force report from that included that the panel was just shocked at how little evidence we had and that, really, practicing clinicians had insufficient evidence for every single important decision that they made about opioid prescribing.

So in that context, we don't know the risk of developing an opioid use disorder for a patient started on any of these drugs. We don't know if the dose really matters there, if the formulation matters. And so just to step back, we have a lot of unknowns, and I hope that we will continue to focus on the research that we need in terms of
outcomes for patients.

Those safety outcomes are important, and my patients want to know how likely is it that I could develop an addiction if you start me on this drug? No one wants to develop an addiction.

DR. THROCKMORTON: So to transition a little bit, we want to ask you some questions about what it means to be meaningful to have that impact on abuse that I think we'd all like to have. The background is that the draft guidance that we put out uses that word. It says, "We're going to give you labeling when you've demonstrated that you've either predicted or actually do have meaningful impact on abuse."

I think others have commented in today's meeting that meaningfulness is not a term, a bright line sort of thing. And some people have suggested today that premarket information is sufficient to be able to make a conclusion about meaningfulness. Others have suggested that you can't really know that until you get into the real world or have postmarketing data of varying amounts and things.
So just we're interested in, from your perspective, what does it mean for a product to have a meaningful abuse-deterrent property and what kinds of data you'd be looking towards to make that sort of a conclusion.

DR. BAUMGARTNER: So from a branded industry perspective, as Marina mentioned, we talked about this a lot in our group. And we really came down on the view that, essentially, something analogous to a tier 3 labeling claim is a really differentiating feature to show meaningful abuse deterrence, essentially data to support a tier 3 claim that the product is expected to result in a meaningful reduction in abuse.

DR. THROCKMORTON: For clarity, what that means is that they have conducted a human abuse liability study, a premarketing controlled study that looks at how well -- individuals that have experienced the use and misuse of these products, how well they like the products under various conditions.

DR. BAUMGARTNER: My apologies. I sort of
live deep in this, and I realize it's terminology.
And believe me, I don't follow the terminology,
either. And I think an important point to be made is, as was shown yesterday, in many, many cases,
in vitro testing is really not going to be sufficient to predict the impact this formulation is likely to have.

Data were presented yesterday by one of my colleagues that showed, for example, with intranasal abuse, even pharmacokinetic information didn't necessarily translate to how abusers felt about the product when it was done in a human abuse liability study.

So where human abuse liability studies can ethically be done, we think that they should be done as a minimum.

MS. EDWARDS: So from a generic perspective again, we are in the market. We are attempting to come to the market. And we want to meet the same requirements that the brand product does. So in order to accomplish that, we use the brand as a standard and we identify what we talked a little
bit yesterday about, critical product attributes.
And we've built this box and set the four corners.
And then we set a goal to evaluate our product
against that standard.

So with that in mind, I think that the
in vitro data and some of the in vivo, maybe tier 2
to an extent -- and we have presented up to that
level at a minimum. And in certain circumstances,
possibly tier 3, which would be that human
likeability factor.

But it would all depend on a complexity of
the product itself and in the comparison between
the technology being used for the generic to match
the brand would determine the level of data.

With regard to the postmarketing data, from
a generic perspective, I think that we would be
relying on the brand product to establish the
effectiveness of that abuse-deterrent component of
the product. And I don't think it would be any
added value from a generic perspective to have to
provide that data in order to demonstrate that
there was some meaningful abuse-deterrent
components to a generic product.

DR. Michna: I certainly agree that you have to put these drugs in human beings because that's always the question. Does laboratory data suggest what happens in humans? And frequently, that is not the case, so I agree with that.

At the same time, I wouldn't want to make the hurdle so great for generics that we don't develop these products for appropriate drugs that have been past their patent life and effectively giving the branded product a lifelong patent. So I think there has to be some accommodation that will address both of those needs because, as we said, it's access of care.

I don't write branded products because I can't. The insurance companies won't let me because of the cost. There are times when those might be appropriate.

So anything that we can do to reduce that barrier to access to care for those patients deserving of that particular molecular entity, for whatever reason, and certainly when a drug is
reasonably off its patent, I think that would be the approach that I would recommend.

DR. KREBS: So I think the conversation so far, it sounds very reasonable in terms of a label for tamper deterrent. I just continue to worry about the idea that these would be broadly abuse deterrent. And there, what I would really like to see, actually, would be studies in the patients for whom the drugs are intended.

It's hard to imagine. It's kind of funny to think about actually testing drugs only in the people who aren't supposed to get them and not in the people who are. So I think we need at least prospective observational studies that actively ascertain abuse, misuse, and addiction outcomes in patient populations as well as the kind of big picture epidemiological surveillance data if we're really going to say that these are making meaningful differences in terms of abuse and the epidemic of abuse.

So that's what would be meaningful to me, not that I would want to discourage the development
of tamper-resistant properties at all.

DR. THROCKMORTON: So I'm going to meld this discussion into the next question. Then I'm going to go back to Erin, because I'm going to make it harder for you, Erin.

I think we all agree it would be terrific to have better data. I'll probably say something more about that later on. But you're going to have to make a decision, so you have to choose under what circumstances you are going to choose to take an action, some of that ladder of actions that we've talked about. And so the next question actually asks at that. "Given what you know or what you believe you'd like to know, when would you act?"

So think about this both in terms of what it means to be meaningful and also in terms of what it means to be sufficiently sure that it is meaningful to take an action, take an action to remove a drug from the market, take an action to not approve a drug, makes it a little harder sometimes in those circumstances maybe to ask for large amounts of data.
So let's talk about this not only in terms of meaningfulness, but when it's meaningful enough to have you recommend that we do something that would impact availability of a product on the market. You want to answer that one.

DR. KREBS: So there, I think we just need to balance benefits and harms. So I guess what I'm arguing a little bit here is that the benefits of some of these new formulations might not be as broad as we are hoping. It's possible, but that's testable and knowable with time.

So if it's just approving them, fine. If it's taking regulatory action to remove generic alternatives that are much less expensive and more accessible, I mean, that's a potential harm.

I would not be ready to move in a regulatory manner against existing, accessible old formulations unless, really, the new formulations clearly were showing real benefits. Otherwise, we may end up just really devoting a lot of resources and investment in a strategy that doesn't make a huge difference in terms of the population-level
abuse and addiction problem that we have.

DR. MICHNA: Yes, I agree on that. I mean, it's the degree of the problem. Right? The old OxyContin was a significant problem. In that case, in a similar situation, I think it's a no-brainer that you would remove that non-abuse-deterrent product.

The question goes to generic morphine. Yes, it is misused. It is abused, but certainly not to the degree that we saw with OxyContin. And the question is, are you going to force all generic morphines to have an abuse-deterrent technology and add that extra cost, which we have heard about at multiple levels, and insurers can speak to this, when the overall benefit to society is probably limited.

The problem with these abuse-deterrent formulations, if you're looking at the hardcore addicts, they're just going to move to other things, which we have seen. Right? So now, I talk to my addiction friends. Patients aren't coming in addicted to OxyContin. They're addicted to the
short-acting opioids right now, and that's what we're seeing, or, of course, heroin, which is dirt cheap now.

So we have made an effect, and certainly, OxyContin reformulated is not the drug that's desired as it used to be. And that's a good thing, a good thing for the company, a good thing for physicians and their willingness to prescribe that product. But did we change the whole effect on society?

I guess that question is going to take some time to evaluate, but I think early signs show that we're just getting a squeezing-the-balloon phenomenon in that regard.

DR. RICH: That's a good point. And really, again, I think I am going to have to agree with Edward that the provider is going to need to see that there is overall value to switching to these formulations. And we really do need good clinical evidence in trials, which really, as suggested again, that there is a substantial reason to switch over to many of these products.
We want to do the right thing, but at the end of the day, providers are going to need to have a good, meaningful amount of evidence to suggest, again, that is worthwhile. And as a side note again for those providers at the desk, meaningful sounds too much like meaningful use, re-certification up here, which it has bad connotations.

DR. THROCKMORTON: That's been pointed out. So can you say what kind of evidence you think you'd consider persuasive? How's that for not meaningful?

DR. RICH: For those of us that look at guidelines, look at evidence again, many of us in our professional associations are tasked with looking at and going through, looking at data, looking at how the data is formulated and put together.

We are looking for the key word of "evidence-based" as much as possible. And there are those of us that are tasked from our professional associations to look at data, look at
guidelines, look at studies, and report back to our professional associations, and from the quality of those studies.

So again, we're going to be evaluating the studies, I'd say, from an evidence-based standpoint and looking at all that goes into that.

DR. THROCKMORTON: Dr. Woods?

DR. WOODS: I think we are skirting a lot of issues. And what we're really talking about is evidence that is gained from real-world use and abuse and relating that to some less-well-evidenced set of sample of people under given circumstances.

For example, when we were talking about OxyContin abuse, we're talking about real-world use, but that's an epidemic that has very little precedent, at least from a pharmacological point of view, because it's oral abuse. And these are people that don't always have a long history of drug abuse that precedes it.

So it's a peculiar population that is producing the social problem relative to, say, crack users, for example. I think, in drug abuse
assessment liability, in a general way, we have problems, major problems that we don't really understand well yet.

We can study drug users, drug abusers, in the laboratory under very well-defined conditions, but those conditions are not the conditions that the person on the street deals with. So we don't know what the boundary conditions are for the findings that are based in the laboratory, although we believe, from some points of view, they're the most reliable pieces of information that we have.

So we face this sort of problem all the time. We face with respect to -- and it's not necessarily just related to drug-abuse epidemics. For example, there's a continuing controversy about the effectiveness of anti-anxiety medications relative to what might be abuse of them when taken chronically.

Say, for example, the guy who's been taking for sleep promotion, a benzo for 15 years. I would suggest to you that we don't have the kind of evidence to evaluate that very effectively, for
So I think those kinds of problems exist, and I think they exist under these circumstances that we're talking about. So be careful with respect to trying to generalize findings in a simple way from one study population to another. That's all. Thank you.

DR. KREBS: The study I would design, probably the postmarketing study, would be an open-label, long-term prospective observational study where at intervals, patients who are receiving -- and it should be comparative, so active drugs in both or as many arms as there are, and with active ascertainment by doing drug screens at regular intervals, doing patient-reported outcome assessment that have been developed for some of the opioid abuse-related metrics, and also chart reviews and looking at behavior that could be indicative of developing abuse.

There is not a single test for abuse or not abuse, so it would be really assessing all of those things. They are done. That's been done in other
types of research studies. It is doable. But it
might have to be mandated because it's not
necessarily cheap to do stuff like that.

When you look in chart reviews from clinical
practice, there is evidence of misuse again, not
crushing, snorting, injecting, but lower levels of
gray-area misuse behavior on up to a third of
chronic pain patient charts. So it's not that this
stuff is so rare that we wouldn't detect it in a
longitudinal study.

DR. THROCKMORTON: Would you take action in
the absence of that sort of data, actions like
refusing to approve a product or actively taking
something off the market? Because I'd imagine that
kind of study would take substantial time to
perform.

DR. KREBS: I think, in terms of taking
something off the market, again, like a generic
morphine product, take it off the market. In the
absence of that kind of high-level evidence, I
would not.

DR. MICHNA: Yes. Erin, the dangers of
doing those studies is that -- and many people have shown this, including us -- once you pay attention to patients, their behaviors change. I can take very high-risk patients and put them in a controlled study. I can control their behavior. But once I stopped watching them, that behavior then is re-exhibited.

The same thing has happened in the educational world. You take high-risk kids at school, and you spend a lot of time with them in high school, and then you send them to college, the statistics are, those kids are no better off than the ones you didn't.

So that's what I'm saying. You've got to be careful in controlled studies. That's why, maybe in this situation, real-life evidence is going to be the best we're going to have, and we're going to have to take intermediate approaches until then.

DR. KREBS: But you don't have to do those studies in a highly-controlled environment. I believe you could recruit primary care --

DR. MICHNA: But just paying attention, I'm
telling you, it changes behavior.

   DR. KREBS: I will tell you, too, that, boy, do I pay attention. And you'd think that people wouldn't continue to have positive drug tests, but they do. So again, I think you could recruit patients from a primary care setting, give them free drugs, and some compensation for the bother of having to come in for an outcome assessment by an independent researcher every once in a while, and you could detect outcomes. I believe you could.

   DR. GOOD: So you asked for the next steps. I don't know if FDA has the regulatory authority to require that all new opioids coming to the market have an ADF, but if you don't have the regulatory approval, then strongly suggesting that they do.

   I think you know, Doug, that VA was disappointed with Zohydro entering the market, and especially since it didn't have any abuse-deterrent technology with it. That drug, Vicodin, has a built-in abuse-deterrent formula in that it has acetaminophen, which limits the number of pills you can take a day.
Also, we heard in the public comments several times this issue of seat belts. And while I don't find anecdotes to be useful to drive policy, I think it's reasonable to -- I will admit, I don't know what the evidence base was for seat belts when that decision was made. But had there been a decision that let's gather some information, information that would have been conclusive could have been easily gathered to make that decision.

Again, I think this is not as easy to get the type of evidence that we would like. But there are a lot of smart people out there. The industry is very smart. You've got a lot of great people. Just talking about all the science that's going behind this indicates the level of academic interest that our industry partners have and academicians.

So I think it's a difficult question to do. And I think that it may be that the level of evidence might not be randomized controlled prospectives trials, but I think there can be thoughtful levels of evidence.
We heard from RADARS several times. And
from the RADARS New England Journal of Medicine
report, where they looked at OxyContin, they said
it's important to note there is no evidence that
OxyContin abusers ceased their drug abuse as a
result of the abuse-deterrent formulation. Rather,
it appears that they simply shifted their drug of
choice, most commonly heroin, a drug that poses
greater public health risk.

So I think we need to look at evidence and
try to figure out the societal benefits as well as
the benefits for individual drugs.

DR. BAUMGARTNER: So I could talk more.
This is a big topic. There are a lot of things to
discuss. You have mentioned what's sufficient
evidence to act. First, I thought it was from a
prescriber level, and then I am thinking for
regulatory action, as well, so I will comment on
that as well.

I think the branded group also discussed
this extensively, and I think we settled on, again,
if an abuse-deterrent formulation comes in that has
labeling to describe it, essentially, abuse
deterrent at the level of a tier 3 claim, which is
human abuse liability studies, that's a significant
advancement. And we do recommend that FDA then
take a step back, review the risk/benefit of all
the other similar products on the market, and make
a judgment.

I think it's our view, as was presented by
Marina earlier today, that if an ADF product comes
on the market, there should be all haste made at
taking the non-ADF formulations and getting them to
the degree where they are abuse deterrent, but a
two- to three-year horizon, we think is reasonable.
And otherwise, there may be no place for those
non-ADFs on the market anymore.

The other thing I would say is category 4
data, which is the postmarketing epidemiology data,
is great to have, but it's not always easy to get.
We were fortunate to have a pretty good example
with OxyContin, where there was a high level of
prescribing and there was a marketplace shift.

I think if you can't show -- and I think we
have shown that there was a major impact on abuse in the real world, but we're not always going to have that much data available. It's going to be more difficult for drugs that are less prescribed. I think, waiting for that to come in to be the marker for taking an action, there will be a lot of unnecessary morbidity in the meantime.

MS. EDWARDS: So I would like to say this is one area where I think the generic group agrees with the branded group in that once a product is brought into that arena of having those characteristics of some properties for abuse deterrence, then FDA should look at the other products on the market.

But I think our position was a little more cautious in that you don't want to create a drug shortage. It would have a significant impact on the patients. I heard something very interesting today from the VA in looking at the cost, the significant cost that just that small portion of the population is spending on a generic product. So yes, the decision does have to be made, but it
has to be made with caution.

Also, there has to be a path forward, just another thought I have, because one of the things that are blocking the generic industry right now is we don't have a path forward in order to bring forth some of these products. And I know that the agency is working on that, and we're very excited and look forward to having some guidance on that aspect as well, but I think -- and, too, we're comfortable with some answer on meaningful data. That may be part of what's slowing down progress in terms of getting generics approved with these properties.

MS. BENNETT: I just want to clarify a point with the brands and the generics. Do you see a difference, the bar to not approving generics that are coming on the market without ADF properties or brands without ADF properties versus taking something that's on the market off?

What we heard this morning was it sounded easier to block stuff coming on the market than it was taking stuff off because we have heard people
talking about a phase-in period. Could you discuss that a little bit, your differences there?

DR. BAUMGARTNER: I'll try. I think we would agree with Dr. Good, which is that we're at a point now where this technology has advanced to the point where it's been shown it can be done. And there probably should not be approval of new chemical entities or new opioids without abuse-deterrent technology in them. It should be a cost of entry, I think we believe.

I guess that would go also for entry of generics. I think the FDA has already ruled that there's no place for a generic to the old OxyContin. And I think we would believe that way of thinking should be extended.

As far as the barrier to removing products already on the market, I think I already stated that we think it's reasonable that there's a two-to three-year phase-in for that, but the ultimate goal should be to get those non-ADF products off the market.

MS. BENNETT: Is that a consensus within
your industry on the branded side, do you think?

DR. THROCKMORTON: Consensus that the science is sufficient that we are in a place to require. In other places, people talked about, we're still in the early stages of abuse-deterrent technologies. And we have taken that to mean that we needed to wait before we prescribed, required, their development, cost entry I think is the way you said it.

So I'm just asking -- you're saying something different, and I just wanted to see if that was something you meant.

DR. BAUMGARTNER: I guess I'm now missing the subtlety here. Could you re-say it?

DR. THROCKMORTON: You seemed to say abuse-deterrent technologies are good enough, that we can require them for all new products. Others have said abuse-deterrent technologies are still early on. We have a small number of products on the market with established characteristics. There's a lot of fabulous work going on that we have not yet seen through to development. It's
early to require that technology as a part of an approval.

So I was just trying to -- those are two different positions on where we are in terms of the science right now.

DR. BAUMGARTNER: I will look to my colleagues in case I misspeak here. There are several of them here. I believe our view, the general consensus was, in situations -- I think it was mentioned earlier today -- in situations where there is an unmet medical need that's not being satisfied by an abuse-deterrent formulation on the market, that might be a situation where a new drug could be approved without abuse-deterrent features.

We thought that was pretty rare. We actually couldn't come up with too many examples. I think we talked, for example, an oral solution where there is need for pediatric dosing, and then we don't really have, at least to my knowledge, have a way to impart abuse-deterrent features on that yet.

Those sorts of things might be an exception,
but unless the product offers a remedy to a unique unmet medical need, I think it should have ADF features for approval. Agreement? Yes.

DR. THROCKMORTON: Thank you.

DR. BAUMGARTNER: Again, with 14 companies that I'm trying to represent, I think the word "consensus" is fair.

DR. THROCKMORTON: It's just that those are two different positions that we have heard, and I just wanted a little clarity. No. I understand. Thank you.

MS. EDWARDS: So I would agree with coming to the market, but again caution, because when you make that decision to withdraw, those are older products. Those products are generic products. And until you afford us a pathway as a generic industry to get our products approved, it could create a big gap in the marketplace in terms of that new medication that you need to treat your patients.

So I think you have to take that into account before being willing to make any of those
kind of decisions. There has to be a pathway for approval of a generic ADF-based product.

DR. RICH: Doug, I would clearly second that and say that, in particular for the question of removal again, I think you'd really truly have to apply that risk/benefit analysis before you actually embark upon that, the concern being, again, that you are going to limit the access, again, to patients who truly need products if we act too hastily.

So certainly, phase-ins must be part of that, but again, looking at the entire risk/benefit analysis and all the factors that go into that before you make a decision to remove a product.

DR. MICHNA: Yes. I would agree from a clinical standpoint, any new product, I think it's necessary to have abuse-deterrent technology. I mean, just look at what we went through politically with the last drug, especially from the state I'm in, the state of Massachusetts. There is very few physicians that are going to actually go out and write that drug after getting that kind of
political lashing that we got, which we can argue the merits of, but that's the reality that we have to deal with clinically now.

DR. THROCKMORTON: Jim, did you have something?

DR. WOODS: I had a half-baked idea that I decided not to bake any further, develop further.

(Laughter.)

DR. THROCKMORTON: So I think this sounds like a logical break. I think this question raises things that we're going to be talking about through the afternoon as well, but in the interests of lunch, and timing, and things, I'd ask people to be back at 1:15. And then we'll have about an hour and a half, I guess, to have some additional discussion. Thank you very much.

(Whereupon, at 12:16 p.m., a luncheon recess was taken.)
AFTERNOON SESSION

(1:21 p.m.)

DR. THROCKMORTON: If everybody could sit down, we'll go ahead and get started this afternoon. I'll turn the mike over to Carol Bennett in just a minute, but we have one additional panelist that's been able to join us for the afternoon, and I will give him an opportunity to just introduce himself.

Josh, you want to say who you are, and then we'll start back up again?

DR. SHARFSTEIN: Excellent. Thank you, Dr. Throckmorton. My name is Josh Sharfstein. I am currently Secretary, Maryland's Department of Health and Mental Hygiene. And I formerly was the principal deputy commissioner of FDA. I am a pediatrician.

MS. BENNETT: Thank you for joining us. So where did we leave off? We were discussing what we had in the announcement as question 3 for this day.
And it deals with under what circumstances FDA
should refuse to approve or withdraw approval for
an opioid lacking abuse-deterrent properties.

We had quite a bit of discussion on that
before lunch, but I wanted to know if people had
further discussion on that issue or had any further
points to make on that matter.

(No response.)

MS. BENNETT: No? We're done on that?

Okay. We'll go on to the next question, then.

DR. SHARFSTEIN: Are you never coming back
to that question?

MS. BENNETT: If you have an opinion, you
might want to speak about it now.

DR. SHARFSTEIN: Is that it? You're putting
it to bed?

MS. BENNETT: Sorry. You can always weave
it in later.

DR. SHARFSTEIN: Was there a consensus or
no?

(Laughter.)

DR. THROCKMORTON: Funny you should choose
that word.

MS. BENNETT: Yes. We had that discussion.

DR. SHARFSTEIN: Was there a strongly --

MS. BENNETT: The brands and the generics
were in more agreement than perhaps we thought they
were, that we were along the path of getting to a
world where we could start not approving opioids
that were not abuse deterrent, but the
practitioners, I believe, were very concerned about
that, that we were not quite there yet. And the
focus should remain on the patient, not so much the
abuser.

Is that fair?

DR. THROCKMORTON: Fair statement, fair
statement.

DR. SHARFSTEIN: I would say, from the
public health perspective, it's a hard line to draw
because my view is that there are a lot of patients
who are at risk for addiction. It's not so easy to
say this patient versus that patient. I guess I
would say, at a certain point, when you have a
reasonable number of drugs that have
abuse-deterrent formulations, that allowing drugs
to come on that could upend a stable situation
would be a very poor choice, not only for public
health, but for individual patients who could wind
up getting into trouble.

So I guess I would say it certainly would be
a goal to get to a point where FDA felt comfortable
to doing this. I'm not sure where they are now,
but I think my position would be that, ideally,
you'd want approaches to be class-wide so that you
could protect patients no matter what they need.

MS. BENNETT: From your perspective, from
the state level, do you think we're close to being
there or we're not sure yet?

DR. SHARFSTEIN: I don't think we are
especially close to being there because I don't
think -- and again, I am definitely more at the
state level these days than the FDA level, so I am
not as familiar with exactly where we are on all
the drugs. I know there are a couple drugs that
have these types of properties, which are sort of
in the process of getting evaluated, so I wouldn't
say that we're there yet.

MS. BENNETT: Yes?

DR. BAUMGARTNER: I guess I don't want the group to be left with the impression that the branded industry or generic industry, I maybe can speak for, is not interested in the welfare of the patient. That's certainly not the case.

I think what one of the benefits we think we see to these abuse-deterrent formulations -- and I'll take, for example, the hard tablet that's been applied to OxyContin, I think, Opana, for example -- I don't think we know a lot, as was said previously about how a well-meaning patient transitions over to an abuser. And I think there is some data to suggest that maybe the first start is they start to chew that, that controlled-release tablet.

So even I think there is even patient benefit potentially to having abuse-deterrent formulations available. The other advantage they offer is if you have even a well-meaning patient or well-meaning caregiver who wants to crush the
tablet and put it in the applesauce, or to have an
NGD [ph] or something like that. And you have a
tablet that really can't be done, you can perhaps
offer protection against inadvertent misuse.

DR. KREBS: So actually, I think that is a
really great point. So part of this today is we're
using this broad term of abuse deterrent, and we
are not being very specific in our language when we
talk about these things. Addiction is different
from abuse, is different from intentional or
unintentional misuse. And why are you
unintentionally or intentionally using the product?

But I think accidental use or accidental
exposure -- for example, one of my patients who
wanted to reduce her fentanyl dose just thought she
would cut a third of the patch off. We need
products that don't allow people to accidentally
poison themselves when they make these mistakes.

So those kinds of products, if there is an
improvement here, that would be great to apply that
as soon as we can. Just my concern is more about
labeling something abuse deterrent when, really,
all it does is prevent a certain kind of tampering that we don't see very often in practice.

I think the most common pathway is really that a patient is seeking relief, not a high, and gradually maybe starts to feel they need more drug to get relief or relief from their pain or from their emotional distress and gradually starts using more and more, finding that they are thinking more about it, craving, losing control over their use of the drug. It's still usually just by the same intended route.

That's really important. If we can reduce that harm, that would be very important for our patients, so just wanting more specificity about what are we trying to prevent with the formulation.

MS. EDWARDS: I would agree to that.

Probably this is more of my opinion right now, but thinking about what our goal is as an industry, we are trying to prevent abuse of our products. But if you separate that from someone that's going to get addicted, they're not going to get addicted probably from abuse.
It's exactly what you said, the normal oral route of administration. And there's nothing that we can do from an ADF perspective that's going to change that oral administration, that's going to potentially lead to addiction.

So I think there is a line that needs to be drawn. And I think what our goal as an industry is, is not to contribute to the drug abuse of opioids. That bucket is there. We don't as an industry want to contribute to that bucket.

MS. BENNETT: Going along to the next question, then, what products should FDA consider to be available therapies when assessing or re-assessing the benefit/risk profile of an opioid product? And I will call on people if nobody speaks up.

MS. EDWARDS: We have a question over here.

DR. THROCKMORTON: Mary? Is Mary in the room? No. You were going to project the questions. Could we do that? That would probably help the discussions. Thanks.

MS. BENNETT: This deals with the
comparison. When FDA is looking at the benefits and risks of a drug, we are often trying to compare it to what else is available, and we would like some input on what we should be looking at, what other types of available therapies might be present. Just turn your mike on and start speaking.

DR. SHARFSTEIN: So this is similar to the previous question because I think it really depends on what available therapies there are. If you have enough that have certain protections, you don't want to introduce in less protections. It's very similar in other areas of FDA, where if you said, "I've got something to treat strep throat, but it might cause kidney failure," but people are dying of strep throat, you're fine until there are drugs that don't cause kidney failure.

You're not going to let one come back on the market when you've got a good number of drugs that don't cause kidney failure. You're going to take that one off and some new antibiotic comes up that could cause kidney failure, there's absolutely no
benefit and potentially worse than what's on there.

So what's safe and effective in the context really does depend on what is available. And so I think it's for the clinicians in the field to say whether they have a reasonable number of products. There's a lot, particularly for what the use is, if it's long-term treatment of pain with opiates, there's probably a certain number where you could get professional input. We have a good number. This is reasonable.

So if something were to come on the market that were to not have the same risk/benefit, it could really undermine the progress that you've made with the ones that are on the market.

So I think you get a lot of input from the profession there, but I do think it speaks to the previous question, too. You want to have enough alternatives that when you are making that risk/benefit judgment, you're putting it in the context of what's available for the clinician.

DR. RICH: One, I would add to that, again, looking at the alternatives again. You're looking
at, again, not all in terms of the benefit, in
terms of pain control or pain reduction of these
products -- they are the alternative
products -- again, you have to take into their side
effect profile all the alternative products, what's
out there, how does that affect, is the side effect
profile of an alternative product actually worse in
some respects than what may be encountered with an
opioid product like non-steroidals and cardiac risk
profile for managing chronic pain. In some
instances, actually, the opioids actually may be
safer for those individuals.

So again, all that must be taken into
account when assessing the risk/benefit ratio for
your opioid product or a particular opioid product.

Does that help?

MS. BENNETT: Yes. That helps. I would
also like to call on our patient representative to
see how important, from the patient perspective, is
a broad range of choice or not choice.

MS. KRIVACIC: I think a broad range of
choice is very important. And I think, in terms of
taking an approach of when to move from one drug to another is probably the best approach in changing -- moving to these abuse-deterrent opioid formulations. I think it's a product-by-product step because if you move too quickly in terms of cancer therapies, for late-stage cancer patients, usually two different routes of administration are always utilized at that advanced stage. A lot of times, the liquid route is one that is used quite often.

Just from my own personal experience with my late father, back in the early '90s, that was really the route that we could utilize with him at the end. And that was a very tough approach at that time because I was a child in the family looking for the different pharmacies at that time that had liquid morphine.

So that's very important to have these additional opioids that are very, very key to patient suffering or alleviating the suffering and the pain.

DR. GOOD: So I think we need our
pharmaceutical industry partners to develop more non-opioid pain alternatives. We need payers to step up to the plate and provide more integrated pain management clinics to support that. Regarding opioids, we need to fund more opioid treatment centers, where we can use these drugs more appropriately.

But I think most clinicians, as well as patients -- I think the assumption is that we have all these patients that are clamoring for opioids. Oftentimes, it's very difficult to convince a patient to take an opioid. And I think we heard that earlier today from a patient who gave his story.

So we need effective treatments that are alternatives to either use in conjunction with opioids so we don't have to be so dependent, and just use them for breakthrough pain, or have lower doses so that we have fewer side effects. We need other alternatives, both medication-wise and non-medical.

MS. KRIVACIC: I think another component
that maybe is a little outside of this discussion here today is the whole insurance issue related to re-assessing the benefit/risk profile of utilizing these new technologies or new drugs with the tamper or the abuse-resistant technologies, and what that would really do to affect the entire payment or reimbursement for patients.

As we know today, patients are really paying for a lot more of the drugs that we're getting. And those costs, especially in the area of oncology, are very, very high just for cancer treatments, 300, 400 a month.

So what's happening is a lot of these patients are then going to various pharmacies and calling the pharmacies to see if they can negotiate that price or if there's a lower price. And that's happening in the pain world as well.

So it's just kind of exploding all over, and that's another area which is a huge burden to the patient that needs to be considered.

MS. BENNETT: For the prescribers on the panel, how constrained in your choice of what to
prescribe for the patient do you feel, either by
payment, or do you just find your prescribing the
same types of opioids each time? Or is it more
tailored than that?

DR. RICH: I'll jump right on that. From
the prescriber standpoint particularly again -- and
I am not singling out any insurer whatsoever. But
again, from a governmental insurance standpoint,
private insurers, it's a big issue. And that may
force many prescribers, again, to choose more than
likely the generic products and/or less expensive
product, or other formulations, which ultimately
may not be tamper resistant, et cetera.

That decision at times is driven by
formularies and by a prescriber standpoint, when I
think of the hassle factor in terms of dealing with
formularies. And you're dealing with a 10- to
15-minute visit with a patient who is seeing you
for not just pain management, but for their
diabetes, and their hypertension, and everything
else, guess what? You choose the least painful
alternative to the prescriber at times.
So, yes, it is a factor, again, all of us have to take into account.

MS. EDWARDS: So I currently work in VA. And so Bernie has already spoken to our formulary. I pretty much prescribe all generic drugs. And prior to my work in VA, I worked in mostly safety-net healthcare settings where people were uninsured, or underinsured, or on Medicaid, or on Medicare. And in all those settings, I have generally been prescribing generic drugs.

I think that, for the most part, in terms of the opioids, the generic alternatives are fine. I have not actually felt overly constrained by the availability of the generic options. Often, we can get the drug.

But I think what -- especially some of my colleagues who practice in private settings actually can have even a harder time with is getting things like urine drug tests approved, or the frequent clinic visits, or things like case management to follow a patient carefully and make sure that they're not getting in trouble with these
high-risk medications.

If we talk about seat belts, I think those are the seat belts. And so of course, payers make decisions not just based on one drug or another, but what they are going to cover overall. If, for example, we lost our inexpensive generic opioids, might payers be even less likely to spend money on things like drug testing or other kinds of safety measures.

So I think there are real trade-offs if these products get more expensive.

DR. THROCKMORTON: You related the availability to the seat belts. And I guess I'm going to start out by asking Bernie and maybe others, do you collect information about that systematically? That is, the availability of medicines and the changes of costs and choices by formularies and things on people's ability to get pain medicines, or urine drug screens, or something like that?

It goes to access. It goes to availability of therapy. And people talk a lot about actions
we're taking a narrowing available therapy. Do you
look at that systematically?

DR. GOOD: So I'll speak more generically
just in terms of the decisions that we made, as
best as we can, because we have an integrated
healthcare system. We have adverse drug-event
reporting, which is rolled up nationally. We have
our drug benefit. We have all that information.
We have this all tied to clinical things, including
visits, diagnoses, and hospitalizations, et cetera.

We tried to go back and look at the
decisions that we've made and to see if there are
any unintended consequences. Some of those efforts
we have published. I haven't examined a specific
issue in terms of chronic pain. But the other
thing that we do is, we try to query our
prescribers.

So next Monday, within the week, we are
going to mail out a survey -- and hopefully, you'll
fill yours out, Erin -- to most VA prescribers.
And we ask a lot of questions about do they have
access to the drugs that they think they need for
their patients. Is here too much of a hassle factor? Are there too many hoops to jump through?

So I don't know. We've had several surveys in the past, and we've looked at those and carefully considered those. So we will look at what we get from our providers. We have some pain questions in there. So we'll look at those.

DR. THROCKMORTON: Is that a longitudinal survey, Bernie, or just --

DR. GOOD: This is a snapshot. We have done several snapshots, so we can look and we can compare, but it's been several years since we've done our last one, so it's time for us to do it.

DR. BAUMGARTNER: So regarding the available therapies, I think the branded industry would like us to be at a point in the not-too-distant future where there are many abuse-deterrent formulation options across all the different active ingredients so that availability doesn't become an issue and there are choices between these that have demonstrated to be an abuse deterrent.

The other way to look at the question
is -- and I thought perhaps being asked from the prior question about when would regulatory action be taken. Given the reassessing the risk profile of a particular active ingredient, we viewed available therapies as products with the same active ingredient, the same or similar dosage form, and the same route of administration.

I don't know if that helps in the regulatory side of the question.

MS. BENNETT: Yes. Is the generic industry in agreement with that or do you take a different approach as to what is available therapy?

MS. EDWARDS: I actually I had a slightly different thought. I agree with the classification, that that's how you would look at it. I also feel it's really a decision from a practitioner perspective, because you're going to select what you feel is best for your patient.

There are also indices that we use in the industry to evaluate what products are being used the most. There are things like IMS data, where you look at usage, and cost, and all of those
factors. And that data is very useful to evaluate the impact of a market removal or an addition to the market.

I think that might be a viable option in this situation, where in making that decision, you look at the actual usage of which prescriptions are most prescribed, where does the cost lie if I were to -- and they even have business models that say, if I were to remove this from the market, what potential impact could that have.

So that might be a reliable source from a business perspective to actually help making these decisions. But in general, I agree with the categories of associated or available therapies.

DR. SHARFSTEIN: I would disagree. Yes. I think that the appropriate place to look will be the care of the patient and not necessarily look at it from the vantage point of the product and whether an equivalent product and the exact same active ingredient and form is the same, but rather, whether or not there are available therapies for the patient that are effective, and it might be
different.

So to my analogy with the antibiotics, there are available antibiotics that absolutely meet the need, and there's a good range for different things for clinicians. The fact that someone might be coming on with a new chemical entity but has a much worse risk profile would mean that you wouldn't approve it, or if there were one on the market that had a much worse risk profile, you might go back and take it off the market if you've got a bunch that take care of the clinical need.

So I think that the point of reference should be the clinical care and not the product.

MS. BENNETT: Should we be concerned about any particular subpopulations in that analysis?

DR. SHARFSTEIN: Well, I guess what I would say is there needs to be a meaningful benefit of a product without abuse. In other words, there's got to be -- it could be cost. I thought that point that you made was excellent. Cost really does matter for patients. And it could be that there's a subpopulation that really clearly benefits.
But if there is a clear disadvantage of a product, and there's an adequate number that are on the market, and it's meeting the purpose of clinical care, I don't think it serves the purpose of choice to have a clearly inferior product from that perspective out there. And I do think the point of reference should be the care of the patient for that.

I'm comfortable saying this is really a different kind of drug. It has a different kind of advantage, or there is a subpopulation that really benefits, or it's way cheaper. All those are potential benefits. But if there is no real benefit, it doesn't matter if it's a different chemical entity to me.

DR. THROCKMORTON: Can you say a little bit more about the kinds of benefits you're thinking about, Dr. Sharfstein? So to an individual patient, people value different kinds of choices. Are there particular things a patient might value more than another?

Some people think we have whatever, five or
six opioids on the market. Are those enough? Is there enough? Is that enough of a choice for individuals? How do you think about those things?

DR. SHARFSTEIN: I guess I think there would have to be a real explanation, what the benefit is. If the benefit is that it comes in a cooler container, and maybe there are some consumers that really like the container, I might say FDA could weigh in and say, that's really not where we're going to base our decision.

But I do think that, if there's a meaningful benefit for a subgroup, then you're perhaps in a bit of the REMS territory if it's a new product that's coming on the market. And you can say we really want to make sure that we're limiting -- we're doing this in a way that you get the actual benefit.

So I do think that it definitely matters what patients think and there are different possible ways they could go about it. I think the challenge you have is, we think that in left-handed people who, like sailing, this really works better
based on a post hoc analysis we did, and I've got five left-handed people who like sailing here who will tell you how important it is for their pain, then you're going to have to make a decision on whether that's really a meaningful finding or not. That's where the FDA's judgment comes in. But if it is meaningful and there's data that support it, then you're in the, I think, REMS territory. You have the option for patients.

I was just responding to the fact that it's different doesn't necessarily mean it's a choice worth having if it's really an inferior choice.

DR. THROCKMORTON: Great. Thank you. That helps.

Let's move on to the next question, which relates to what kinds of products we should be working to encourage abuse-deterrent formulations development for. So historically or up to this point, I'd say a lot of the discussion, a lot of the activity we've seen internally, talking with sponsors and obviously the three labels that we've made to date, are in extended-release, long-acting
opioids.

They have a disproportionate risk for abuse and misuse relative to the immediate-release products. They are high potency, high doses of opioids, by and large. And so that's been where we've been focusing. Yesterday and today, there have been comments about thinking more broadly, thinking about immediate-release products that may potentially benefit from abuse-deterrent technologies.

The flip side of that, though, is important for us, too. Are there kinds of opioids where an abuse-deterrent technology is less valuable, less valuable because of a patient population that might be used and less valuable because it has other features that may make it less attractive for abuse?

Whatever other features make it just less important for us to devote the resources to encourage their development, I'd like the panel to discuss those other classes of products that either should warrant support or might not necessarily
support the abuse-deterrent formulations.

MS. KRIVACIC: I think, in thinking of this one area -- and I don't know if I am correct on this; this is my opinion. But one area would be maybe the morphine pumps. Are those really -- I mean, they're utilized in very chronic severe pain patients, and are those really abuseable? I don't know. But I think that's a real convenience thing for those patients, but also a real necessary thing because many of those patients are not mobile, so looking at something such as that subclass, if you will.

Another would be perhaps suppositories because of patient inability to swallow. As I mentioned earlier, just the advanced stage of cancer patients or even some of these severe chronic diseases that, or chronic-pain-associated diseases, that have that effect where a patient cannot swallow, such as a lot of the autoimmune diseases that we heard about yesterday, Ehlers-Danlos syndrome, that's where I think we need to be very careful.
Maybe if FDA and others on this panel can enlighten me about that area, if there is a potential for abuse, that would be great.

DR. SHARFSTEIN: I apologize if I am talking too much. It's been four years since I left the agency. I have never been invited to one of these panels before, so I'm assuming it's going to be four more years until I'm back.

(Laughter.)

DR. SHARFSTEIN: So this is my only chance here. I did have a recusal for some of that period.

I guess you have the public health phrase in there. The way I would think about it is, what is being abused or diverted, and does FDA have a handle on the kinds of prescription drugs that are in fact creating part of the secondary market and the problem, and that it's really important for FDA to have a handle at the public-health level of what's going on.

So there's definitely the issue of patients getting into trouble, which I thought was explained
really well. There's also the issue of the secondary market and how much things can be sold for, and what is actually being sold, what's being picked up when the police go out? What are the products that are out there?

So from my perspective, this should be driven by what is actually contributing to the public health harm. My guess is that there is quite a contribution from the short-acting drugs, too, and that you can use that data to understand where the need is for further attention, and that having that kind of surveillance at the public health level will be helpful to FDA in answering questions like this, rather than us -- you have some very good questions. I don't know the answers. But if they're finding suppositories being sold all over the place and the whole secondary market is suppositories, then you've got to worry about suppositories.

So it's more of an empirical question, what is actually causing the public health harm.

DR. THROCKMORTON: Just a little bit, just
from what you're seeing, it sounds as though you
feel like immediate-release products, at least your
sense is that there's a market out there, either
for diversion or for patients that are potentially
going into trouble using.

DR. SHARFSTEIN: I think so, although I
don't want to speak definitively to it because
we're maybe seeing a little bit of the data
nationally. And you have the ability, perhaps,
working with DEA to have a better sense of it.

DR. RICH: Doug, I would say that, from
looking at the issue this way, immediate-release
products really, ideally should be used for acute
pain and for breakthrough pain in most instances.

We know, however, again, that in many
instances, the immediate-release products are still
being used for chronic pain management. And I
think, because of that, they in particular, in that
situation, you're clearly at risk of abuse and
misuse. And I think when you look at that
scenario, in many respects, there is probably a
case for looking at change in the formulations of
some of the immediate-release products, knowing
that they are being used more for chronic pain
management instead of just acute pain management.

DR. KREBS: So I was just going to say that
we know from national epidemiological data, the
National Health Interview Survey, that the majority
of people who self-report that they have misused
opioids report that they received those opioids
from a friend or family member, typically without
paying for it. And then the second most common
source would be from a single physician.

So most people who acknowledge misusing
opioids are not going to drug dealers, or pill
mills, or using. And I think most of it is
low-level oral abuse. And I think a lot of it is
casual diversion of really overprescribed
short-acting opioids.

There have been a number of small studies,
not big ones, but small studies showing that if
someone has a minor procedure, dental procedure,
urologic procedure, that the average number of
pills prescribed vastly outnumbers the average
number of pills taken. So most people might take
two or three pills, and then have a bottle of 57
left in their cabinet.

I think, if we surveyed the room right now
and said how many of you have an old prescription
bottle you're just kind of hanging around because
if something happens, you don't want to have to go
to your doctor and get a new prescription, that
everybody's medicine cabinets are just full of this
stuff.

So I think that these low-dose commonly
prescribed immediate-release products are a big
part of the early pipeline to opioid use disorder.
They are important, but I don't know that the most
important intervention would be to try to prevent
changing the manner of use or preventing crushing,
norting, injecting.

I think most of the money there is probably
in changing the prescribing patterns so that if
somebody has a minor illness, maybe they don't need
opioids at all. If they do, maybe they just need a
couple days' worth.
So I think they are important, but I don't
know that these kind of abuse-deterrent
formulations we've been talking about have a big
role in preventing their abuse.

DR. SHARFSTEIN: I would be willing to bet
that Doug has flushed all his extra down the
toilet. That's what I'm guessing. Is that
correct, Dr. Throckmorton?

DR. THROCKMORTON: Yes. That is correct. I
also supervise the Drug Take-Back Day at the FDA.

DR. SHARFSTEIN: I know.

DR. THROCKMORTON: So I feel obliged to have
taken care of that, absolutely.

DR. GOOD: A lot of happy fish in the
Potomac.

(Laughter.)

DR. THROCKMORTON: Would you say that again
for the record?

DR. GOOD: I see a lot of happy fish in the
Potomac.

DR. THROCKMORTON: Other comments? So this
is about products that may benefit from
abuse-deterrent technologies, recognizing there are many other activities that are probably important to do. This question was focusing on the abuse-deterrent technologies.

Are there other comments? Dr. Woods, you're learning forward. I don't know what that means. Sharon?

DR. HERTZ: I just would like to follow up with a question, which is concerning the immediate-release products, to what extent, if any -- I guess it shouldn't be a leading question -- what potential impact would there be on abuse-deterrent formulations that might have negative consequences in that space, based on how you're seeing the products used legitimately?

MS. EDWARDS: I think that Susan's point about people with complex medical illness and end-of-life care needing access to products that are easy to absorb through a variety of mechanisms, I think that that's a big deal. So I have to make sure that some of these special products are available. Some of them may be too easy to abuse,
some things like fentanyl nasal spray. These kinds of high-potency, easy, really quick-hit products, there is a place, but maybe they need a different level of regulation.

I'm not a palliative care doctor, but I always think, if you're going after immediate-release products, you probably should make sure, with that constituency, that there are available formulations that will work. Otherwise, it's just my generic comments that I've made several times about the unintended consequences of increasing costs and that kind of stuff.

DR. BAUMGARTNER: So there is actually probably sufficient data to show that immediate-release oral opioids are being abused. And the branded industry group does feel that immediate-release opioids should also be a target for abuse-deterrent formulation technology development.

Of course, they are not all created equal and Dr. Hertz brought up a point this morning about different methods of abuse routes, for example,
with a low-dose acetaminophen combinations.

So the technology probably does need to be
directed toward deterring the abuse that's going to
make a meaningful change in the population. And
granted, I think we admit -- and it's a point
that's been brought up repeatedly -- the drug still
does need to be available when the patient takes
it.

So we haven't been able to really solve the
problem of oral intact over-ingestion. But it
doesn't mean that advances can't be made, even if
the frequency of abuse is less, that advances still
can't be made in tampering with those products as
well. I think hydrocodone APAP is snorted.

Why someone would do that is not clear, but
I think the data does suggest it's happening. And
I think we would feel that, if we can prevent that
from happening without impacting legitimate
patients, that's worth doing and it's worth
incentivizing as well.

MS. BENNETT: That was one follow-up
question I had. On the IRs, it sounds like most of
the abuse, you think, is through oral ingestion?
But of course, most of the abuse-deterrent
properties we've been talking about are snorting,
intravenous, crushing, and grinding.

What kind of abuse-deterrent properties
would be useful in the IR space, given the
different ways that they are abused?

DR. KREBS: Someone earlier brought up
overdose prevention and if there was a way to make
them harder to accidentally overdose on, wouldn't
that be a great thing. So there are ideas about
harm prevention, maybe not preventing the person
from taking it, but preventing negative outcomes of
that. I don't know.

DR. SHARFSTEIN: I would just say I think
the point that -- sorry, I don't know your
name -- the doctor in red was making, it may well
be true that there's a huge amount of misuse or
trouble just from oral ingestion, but that doesn't
mean that there isn't also a problem with
formulation.

So what I was suggesting is you look at
where there's a problem with the formulation. What
is getting injected? That would determine FDA's
level of concern about this particular side of
abuse deterrence. Just because there may be more
people having problems another way doesn't mean you
wouldn't be able to take action where there is
something preventable.

Then you get to the question of, okay, how
do you deal with the issue of people taking too
much, and there's a wide range of things. The
Maryland Board of Physicians yesterday adopted an
hour-long CME requirement for every licensed
physician in the state, first one they have ever
done for appropriate prescribing, so just a little
bit of a step there.

You also can think about packaging and other
things that might help reduce the challenges, but
there is a certain amount of risk you may not be
able to get rid of, but that doesn't mean you
shouldn't take steps to get rid of risk that you
can.

MS. BENNETT: So from a generic perspective,
I would suggest that most of these products that we're discussing are generic products, the immediate-release products. I have heard several times today that one of the impacts of the abuse-deterrent formulations have been that there's been a shift in the abuse and that shift has gone to the immediate-release.

So taking that into consideration, I would suggest that there would be a need to address these products if there's a public health concern. They would need to be addressed by having those properties or at least looking to see if we could impart those properties on these products.

What would be interesting here is that since they are already generic products, would there be an appropriate regulatory pathway by which we could bring these products to the market without incurring a significant cost or add significant costs to the product by having to go through a new product approval process.

We talked about that earlier, about possibly some 505(b)(2) options, would reduce costs so that
we could take some of these older products and bring them up to today's standards if indeed they did demonstrate the propensity for some type of abuse and it did have some type of public health impact.

DR. THROCKMORTON: Dr. Sharfstein, can I follow up on something you said about patterns of abuse? And Sharon, you may want to talk about this, too, because it goes back to the last slide from your talk this morning.

So the three routes of abuse that we've been focusing on, I would say, historically has been the oral, the intranasal, and the injection abuse. And different drugs have different patterns of those. Some of them appear to be attractive for oral abuse for whatever reason, more than IV, whether it's formulation or whatever else.

One of the things the FDA has been concerned about is changing those patterns in unfortunate ways through a new formulation. So if a new formulation is hard to snort, but easy to inject, and the risk then is that people are going to move
from one route of abuse to maybe less dangerous to
a more dangerous route, the first question is just,
does that make sense? That is, to think about what
we've talked about, looking in an integrated way,
understanding how they are abusing a particular
product -- so, Josh, your point about the
epidemiology of abuse of a product -- and then
trying to understand the nature of the shift that
would happen if a new formulation was approved.
And is the shift in a direction that most would
make sense from a public health perspective or is
it a shift that's concerning?

First, does that resonate with you? Is
there something? And then the second -- and
Sharon, we don't have your slides up -- how do you
communicate that? So this product is really
terrific at reducing intranasal abuse, but isn't
going to do anything about oral, or let's say maybe
it's spectacularly easier to abuse by an injection
route.

How do you factor all of those things in
when you're talking about whether or not to give a
product a single thing, a claim as an
abuse-deterrent product?

DR. SHARFSTEIN: I guess I would say that
from a public health standpoint, we really don't
like injection because of the potential risk of
infection, probably higher through injections. And
I don't know, that may be the worst kind of thing.

DR. THROCKMORTON: So even though it's less
common, for instance --

DR. SHARFSTEIN: I think that's part of it.
I mean, it's an unfortunate kind of thing to reduce
to numbers, but I think, all else being equal,
you'd rather not have injection.

I think the advantage of having a good
surveillance system is that you know what really
matters, and you can look at the overall problem as
well as what's causing the problem and target the
strength of their limited resources, the thinking,
the methods, all that to the area where you're
really seeing a particular issue.

If the issue is chewing when it shouldn't be
chewed, or snorting, or injecting, and having a
A good system to really understand that, then you can work systematically on the particular problem spots. It's probably not unlike a lot of other things. You don't know for sure what happens when a particular drug gets approved on the basis of certain studies, and you're going to be doing postmarket surveillance to understand what's going on, and any change that you're making, you're going to want to watch pretty carefully, which is another reason why you're going to want to have a good surveillance system.

In terms of the claims, that's a tricky one. I mean, I guess my guess is that you may want to have some basic claim that you think that this is a product that's going to meet certain a FDA standard for reduced risk of blank. You may want to -- rather than have it be, like, slightly less snorting, but might be this, there are only so many ways to do it, but some basic standard that your agency is going to be comfortable if a product meets.

Then again, once you have enough products in
the class that meet that, you're holding out the idea that you might look to see whether it's time to put some pressure on the other ones, give them some time. And if they can't come up with a similar level or meet that standard, then they are going to have to come off with some notice. So you're both fair, but also, you're making the whole thing safer.

Again, here's another example. It goes back to the first question, which I promise not to completely open up, but say you have one product on there, and there are left-handed sailors who really like it, and there's question about whether or not that's even a meaningful finding, but you can tell that, literally, it's not on anyone's radar for abuse. It's just not epidemiologically on the radar screen. It's just not happening.

That may be different from one where it turns out that's the number one thing the police are finding and everybody's using. So it allows you to see where -- even when you're going to when would you start to apply your standard against
available treatment, that might be influenced also
by your sense of the nature of the problem and
where you're actually having problems.

DR. THROCKMORTON: Thank you.

DR. KREBS: I agree. I think the big
picture is so important here and watching for
shifts that are more hazardous, not just shifts
from, say, oral abuse or intranasal abuse to
injection abuse, but injection of these drugs to
injection of heroin. If all we accomplish is that
people who are injection drug users stop using
prescription drugs for injection and move to
heroin, we have not accomplished enough.

So I think heroin is kind of a competing
formulation out there that is important to keep in
mind. People who are addicted to opioids, it's on
the menu.

MS. BENNETT: This was raised yesterday in
the public hearing, raising the issue of there are
different kinds of abusers. And we've seemed to
talk about them as a unified group. How much
should we be paying attention to, basically, for
lack of a better term, hardcore abusers versus opioid as a gateway to the abuse-deterrent aspect of keeping people out of this space to begin with?

DR. KREBS: I think the absolute critical thing we need to focus on is the pipeline here. It's the beginning of the pipeline. That's what's changed with this epidemic. Just far more people with vulnerability to addictive disorders are being exposed to drugs that have physiologic properties that can cause addiction, abuse, all these things.

So that's really, to me, it's the front of the pipeline, where almost all the energy should be focused. And I know it's not just FDA there, but really, that's where we make the big difference.

This very high-risk population we have been talking about, manipulating drugs to get high, are an important population. They are probably at the highest risk of dying in the short term. You don't want to forget about those people, but those people are not the majority of people with opioid use disorders. And if we focus on them too much, we actually may impair our ability to recognize the
more common opioid use problems.

A colleague of mine said that one of her patients said to her, "It's not fair that I have an addiction when I never got high." This was someone who developed an iatrogenic opioid addiction just seeking relief from pain medication, and gradually taking more and more, and then finding that she had lost control.

So those kinds of people, let's remember, those things, that addiction isn't always someone who is intent on getting high.

DR. RICH: I would first say to you again that all of the population groups that you mentioned are important. They all have problems. I would say to you that in most primary care practices, in most average communities, it's still probably the individual who is overdosing or misusing the pill formulation that they've got, whether it be from the medicine cabinet at home or from the prescription they just got from a provider.

But still, even in every community large and
small, you still have a subset of individuals that
are still modifying, and injecting, and otherwise
abusing these medications. So I really say to you
again, you can't really ignore any of the
categories with how you act on this issue.

DR. SHARFSTEIN: I would just agree to that.
From a public health perspective, you've got to try
to hit this problem at every particular level. It
matters for the prescribers. It matters for
patient education. The shift to heroin is a big
deal, and there's a lot that needs to happen there.

There's just so many different angles. I
think it's hard to say. You don't want be
paralyzed by saying, well, if you just do this,
you're not taking care of all these other things,
because then you wouldn't do anything.

MS. BENNETT: For our innovators and
generics, can you hit all of those questions?

DR. BAUMGARTNER: I'm not aware that we've
solved the oral intact over-ingestion. But I guess
trying to address the comment about starting early,
if a tamper-resistant formulation is available, it
may at least help deter that transition from taking
a non-manipulated product to a manipulated one.
It's not going to solve all the problems, but it
should help.

I was going to remark on a comment that was
made earlier. In a way, a colleague of mine once
said, when a physician is prescribing an opioid,
they really shouldn't just think about that
patient. They should think about the other people
in the household. And it's a big responsibility to
prescribe an opioid.

Again, I think our view is, these
formulations are not solving a problem, but they
are perhaps addressing these changes. They are
helping address some of these transitions that we
were talking about.

MS. EDWARDS: So it sounds like the big
issue that hasn't been addressed from an
abuse-deterrent perspective is that oral use, where
you go from the one to the two, and that is a
potential issue. And looking at the technologies
we have addressed at this meeting, we haven't
addressed any technology that addresses that issue. But I would like to think that there is technology being developed. I can't actually talk about it, but there is technology being developed that --

DR. BAUMGARTNER: You're among friends.

MS. EDWARDS: Yes, right here. Right? Here's my favorite friend. But there, I do think the industry does have the capability to develop technology -- that might be a better way to put it -- that would address that multiple-tablet oral use and impact absorption based on taking multiple tablets.

So yesterday, we talked about emergent technologies, and that might be a very interesting area to look at as the area of concern for the next stage of development of our abuse-deterrent technology.

DR. RICH: I would second that. I just wish we had the technology so that if a person took two tablets, that's okay. But if they took four, some mechanism would automatically deactivate those tablets.
MS. EDWARDS: Emerging technology.

DR. RICH: Absolutely.

**Questions and Answers**

DR. THROCKMORTON: That's helpful. We've got about half an hour, so I'm going to transition to the next set of topics. And I am going to be combining some questions. Let's go to the next one and see what we've got as far as a question. Actually, go to the next question.

Yes. A big issue for us is around incentives for development and then incentives for appropriate use, and lots of discussion, we could have around that. So one question is -- let's see if this is even the right question. Go to the next one, even, next question.

Yes. when Dr. Woodcock had talked yesterday, as we've talked about the goals of abuse-deterrent formulations development, we have talked about it in two ways. One, we'd love a breakthrough technology that just knocked the ball out of the park, prevented oral abuse, prevented taking too many pills. That would be wonderful if
we had that.

Failing that, what's important for us to do is set up a paradigm of incremental improvement so that, as technology gets better, we support it so that it happens efficiently and then encourage its use, two pieces of that. One is encouraging the development, if you will. Second is convincing Bernie to pay for it and bring it into the VA system, and other payers and doctors to make choices about using the technologies.

This morning, we heard some very clear suggestions from the brand and generic industries about specific things that could be done to incentivize development. So the first part of that -- and there are other things that we need to talk about, and we can certainly do that.

But that second piece, that piece of, are there things that the FDA could be doing that would encourage better understanding of these products so they are used more effectively, other actions that we should be thinking about doing to encourage their use more broadly once they are developed,
again, in this iterative second-, third-generation sort of way? And are there things we should avoid doing because we're going to make things worse if we do them, negative consequences or unintended consequences?

Two questions, what should we do and what shouldn't we do? Josh?

DR. SHARFSTEIN: I was going to say, if there are areas where FDA can establish tests that don't require clinical studies, that would, I think, probably rapidly accelerate this. That would be dependent on the science. But if it's like, look, what we really care about from the drug delivery perspective is that the same amount of drug is delivered as it was before, essentially, but now you're going to meet this other test, it may not be necessary to do a big study.

So I think you can radically reduce the cost to the manufacturers to the extent to which FDA can feel confident enough about alternative approaches.

DR. THROCKMORTON: Bernie?

DR. GOOD: So I would take a completely
opposite approach. I think we need -- I would hope that you would encourage those companies who are developing these progressively better abuse-deterrent properties to study them clinically, to know that we are benefitting society, and it's not just decreasing the abuse in terms of crushing or snorting, but that, actually, at the end of the day, we have fewer deaths, fewer unintentional overdoses, et cetera, and that there aren't unintended consequences like people going to heroin, or whatever it is, that's accomplishing what we want.

So I would not be happy with surrogate endpoints just to show that it's harder to crush or harder to misuse.

DR. SHARFSTEIN: Just to jump in, doing a study where you're trying to have an endpoint of death or transition to heroin may be a massive study, unbelievably expensive, and keep people from actually ever pursuing it. So I think you have to weigh that against -- generally speaking, studies for approval aren't measuring the impact on
society. They are measuring the impact on a relatively discreet group of people, and you require postmarket surveillance for the impact on society.

So I think that it partly depends on the science. You could argue it back and forth theoretically. But I think if you have a very strong reason to believe that the person is getting the drug that they need to get, and there are ways to design an approach to make it harder to abuse, that what you really want to do is lower the barrier for that to get adopted, but we may disagree a little.

DR. GOOD: So it's unfortunate that you weren't here for this morning, when we did talk about this more. But we're talking about billions, and billions, and billions of dollars on the backs of patients with chronic pain as well as on pairs. It may be the right thing to do, but we don't have that evidence at this point.

So the studies may be hard, but if we're spending billions and billions of dollars to do
this, I think we have an obligation to show that it's actually doing it. And it may be the right thing to do. It would be really nice to have that evidence.

DR. THROCKMORTON: Phil?

DR. SKOLNICK: I think one of the speakers made this point this morning, and it really struck home with me. The most important thing that the FDA can do to encourage the development of these products would be to have a very clear set of regulatory guidelines so it mitigates the risk of the developer.

Without those guidelines, you will put your funds somewhere else, which have a much lower regulatory barrier. And I think, once that's established, the marketplace will determine what's being sold and how good these things are. But without those regulatory guidelines and a very clear message from the FDA that you want that, people are going to be afraid to invest significant amounts of money in innovative technologies.

DR. THROCKMORTON: What about uptake, Phil?
So it's two questions I was asking. One is the developmental piece. I will say, honestly, we've gotten a lot of really good advice over the last couple days and in other ways about potential ways for us to go about that.

Important for us to think about is how to encourage these products once they are developed, once they have the appropriate formulation. They do meaningfully reduce abuse. Are there ideas there as well? Because that's a thing we've had somewhat a little less conversation about.

DR. SKOLNICK: From my estimation -- and it's a point that Dr. Good made before -- it's the tension between formularies, what insurance companies are going to pay for and reimburse versus the benefit. And the insurance companies are actually very thoughtful. And if a drug has a very clear benefit and it benefits the patient, reduces the overall healthcare cost, then they will be reimbursed even at a premium.

Now, it may not be true with Medicare and Medicaid, but certainly, while we still have
private insurance, they make those sort of pharmacoeconomic determinations. A good example would be depot naltrexone, which is very, very expensive, but many companies reimburse for that for prevention of opiate relapse because it's been shown that it has a positive benefit in terms of an economic benefit for the patient and the payers.

DR. THROCKMORTON: Dr. Hertz, you had a comment?

DR. HERTZ: So we have heard a couple times now, somewhat impassioned pleas for the development of these clear regulatory guidelines. And so I guess as people comment on this, I think we were trying to capture some of that in terms of what "meaningful" meant in an earlier question.

But if people are thinking that we need some kind of clear set of guidelines other than evaluating products on a case-by-case basis, based on what's available at the time, what could that possibly look like? I mean, that's the other part of the question. It's not that we oppose the idea of having a guideline. That's clear. It's just
hard to imagine what that would look like and how it would remain relevant.

MS. EDWARDS: So from a regulatory perspective, there have been guidelines established for new drugs, and you've been able to ring several drugs to the market. We're able now to, in some near time in the future, look at the epidemiological impact and see if those drugs really matter, if those are the right guidelines.

So I think you have to continue in that path. When it comes to generic drugs, it has to be on a case-by-case basis, and they have to be product-specific guidelines to address how we can bring a competing product to the market.

Without those guidelines, I think the cost of research is really what drives the cost of medicine. And so once the agency, in collaboration of course with the industry, were able to do that research up front and come out with guidelines that will give us a clear path, that's been the history of what's driven the price of generic drugs and made those products more affordable for the public.
DR. SHARFSTEIN: I guess I would say, intuitively, you want to make sure that you're deterring abuse and, at the same time, the person is getting the medicine. So for the person getting the medicine, there may be a guideline that somebody could use, you could show under certain conditions, that, yes, the person is getting the medicine. You haven't really messed up what you're trying to sell.

In abuse deterrent, you might think even if you are going to apply it case by case, the kind of studies that you would want done, you might say, heat it up and see what happens to it, mix it in different solvents and see what happens to it, convene a group of pretty talented amateur chemists and see what they can do with it, whatever the different issues are, and you could say here are the things we'll look at. Even that might be helpful in terms of reducing the potential cost and confusion.

DR. BAUMGARTNER: I guess I will comment on the two questions that are projected here from the
branded industry's perspective. I think the actions FDA are already taking will continue to incentivize incremental improvements, labeling, if we could grant some degree of exclusivity related as a reward for innovation, things that were mentioned earlier, doing what FDA can to incentivize proper reimbursement for these improvements. So I think it's the same and should also hopefully incentivize further improvements.

As far as circumstances where you might refuse or initiate withdrawal of a product on the market, like first generation, I think our view is, there's a big difference between abuse-deterrent formulation and not.

So once FDA has declared via labeling that a abuse-deterrent formulation is abuse deterrent, there's probably a higher bar to take action against that because a determination has been made. And I'm not sure where that bar would be. Again, it's probably reflecting on the entire -- as has been mentioned earlier, each time anyone is approved, looking at the risk/benefit of that
molecule and the various formulations that are available.

MS. KRIVACIC: I know we have been talking today about the abuse-deterrent products in general and the regulatory actions surrounding that. And then I look at the second question here, under what circumstances might we refuse to approve or initiate withdrawal of a product with first-generation abuse?

I start to think about, we have been in the defensive mode here, trying to set up an abuse-deterrent system for these opioids. When do we bring in that offensive approach? A good defense needs a good offense. And when I think of that second question, I think about, well, a hundred years ago, 1914, when there was -- and we're sitting at that same date here today, when the Harrison Act was put into place, the Harrison Narcotic Act, to avoid I guess this whole opioid abuse issue.

I am thinking more, at that time, they were even talking about getting away from opioids. And
here we are, a hundred years from that date, and we
have gone leaps and bounds in terms of technology.
A lot of great things have happened that the FDA
has done with regard to this abuse-deterrent
approach, but I am just wondering when that first
generation of abuse-deterrent property could be
refused is when we get an innovative, non-opioid
product.

Can that be part of this discussion? Maybe
it can't because of the whole insurance cost issue.
But it is something that is really needed. And I
am thinking about the billions of dollars that we
have been talking about with this whole program.

Maybe the answers we already have are out
there. I don't know, but surely, there is more
here than just the defensive approach. We have
moved so far in other areas with pharmacogenomics
and targeted treatments. Now is maybe that time
for the pain area. It's there.

So anyway, that's my thoughts on this topic.

MS. BENNETT: Does anyone have any -- we are
particularly interested in knowing what we should
not be doing. What can we avoid?

   DR. THROCKMORTON: I think it's the next
questions, just to show that one.

   DR. GOOD: That's a sign from God.

   (Laughter.)

   MS. BENNETT: A sign.

   DR. THROCKMORTON: Last questions, yes.

   MS. BENNETT: What should the FDA avoid
stepping in here?

   DR. SHARFSTEIN: I would say, from my
perspective, I don't think FDA should conceptualize
this as pitting patients with pain against patients
with addiction. And there are so many patients
that cross back and forth and there are risks in
all directions. And the reason to do this is
because we need better products that serve the
patients who could wind up in either category,
frankly.

   There are a lot of patients with addiction
who have a lot of pain and need their pain treated,
and there are a lot of patients with pain who are
at risk for addiction. And I think too often the
discussion is about, while there are benefits for
pain and risk for addiction, we really need to
focus on this group of patients and not that group
of patients. And I think, if you conceptualize it
that way, then you realize the importance of moving
this forward because it's all for really
fundamentally the same group of patients.

DR. RICH: Yes. I have to concur. I really
think you're going to have to be very careful, in
all these discussions, that, again, we are trying
to separate our facts upon the legitimate patients
with pain needs versus those that are abusing in
all the various categories of abuse.

How you necessarily do that, I'm not sure if
I have the answer to that. I am just pleading for
the fact to try to be very careful in whatever we
do to make sure that we don't limit access, we
don't limit supply, and we don't make it more
difficult for the right providers and the right
patient to have access to these medications.

DR. KREBS: I would just say, let's not put
all of our eggs in one basket. As we have talked
about, this is a multifaceted epidemic. We are
dealing with complex human beings. And so weighing
benefits and harms of each decision in the big
scheme of things and thinking about opportunity
costs to investing very heavily in one direction
rather than another, I think those are the really
important things to keep in mind.

DR. RICH: One other comment I would say
is -- and not taking anything away from what we've
been doing these past two days in terms of talking
about safe formulation. But I remind everyone in
this room that the problem of misuse and abuse of
these medications, as Erin just said, is a problem
which has multiple solutions.

Safe formulations are just part of the
solution. And as someone who actually goes out,
practices, and educate, practices about safe
prescribing, this is one other tool that I will
take to practices and such. But there's a lot of
the tools that I take out to practices, including,
again, the contracts, the agreements, the proper
screening of patients. The list of things goes on,
and on, and on. This is a part of a solution, but it's not just the only portion of it.

MS. EDWARDS: From a generic perspective, I think the agency -- again, I have to go back to the regulations and the path forward -- should provide that path forward. I think if we're able to bring generic products to the market that have some of these properties, it might give us a broader breadth with regard to how we could evaluate the impact of these products because they would be more available. We could actually gather more data as to whether or not we actually are having an impact on the reduction of abuse as one part of this problem by the use of these technologies that we are bringing.

So again, I think it's very critical that we define that path forward to have the ability to bring that ADF product on behalf of generic industry.

MS. BENNETT: Well, it sounds like we have covered the terrain quite well this afternoon. I'd like to ask any of the panelists any final
thoughts, anything we haven't discussed and we
should have discussed or anything you'd like to
emphasize that we have discussed.

DR. WOODS: I would like to say that, in my
role as a cheerleader, this is a fine meeting. All
told, the FDA should be congratulated for getting
everything together. And those people that have
participated have participated in an honest, good,
straightforward way, even though there are
stakeholders that obviously have different
interests. It's been fantastic meeting, and I
think that you've done a fine job in putting it
together.

MS. BENNETT: Thank you.

(Applause.)

Closing Remarks – Douglas Throckmorton

DR. THROCKMORTON: Thank you. I'm going to
take that as a segue to some final comments, and
we'll get everyone off to trick-or-treating or
whatever one plans to do this evening.

First, I'd like to reciprocate my thanks to
the panelists, my thanks to the public speakers, my
thanks to everyone that's participated in the discussions over the last couple days. I need to thank Georgiann Ienzi, Mary Gross, all of the other people from the FDA that has helped put this together. I know that many of you had discussions with them about travel and one thing to the next. This could not have happened without them. And I see Georgi. I don't know where Mary's run off to. Where did she go? But thank you, guys, very much. I really appreciate everything that you guys did to make this possible.

Then finally, I guess I'd just like to thank the community. I think this is a genuinely important topic. It's one that is a high priority for the FDA, but as many people have commented, it's within a larger framework of activities.

This is not the only thing the FDA is doing around opioids. I encourage you to go look at the website. We have a lot of things going on. We understand that this is not going to get solved by one thing. A hundred years, the 1914, is interesting. So we're at 100 years. We're still
struggling. My guess is, we still have some more
work to do. A single thing is not going to solve
all of the activities, the challenges that we have
here.

I have to say congratulations back, though,
because I think we have made genuine progress. So
I am an old cardiovascular developer. Coming into
an area like controlled substances and watching the
growth and development of new products, of new
innovative formulations, has been enormously
gratifying. In the last three or four years, to go
from a place where we were talking about one or two
products to a place where more than 30 IND
discussions have been had about specific products,
I think the industry, the whole endeavor, needs to
congratulate themselves. That's terrific growth.
That's real progress. I look forward to seeing
where that takes us in the next few years.

I have learned an enormous amount in the
last couple days about the manufacturing science
that's making that possible. I know that the FDA
would do what we need to, to try to encourage that,
the science work that Mansoor Khan, and Rob Lionberger, and the staff are doing internally, the work that we're supporting externally, the work that the manufacturers are doing. That's really the foundation for all of this. This is really all about formulations, science at its base, and as best as we can, we're going to support that.

I will not try to summarize everything that we talked about the last couple of days. I think there have been some general themes that have emerged.

I would say there is a central theme of the importance of data, whether it's to understand what's driving people from appropriate use to misuse to abuse to end-stage intravenous drug abuse or something like that, understanding that better, to who benefits from these products when used in a short term versus who's harmed by them in the short term or in the long term, who benefits from them in the long term; data that allow us to predict the effect of a product using -- the clinical effects of a product using non-clinical testing; data that
allow us to predict the long-term, real-world effects of a product using premarketing controlled clinical data.

We need all of those things filled in, and we need the surveillance system that many of you have talked about, this surveillance system that would allow us to understand, in a much better or much more nuanced product-specific way, the impact of the things that we're doing here, that we're talking about the regulatory decisions we're thinking about.

It is one of the things FDA is working to encourage, so the products that are being approved with abuse-deterrent technologies have to date also been required to conduct those postmarketing epidemiologic studies to try to understand the real-world effects of these new formulations, of the labeling that we've given them, that hopefully we'll find out that they are as effective as we all would like them to be about reducing abuse. That's the importance of data and the scientific uncertainties, trying to address some of them.
Importance of communications. Patients, physicians, payers all see these things slightly differently. All of them, I think, are understanding our labels and making choices about whether or not to use the product, whether to pay for the product, whether or not to put it on a formulary. That continues to be something we're working on, trying to understand how best to communicate what we understand about the science of these new products.

The importance of continuing to support progress here, progress, what was it? Someone talked about time and money, one of the commenters this morning. Clarity of pathway, reduction of uncertainty. I think Dr. Skolnick talked about a reduction of uncertainty, facilitating the support, facilitating the continued work in this area by making it clear that there is a pathway to its development, there is a pathway to appropriate licensure and appropriate labeling, we're going to be supportive of it, and to do this in as an efficient a way as possible.
Clearly, guidance is something that we recognize. As Dr. Lionberger talked to yesterday, we are working on draft guidance for generics, understanding the importance of that space in the medical healthcare system. We're also continuing to work on the innovator guidance around abuse-deterrent formulations. I'm sure there are other communications that we're going to go back and talk about, other ways to make sure that we lay out the pathway as clearly as we possibly can.

Then finally, I think it's important that we remember the overall goals here. As many people have said in different forms, the patients that need access to pain medicines should have access to them, and those pain medicines should work. And new formulations should not affect that. Those same medications should be available efficiently as best as we possibly can.

The paradigm FDA has been working under has been predict and then confirm. So the current labels predict and impact to reduce abuse. Our work, our goal right now is to get the data
collected to confirm those findings, and with that understanding, move to the next generation and the next products, and make incrementally better choices in terms of developing these products.

At the end of the day, we are making sure the patients have available medicines to treat the pain that they deserve, and we find a way, separately, to reduce the abuse and misuse of opioids.

Thank you very much. I sincerely appreciate everyone's efforts, and have a great day.

(Applause.)

(Whereupon, at 2:46 p.m., the public meeting was adjourned.)