the data that we've analyzed already. And our primary goal here is not to impact patient care. It's to try to be transparent for patient care and hopefully have tamper resistance eventually turn into some degree of abuse resistance.

DR. NUSSMEIER: Well, there may be some reason to rethink that from a risk/benefit perspective.

DR. HADDOX: Well, that's the benefit part I'm talking about. Okay. If I clip off a whole cadre of patients who now can't get it, I think I've really decreased in the B in the BR equation substantially.

CHAIR FARRAR: Okay. Dr. Anand.

DR. ANAND: I have a comment and a question. I'm very concerned that the data that has been presented today about tamper resistance is based on very small numbers with procedures that are inadequate and are unclearly described and the timing of the various things is not very clear. Presenting

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the data as mere ranges without showing a median is confusing at best and misleading at worst. That's my comment.

I'm also struck by the fact that all of the children or young people we saw who had died from taking OxyContin or oxycodone were of Caucasian racial descent it appeared to me and we know that there is a genetic variance in the CYP2D6 which is the enzyme metabolizing codeine and oxycodone and so on. Has the sponsor performed any studies on the patients who have died and this genetic variation is seven percent among Caucasians, much, much lower amongst other races. So has the sponsor done any testing to determine whether these were poor metabolizers of oxycodone and could the FDA be considering a labeling change similar to the Warfarin labeling change that has occurred with regard to genetic testing?

DR. HADDOX: The short answer is no, we've not done that study. Is that

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correct, Steve?

DR. HARRIS: Yes.

DR. HADDOX: We have done studies of mortality data and Dr. Cone is there who could summarize that for you if you have an interest.

The other point is that the 3A4 is also another alternate pathway. So unlike some drugs, it's not just 2D6. So one might reasonably argue that if they have a 2D6 low metabolizer that has -- more of the 3A4 route. It's a possibility. I just don't know.

DR. ANAND: You don't know that.

DR. HADDOX: That's right. We don't know that. That's right. You're correct.

CHAIR FARRAR: Dr. Paulozzi.

DR. PAULOZZI: What happens if this drug is wildly successful and in a couple of years sales go up 25 percent and then we find out that a number of deaths associated with OxyContin have also gone up 25 percent,

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say, from 4,000 a year to 5,000 a year. I'm just making up those numbers. What would be your reaction at that point?

DR. HADDOX: I don't want anyone to die from OxyContin. This is a drug to try and help patients. This is a drug I prescribed for thousands of patients when I was in practice and that would be a tragedy what you described.

DR. PAULOZZI: What would you do?

DR. HADDOX: I'm not sure. Obviously, we'd discuss it with FDA. We discuss it with other experts just like we've been discussing the problems that we've seen to date. I don't think there's an easy solution. I think that's why we're talking today.

CHAIR FARRAR: Ms. Krivacic.

MS. KRIVACIC: Yes. I have a couple of quick questions. The first one is have you thought about validating the testing program and when I said "validating" it would

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be kind of in a crude way, but at least it wouldn't be as subjective, more objective, having a third party reproduce what you have done on the testing program. Have you thought about that at all?

And then the second question I have is regarding this whole sales effort. Have you thought about also medical educators going out with the sales reps and educating the physicians, the patients and others as well instead of just the FPI piece.

DR. HADDOX: Well, let me answer that one first and, Richard, you can come up to answer the first question.

We would obviously have more than just the FPI. We have right now a complete suite of education materials that are unbranded that don't relate to any one particular product that are available through our medical education resources catalog. We have medical liaisons that are available to answer some of these more detailed questions.

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We have our medical services who man the toll-free number if the practitioner or patients have questions.

We are also working as part of our risk map, the part that I didn't go into, on a low literacy medication guide to get to the consumer level, the patient level or the immediate caregiver level. As you probably are aware, people who sit around the table and try and write a low literacy document usually don't do very well and, in fact, we tried mightily with Palladone and that was one of several package inserts and medication guides that were analyzed in an article a few years ago and we had done our best estimate to get it to about an eighth grade reading level and turned out we were 10.5 grade. So we were way off. So we have now retained a health literacy expert who is working with us as we speak on a low literacy medication guide to address that aspect.

Richard, do you want to talk about

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the external validation question please?

DR. MANNION: I can tell you that it's not something we've done so far but it's something we would be prepared to consider.

DR. HADDOX: And I know that Richard and other colleagues, we, have discussed our rationale and our thinking behind the tamper protocol at academic fora with other investigators both academic and industry as well as regulators and so it wasn't just something we sat around and dreamt up on our own. You know, we were really trying to interact and come up with what we thought was a reasonable starting standardized protocol. Then we may as we learn more add new elements to that because we use this not only for our internal development but also to evaluate opportunities that might present themselves to us from another company that wants to license a technology to us or something like that. So we have a number of reasons to have sort of a battery that we can

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run a formulation through to get an idea of how it might perform in the real world.

CHAIR FARRAR: Dr. Kosten.

DR. KOSTEN: Thank you. This is just a follow-up on a question that's nice that you have the first slide I'm interested in. That's what you would propose about it in slide number 27. Is that right?

DR. HADDOX: That's what we have proposed in the NDA and obviously when we get around if the FDA gets close to approval, we'll get into labeling discussions and we'll go round and round on that.

DR. KOSTEN: That's fine. Just to go through the data that you have then. Thank you.

Slide 43 as I look at that it talks about thermal extraction. In the thermal extraction, you're talking about a formulation that's releasing 21 percent to 48 percent less than corresponding strength. That means 80 percent to the formulation is

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about there. Now again, I realize you don't provide us with means. So it's very hard to know what that data would mean.

Then you also when you talk about the time for it in slide 41 you're talking about it taking five minutes for the physical manipulation to dissolve essentially your OxyContin as it exists now. But in about ten minutes you dissolve you get about half of the release from, and this is with simple just crushing, for the controlled release formulation. So have you done studies in which you've applied a thermal extraction that is heating it up somehow, looked at that in terms of your ground-up formulation because it appears that that would release quite a bit of the OxyContin?

The other question about that related is then on slide 42. You're talking about tampering for IV abuse, while in this picture you do show that it's a gelatinous mass that's there and this question has

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already been arisen about how you would get that into a syringe.

But more to the point would be when you heat this up and then you then have this extraction what the extraction is is the drug is then in that liquid that's being extracted out of. That's very easy to draw up into a syringe. And I just wonder if you could, in fact, address what appears to me a fairly simple procedure of heating this thing up and then heating up your little pebbles or whatever you want to call those little granule things and then just dissolving it. The OxyContin would come out. I haven't seen that data and perhaps how would this gelatinous stuff, does that disappear when you heat it up? I mean, what happens with that?

DR. HADDOX: Well, I let our laboratory expert address most of that.

DR. MANNION: This doesn't disappear. It actually forms. It gets more concentrated as you heat it up. So it's not

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an oil or a wax or something that's going to melt. It's something that's really a viscous gel.

DR. KOSTEN: So then how did you extract 80 percent of it out of that?

DR. MANNION: You're thinking of a different type of test. The way that the --

DR. KOSTEN: You heat it up first. Let me make sure I understand. You grind the tablets up. You heat them up. Eighty percent is extracted. That's what your materials say.

DR. MANNION: The data shows the difference between the current formulation and the new formulation and that test was done in much larger volume of water. It wasn't done in a volume suitable for injection. It was done in a volume several orders of magnitude larger than could be injected.

DR. KOSTEN: And then this gelatinous thing doesn't form?

DR. MANNION: Not to the same extent. It's a viscosity phenomenon. So the

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greater the concentration of the polymer the most viscous the material is.

Was there any other questions I need to address from your earlier statements?

DR. KOSTEN: Well, it just doesn't seem to match with what you're presenting in slide 27.

DR. MANNION: Okay. Is everybody clear what this slide shows in terms of -- The slide on the right shows that when you do it with the current product you can draw the material into a syringe. When you do it with the new formulation, you get material that cannot be drawn into a syringe.

DR. KOSTEN: And it's not temperature dependent.

DR. MANNION: It's not temperature dependent. This material has been heated.

CHAIR FARRAR: Dr. Gardner. I'm sorry.

DR. KOSTEN: I don't think that answers the question, but that's fine.

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CHAIR FARRAR: Dr. Gardner.

DR. GARDNER: In a few minutes, we're going to have to be working on a risk map discussion and I wanted to clarify with you on your slide 56. You say that the goals of a risk map for OxyContin include (1) to minimize the abuse of OxyContin and I think that's been what we've been seeing today, (2) to minimize the diversion of OxyContin and (3) then to minimize exposure to OxyContin among those under age 18.

I don't see that what you've provided with us as a risk map plan addresses the third one at all and my question to you is with respect to the diversion. Are you basing that on the assumption that if it is less abusable it will be less likely to be diverted or are we also not addressing the diversion of OxyContin in the risk map that you've talked about?

DR. HADDOX: Thank you for that opportunity. The slide that I tended to focus

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on here and showed was focusing on the epidemiological study. In fact, there are other tools for each of these goals and other objectives.

Part of what you said about the diversion is correct. If we are, in fact, successful introducing the desirability of this formulation, if you think about drug diversion, which I do a fair amount, drug dealers basically are a just-in-time, cash only, rapid through-put business model and they are not going to carry on them what is not being desired on the street. So that will be one element if we are successful.

But in addition to that, we provide a number of educational programs to help both prescribers prevent, recognize a potential diversion and also pharmacy safety. The work by the Pain and Policy Studies Group at the University of Wisconsin has demonstrated that a significant source of divergent material doesn't come from doctors,

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doesn't come from patients' homes. It comes from pharmacy theft and we have a number of things that we have put in place there.

But again, when we start talking about diversion, there are two levels of diversion. There's the diversion that I can control, the diversion from my factory, the diversion in my transit from my factory to the first node in the supply chain and in that area we have an excellent record with the controls that we've put in place and I can go into that detail if you're interested.

And then there's diversion once it leaves our control and at that point we do things to try and facilitate, educate, inform and help the other people downstream in the supply chain manage diversion. But once it's out of my control, it is, in fact, out of my control. Rx Patrol, for instance, is one of the elements that we have which is an internet-based, pharmacy theft data clearinghouse that we've set up that people,

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pharmacists and law enforcement officers, can interact with and, as a result of that, being linked with a Crimestoppers Reward Program that has resulted in several arrests since its inception of people who are doing pharmacy theft. So it's a multi-tiered answer.

We also have a dedicated Law Enforcement, Education and Liaison Group sort of analogous to a medical science liaison group for law enforcement officers and for healthcare professionals to teach them about pharmacy security, things they can do to prevent diversion and techniques that are being used by diverters as well as for the law enforcement officers how to investigate diversion cases.

As far as the exposure to OxyContin -- Did you want to stop me?

CHAIR FARRAR: I was going to say I'm not sure this is different between the formulations and so it's not going to help us to understand.

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DR. HADDOX: Okay. All right.

CHAIR FARRAR: Is that fair? I don't want to cut it off. It's just that we have other --

DR. HADDOX: Okay.

CHAIR FARRAR: Dr. Vocci.

DR. VOCCI: Given what we heard today with the parents and also with the clinical pharmacologist talking about the interactions with alcohol and the fact that an in vitro study may be misleading, have you considered doing some clinical pharmacology studies where you would give old and new formulation with alcohol to see is there was any dose dumping or any differential absorption?

DR. HADDOX: Steve, can you address that since we have our pharmacology head there?

DR. HARRIS: Yes, we have as many of you, most of you know, experience with the interaction between ethanol or alcohol and

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some controlled release formulations. It was mentioned earlier that there's not a complete correlation apparently between in vitro test results and in vivo results in the limited number of studies that have been done.

We have examined carefully the ethanol sensitivity of both the original OxyContin formulation and the new ORT formulation and neither one is susceptible to in vitro increases in release. In fact, with higher ethanol concentration, the rate of dissolution of oxycodone actually decreases and the reason we believe this is the case is oxycodone itself is less soluble in ethanol than it is in water and the polymer used to control the release in the new formulation is not sensitive to ethanol.

So we believe in this case there would be a good correlation, an excellent correlation, between the in vitro behavior and the in vivo behavior. So we have not proposed to do an ethanol study.

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DR. VOCCI: In your epidemiology study, you've essentially set up what I would call a one-tailed study because your null hypothesis has both no change and an increase in the number of people reporting a high versus a decrease. I'd like to know why you did that. Even though your P value, you set it up like one-tailed P 0.025 as opposed to two-tailed 0.05. Why would you do something like that?

DR. HADDOX: Well, I'm not the epidemiologist. I have one here with me and we also have a consultant, Dr. David Banks, who helped us design that. So I can't really answer that question for you, but perhaps Dr. Smith can come up and address that question.

This is Dr. Meredith Smith who works with me in Risk Management and Health Policy and she's an epidemiologist.

DR. SMITH: Thank you for the opportunity to talk. As Dr. Harris mentioned, we have been working closely with Dr. David

Banks who used to work at the FDA and has extensive credentials as a biostatistician. This was a suggestion on his part. It's -- At 0.025 level it's quite a rigorous level and in the absence of any data before doing the study to indicate what direction we might expect, we opted for posing the hypothesis in this manner.

CHAIR FARRAR: So you're suggesting a two-tailed test. So it's 0.025 in each direction. Is that my understanding?

DR. HADDOX: Right.

CHAIR FARRAR: That's a standard.

DR. VOCCI: One more. Since you're only -- According to your presentation here, you're only going to ask about what the primary drug and what the primary opiate is. Will you be able to differentiate individuals who come in saying they're heroin dependent but had switched from OxyContin or oxycodone to heroin because that is one of the patterns that is emerging.

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DR. HADDOX: So if I understand you correctly, you're saying if OTR, in fact, has some abuse resistance and because of this behavioral economics they switch from that to heroin.

DR. VOCCI: Yes.

DR. HADDOX: That's not the primary analysis. We do have a checklist as I mentioned here of all the drugs they've used to get high in the past month and then what their preference is, their primary drug. So we might be able to do that. I would have to go back and look at the collection instrument and see. I'm just not sure.

DR. VOCCI: Okay.

CHAIR FARRAR: So I'm going to move that the last question be from Dr. Fleming and then we're going to move into consideration of the questions from the FDA and we'll talk about that in a minute.

DR. FLEMING: Thanks. I have even greater concerns than just the 0.025. Let me

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explain and they're motivated by this issue of the false sense of security.

There are going to be many challenges to interpreting the data from the epi study. There's lack of randomization. There's lack of blinding. There's dissecting the OxyContin from the other oxycodone use. There's the surrogate here of changes in the proportion of OTP enrollments representing changes in hospitalization rates and mortality.

There is also another issue here that makes it complicated. The way this is being designed, it's being designed to determine whether you get a reduction in the proportion of these OTP enrollments that have oxycodone or OxyContin history and you're saying it's a positive result if you're statistically significantly less.

Let me use another example here. In HIV prevention, vaccines, microbicides, offer an opportunity to reduce risk. But when

we study those interventions, we realize that in a trial in which people don't know if this is an effective intervention, they haven't altered their risk behavior. If they think the interventions are shown to be effective, there is something called disinhibition. They're going to increase their risk behavior.

So we don't study those interventions ruling out equality. Those are only defined to be useful if they're so effective that you can rule out even moderate reductions. So that when disinhibition occurs effectiveness is still positive.

You're assessing this in a setting where no claims are being made about abuse resistance. Then you're going to rule out equality. You could rule out equality with a relatively modest reduction. Then when you then proceed to advertise abuse resistance and you set up this false sense of security, your effectiveness could be in the wrong direction.

My concern is much greater than

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you're just using an 0.025 ruling out equality to declare benefit. Why are you not required to show sufficient reductions that you're ruling out even moderate decreases such that when disinhibition or false sense of security occurs you're still at a positive scenario?

DR. HADDOX: Well, those are very good points and I think you articulated that very, very clearly. This is a proposal that's before the FDA right now. We will obviously be happy to engage in discussions with them if they get close to approve on this as to what the post marketing commitment will be and I think those are very valid considerations that you raise.

Obviously, I don't want to have a drug with an abuse resistant claim unless it, in fact, is effective and so right now I think we can argue that we have met some degree of tamper resistance, but the abuse resistance is yet to be determined, if any.

And I think that what you raise is

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actually a good point. Is it a meaningful increment, I guess, if I could paraphrase what you're saying in abuse resistance? And we'll have to discuss that and we'll see what the data tells.

CHAIR FARRAR: Okay. I'm going to bring the question period to a close.

The next order of business, in fact, that last order of business, although it's a sizable one is to review the questions for the Committee that have been put forward by the FDA. You have a copy of them in your book and handout.

Just a note, we've not been asked for a vote and we're not going to conduct it that way. We're being asked to provide our opinions and suggestions with regards to these questions specifically.

While it's not mandatory that everybody provide an opinion, it's clearly in the interest of the agency to get opinions from as many people as are willing to provide

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them. And as such, I want to be sure that everyone gets a chance to provide their opinion.

What I would ask is that as you do this process, as you provide your opinion, that if you agree with something that's been said before that you don't necessarily repeat all of it but simply indicate that you agree. If you disagree, please state that specifically. We do want to try and be clear about what we're trying to address here to come up with some conclusions.

And before I get started, Dr. Rosebraugh.

DR. ROSEBRAUGH: I just wanted to have a point of clarification because I heard people talk about approval of this as if the formulation and the indication are a package deal and that might have just been my interpretation of it. So I just wanted to be very clear that they are not tied together. So, in other words, if the sponsor would have

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come to us and said, "We have this new formulation that's bioequivalent and we just want to use this new formulation," we may have said okay.

We are here because they want specific labeling for this new formulation and they want labeling that says that this formulation is potentially better in some aspect. So we could potentially say, "Your formulation is okay. We're going to approve it" and not give them labeling. So you can disassociate those two things in the way you approach these questions. I just wanted to make sure everybody understood that.

CHAIR FARRAR: And I wonder if I could ask Bob Rappaport. You started out the day by indicating why we're here at all and perhaps you could just restate the issue about the fact that we're interested, I think, in developing tamper resistant -- At the end of the day, we're trying to find a silver bullet which won't kill anybody but will do everybody

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who takes it, who needs it, some good and if you could just define that for us so we can put it into the context here.

DR. RAPPAPORT: I guess I'll just build a little on what I said this morning which is we don't know where the line is and that line that will allow us to make a difference in abuse and diversion and the results of that and the line that is just going to actually perhaps make things worse because there's an implication that the product is now safer, particularly in those arenas, than it was before.

And it will be perhaps abused more than it was or at least available for more abuse in spite of the fact that it's a product that is useful in patients who are and legitimately prescribed the product, there is this public health crisis related to its abuse and the consequences thereof, some of which we've heard about today that was very moving testimony.

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But we don't know where to draw this line and we need your help in telling us which of these features -- is there a way, first of all, to measure whether there is some aspect of the change in formulation that will make it less tamper resistant or abuse resistant, whatever you want to call it. If there is a way to measure that, has Purdue done an adequate job of it and, if they have done an adequate job of it, what did it show? And then based on your answers to all those, is there anything that we should put on the label that isn't going to cause more problems than good?

CHAIR FARRAR: Okay. So just with that definition, I guess the way to do is just, you know, let's go around the room and we'll start with you, Dr. Wolfe.

I'm sorry. I made a mistake here. Although Bob stated it very clearly, let me read the question.

DR. WOLFE: Okay.

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CHAIR FARRAR: Discuss the adequacy of the tools we have to assess the impact of a novel opioid formulation on abuse, misuse and diversion of the product in the community. Do the available data suggest that the reformulation of OxyContin will likely reduce its abuse, misuse and diversion?

DR. WOLFE: Okay.

CHAIR FARRAR: Just -- I'm sorry. I'm being asked to do one more thing. Are there any questions about the question or is it pretty clear?

(No verbal response.)

DR. WOLFE: As I was listening and watching Dr. Kashoki's review historically this morning, it was chilling in some way because I think the problem that has arisen starting back ten, whatever, years ago with this drug is due to a false sense of security. There is amongst the elements that were the grounds for this $630 million criminal penalty, felony, whatever, was the

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understating of the abuse potential.

I mean, according to the documents that the U.S. Attorney released just about a year ago, focus groups were held with doctors and doctors were worried about the abuse of this and the response was to essentially manufacture some false sense of security about its abuse potential, less abuse potential, more prescribing.

So here we are fast forward ten years later. There has been a lot of prescribing, more than I think there would have been if the abuse potential had been studied and known and even just speculated knowing what we knew about the pharmacology of this and we're being asked again to say "Yes, it's okay to say that this is tamper resistant, that if it shows it it's going to have less abuse potential."

If I had to bet and other people have reflected this, perhaps more articulately than I can, I would bet that the total amount

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of abuse of this drug will significantly go up if this formulation is approved for several reasons. One, there's this interim problem of the 80 mg. So the smaller doses are "tamper resistant" or at least to some extent tamper resistant. The bigger one isn't and there is a certain amount of confusion there.

But even aside from that, we have these huge ranges of how much you can get out of these newly formulated dosage forms and if the label says at some level in some way or other that it has less abuse potential there's going to be more prescribing and that one pie chart that was broken up that we saw this morning showed that the single doc that accounts for a huge amount of the prescribing of drugs that eventually get into the abuse channel.

So just to summarize, I think that if this is approved, this newly formulated one, it will lead to much more abuse of this drug and I would strongly oppose it for that

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reason. I don't think that the data are in the least bit reassuring. If anything, they decrease the amount of assurance I might have had before I saw them all presented today.

CHAIR FARRAR: Thank you. Ms. Aronson.

MS. ARONSON: My concern is in the presentation of how the drug may be abused or milled or changed. There was less of a focus on the snorting which in some communities is higher than injecting and, as well, I'm a little confused about a population that might hear that this is more tamper resistant, there's a bigger coating on it, so that they may feel they need to take more to get a high with oral ingestion.

CHAIR FARRAR: Go ahead.

MS. KRIVACIC: My concern is, as I had mentioned earlier, just the validation of the testing program that that has not been done by a third party along with some issues about the epidemiological survey that will be

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forthcoming.

I also believe that the abuse potential is not -- It's just too unclear at this stage. It's like we're sort of talking in theory what's going to happen and I think that's a real concern I have.

CHAIR FARRAR: Dr. Vocci.

DR. VOCCI: Yes. Since the drug is bioequivalent, I don't see any problem with it going out. I actually think that since the epidemiology study and some other parts of the risk management plan will determine the impact of this new formulation that the labeling should be deferred until we actually have data on the impact of the formulation.

Also, you know, OxyContin and oxycodone are probably no different in some ways than a lot of other opiates and that is when we look at the data that was presented today, 70 percent of the people obtained these opiates and used them in nonmedical fashion from either a friend or a relative or they

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bought them from a friend or a relative.

They're not getting them from drug dealers. The drug dealers are four percent. So this is not the classical heroin dealer that we're dealing with. We have an issue with too much OxyContin and oxycodone and other narcotics that are in people's medicine chests and I think that not only should Purdue Frederick but possibly all the other opiate manufacturers consider some sort of take back programs for the pharmacies so that the people could turn in unused medication. I think that's something that needs to be done. Also individuals need to be educated about this, when they get a prescription, and that if it is an adolescent or a young person, they also need it.

And then finally, the other data that we've seen today suggest that you can predict fairly easily who might become an abuser of these drugs because they often times use other drugs. And I think a history should

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be taken where the doctor should talk to someone and if they've had alcohol problems or if they're currently using illicit substances, something like that, that should also be strengthened and again, not just for OxyContin but possibly for all the opiates. It's a similar issue.

CHAIR FARRAR: Dr. Nussmeier.

DR. NUSSMEIER: I would agree with others who have said that there has been no evidence presented that this formulation makes it abuse-proof. But I have been somewhat convinced that it's most likely going to be tamper resistant and that it is an improvement if it replaces the current formulation. If it replaces the current formulation, I think the abusers who are looking for the easiest route will be somewhat frustrated.

I'm still very uncomfortable with leaving the 80 mg original formulation on the market at this point in time.

CHAIR FARRAR: Dr. Nelson.

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DR. NELSON: I still don't think we've addressed the innocent misuse of these drugs whether it was unintentional or the first pill or the good kid and all of the other issues that we've kind of alluded to. I still feel that we really should require ironclad pre-marketing data before we put something like this out on the market because it seems to me that post marketing surveillance is going to fail because it often does. For all the right reasons, it's very difficult to do.

And just to follow up on Dr. Wolfe's point, even if this is tamper resistant and they get one-third of the drug out that they normally would expect to get out, it's not that difficult to imagine that they would just use three times the amount of drug. Right. We're not talking about a fraction of a percent coming out. We're talking about one-third or one-half or whatever it is which does raise even a bigger

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issue which is the unpredictability of the amount that comes out. Because if somebody thinks they're getting one-third out, but they're really getting one-half out and they use three of these pills, they're actually getting 1.5 times more than they expected to get. So not only may abuse go up as Dr. Wolfe pointed out. I think that mortality and other adverse effects of this might actually go up.

CHAIR FARRAR: Dr. Kosten.

DR. KOSTEN: Just to go through your questions the way you have them, as far as the first question, no, I don't think. I think extraction is relatively easy with heating and there is 50 percent that comes out within ten minutes when you do a simple extraction. The heat itself appears to release up to 80 percent of the oxycodone, although again the range is 50 to 80 percent. That makes an extraction followed by an accidental overdose quite a bit more likely. So since I treat mostly drug abusers in terms

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of their safety, this is, in fact, making it less safe.

As far as the second question goes, the misconception that a higher non-reformulated strength will also provide a decreased abuse, I think that's a tremendous risk and misconception that's going to go on. I think physicians are going to switch to giving out the higher dose. This will result in its greater abuse and overdose in abusers who take the old non-reformulated 80 mg doses. So you need to have all these doses available before release on the market or withdraw the old dose, the high doses, of the old reformulation by a buyback program or some other sort of thing.

As far as number three goes, as far as manipulation of the extended release properties and --

CHAIR FARRAR: I'm sorry. You're on a good roll here. I hate to interrupt but actually the first two I think if we can stick

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to those and then we'll go back around for the rest.

DR. KOSTEN: Fine.

CHAIR FARRAR: Okay. Thank you. Dr. Anand.

DR. ANAND: Slide 47 of the sponsor's presentation says that the in vitro testing was rigorous and extensive. I beg to differ. The current data do not support the sponsor's claim that this formulation will reduce its ability to be tampered with or its likelihood for abuse, misuse or diversion.

There is real concern that the in vitro testing may mean nothing for in vivo ingestion or the other methods that are available to drug abusers. For example, if this product was refrigerated, if it was put in the freezer, and then put in a mechanical mill, would it powder just as easily as the currently available formulation? Things like that have not been tested.

I also have a major concern that

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if a child ingested multiple tablets or a ground-up version of multiple tablets it would form a bezoar in their stomach and would make even extraction using washouts and things like that very, very difficult. Concerning -- that even when a diagnosis is made in time to save the child's life, we may not still be able to save that patient's life.

So at this time, I have very serious concerns.

CHAIR FARRAR: Dr. Bickel.

DR. BICKEL: I think that the testing thus far has been interesting but has not been parametric enough. I think we need to know how this new formulation behaves in a whole range of different circumstances that have not been fully explored because I know that an addict, sooner or later, will explore them. And the fact that the water extraction, you know, with larger volumes is troubling to me because once it's a large volume there's a lot of ways to get into a smaller volume.

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I'm of the opinion that the label change shouldn't be changed until there's evidence that suggests that this is, in fact, less abusable and certainly the 80 milligram tablet being currently available in the non-new formulation I think is just asking for trouble.

CHAIR FARRAR: Dr. Prough.

DR. PROUGH: Most of my reasoning has already been gone into. I do not think it's likely to reduce abuse, misuse and diversion and I think the misconception that the non-reformulated strengths will also have decreased risk is inevitable.

CHAIR FARRAR: Dr. Paulozzi.

DR. PAULOZZI: I agree with many of the previous comments. I'll just add a few other things. I think that the rates of non medical routes of administration are somewhat overstated by the selection of the data that was presented here. A study of deaths from Oxycontin in 2002 found that only two percent

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of the deaths had injected or inhaled, snorted, the Oxycontin and this is very different from the large percentages that were cited here for people in drug abuse treatment which I think is a different group.

Secondly, I think the rationale for informing physicians about the changes in formulation in the package material seems kind of hollow to me. I think it's really been put there for marketing purposes.

And thirdly, I think the epidemiologic study is a large national community trial with an intervention arm and no comparison arm and interpreting the results will be hopeless. And I am concerned that increased use will lead to increase in overdoses and deaths from the drug.

CHAIR FARRAR: Dr. Kirsch.

DR. KIRSCH: I strongly agree with the comments made by Dr. Anand and Dr. Nelson. So I won't repeat them. I'm fascinated with the poor scientific rigor that was used to

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obtain the data that was presented to us almost to the point of being insulting.

I'm against the label, changing the label, as tamper resistant. I strongly feel that the data does not support that conclusion and I think it would be a huge mistake to unlink the higher doses from the lower doses.

CHAIR FARRAR: Dr. Day.

DR. DAY: I'm pleased that the sponsor has risen to the charge to try to have a tamper resistant or reduction product, that's good. On the other hand, the data collection method still disturb me. I've voiced some of those before and agree with others as well, even in terms of the number of tablets per test, etc.

I'm very concerned about -- So there may be good data, but we can't see here. The data presentation I would not allow in an honors undergraduate thesis to go forward.

CHAIR FARRAR: Dr. Soriano.

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DR. SORIANO: My answer is no to question one based on the fact that I think the methods and the data presented would not withstand a peer review. And also the secondary issue here too is that the risk of exposing more people to abuse and morbidity and mortality of this drug far outweigh the benefits of the potential decrease yield that purportedly hasn't been proven yet. So my answer again is no.

CHAIR FARRAR: Dr. Lesar.

DR. LESAR: My answer to question one is that I don't believe that there's enough evidence to suggest that it will reduce abuse potential. I will say though that this product may be useful in producing mistakes during standard administration such as crushing of a tablet and putting it down a tube. That said, I also believe that the 80 milligram, all the dosage forms, would have to be included if it was to be marketed.

CHAIR FARRAR: Dr. Zuppa.

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DR. ZUPPA: I agree with the statement that abuse of the this drug will increase with this formulation regardless of what's on the product label and I don't want to repeat this, but I think the point that there's very unpredictable release of this new product and that is going to lead to increased mortality for the very reason that at one point, someone will get high off of two and then take two next time and more has been released and will die.

I agree with the point that a third party should be involved with the pre-marketing testing. I agree with the point that all doses on the market should have the same rigor and the same formulation.

Something that has not really been brought up that I have significant concerns about that you brought up is that I feel like if someone wants to inject this, they may very well inject this gelatinous material into their body and besides overdose potential,

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what is the risk of this gelatinous material being in the bloodstream? Stroke? Embolic phenomenon? Coronary? Coronary stroke? Pulmonary embolus? The list goes on. So there's a significant risk there as well and I think if someone has the will to go through the process of trying to inject it, they may very well inject this material.

I'm sorry that I'm going on. I think that if the new product ever does come to market, it should be very distinct in its new formulation and a new appearance. I think that was not a good idea to have it look the same.

And with the testimonies that were brought forth today, I think that overall as we look at Oxycontin regardless of the formulation, I think that the lack of pediatric pharmacokinetic and safety trials really needs to be readdressed for many obvious issues.

And then my final point is in the

post-marketing surveillance we said that it would be four quarters, and I think that there will be a learning process if this new formulation comes to market for the people that want to abuse it and it may take them a quarter. It may take them two quarters. It may take them three quarters to figure out how they can overcome some of the new properties and really abuse it and maybe the post marketing surveillance time should be more than four quarters to account for this learning process that I think will happen.

Thank you.

CHAIR FARRAR: Dr. Cortinovis.

DR. CORTINOVIS: I think that the controlled release Oxycontin is an extremely useful agent in a certain select group of patients suffering from severe pain. From what I've heard, this new formulation is not likely to reduce or decrease in any way abuse or diversion.

The only thing that I've seen

today is that the new formulation will likely decrease ingestion, illicit ingestion, by chewing. Nothing else has been demonstrated to me and if the sponsor wants to put the chewing version into their new label, that's fine.

I think that we have seen that rather easy physical and chemical manipulation can still lead to 50 percent absorption of this product. Well, 50 percent absorption of a 40 milligram or an 80 milligram or a 60 milligram dose is a pretty good whack of oxycodone. So I don't think that this is something that should be ignored and I'm not in favor or the proposed label by the sponsor that has been presented today.

CHAIR FARRAR: Dr. Fleming.

DR. FLEMING: Regarding the second part of the question about available data regarding reduction and abuse, misuse and diversion, there is a striking lack of clinical data, data from clinical trials, data

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from observational studies, focus group data, even as was discussed, data in animals reflecting the safety risks for injection of this as fluid. The aggregate information at this point, as my colleagues have said, certainly doesn't rule out at all the reality that abuse could go up.

A false sense of security is real. Disinhibition is real. The interim problem of the 80 milligram dose. The fact that risk remains with circumstances that arise without manipulation. That there are these potential new risks from injection of this as fluid.

Regarding the first part of the question, adequacy of tools, even the proposed epidemiology study leaves a great deal that would be unknown. There are many issues that would make the interpretation of such a study difficult and it would be important to understand more than the impact of this formulation on the proportion at OTP sites that report Oxycontin exposure. It will be

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important to have more direct insights about the more serious ultimate risks of emergency or hospitalization and death.

CHAIR FARRAR: Dr. Gardner.

DR. GARDNER: I share my colleagues' concerns about the potential for increased abuse and can't support having the 80 milligram in its existing formulation while there's a new formulation out there. I'll speak to the risk minimization program when we get there.

DR. MAXWELL: I think if their label were to be changed it would just simply throw down a gauntlet for every bright addict to go out and find out another way. Please remember that the TEDS data and all the other data that have been presented talk about the administration as injecting, snorting, oral or "other" and without getting in polite company, there are other orifices where some of this could go very quickly.

I also think that in doing these

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studies it needs to be contracted to an independent study group where the links to Purdue are not so blatantly obvious now. The advisory council, whoever is going to do it, doesn't need to be composed of former Purdue employees or people to whom Purdue is currently giving grants. I think there's a tremendous conflict of interest in any data that comes out of these studies.

DR. PASSIK: I'm not certain that if introduced you'd see increases, but I'm also not certain that you'd see decreases in abuse and diversion of the product. I think the existing studies have taken this to a certain point that's useful, but for my money I would like to see now also going to outside labs that do likeability testing and take this drug and manipulate it and then give it to recreational users, see how much they like it, see how much they like it compared to manipulated Oxycontin, see how much they like it compared to immediate release oxycodone.

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I think that if those studies were done, I would be a lot more sanguine about the possibility that this would influence abuse of this particular product and move people away from it.

And I also agree that I think it would be very confusing to have more than one formulation of the drug around at the same time and I think that would confuse prescribers and I don't think that would be a very good idea.

And finally, I would like to see and have a lot more detailed discussion about the RiskMAP and specifically about the education to physicians that will place abuse deterrents in a context and in a package and I know that Purdue does have a track record in trying to educate on this topic, but put it in the package so that abuse -- that the prevention of abuse, misuse and diversion doesn't end with the prescribing of an abused deterrent opioid. It is part and parcel of a

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whole range of interventions that they have to know how to include particularly with higher risk patients.

CHAIR FARRAR: Dr. Sang.

DR. SANG: You know, I'm a practicing pain management physician and I actively prescribe Oxycontin where I believe it's appropriate. But having said that, I'm basically disappointed to see that the data are focused primarily on BA and bioavailability and bioequivalence and really not clinical data. And echoing what we've heard, the lack of internal validity, the potential for bias, the unblinded nature of the data, that they were internally conducted, small numbers, really was a great disappointment to me.

And the clinical data, I agree completely with the idea that you should consider liking studies and really move forward to looking at patients, if not, animals or visa versa.

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The 80 milligram pills, I really have concerns over marketing the old-fashioned 80 milligram Oxycontin in the presence of 10 to 40 milligram OTR where physicians, you know, the vast majority of prescribers as you've shown are internists and primary care physicians and I think it's just too easy for them, for anybody, to pseudo-extrapolate the safety of the 10 to 40 milligram strength to 80 milligram particularly before you present, you apply, you present those data if that should happen. And I do think the volume of prescriptions even including the 80 milligram pills will likely go up and I think it's a slippery slope and I'm quite concerned about that.

So I actually would ask you -- I actually propose to withdraw the 80 milligram pills if the 10 to 40 milligram OTR is approved. I think it's very difficult. There are other options. Certainly, two 40 milligram pills if you can show that. Perhaps

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you could even show that the variability in the amount of drug that's released following a variety of extraction methods is lower than with the 80 milligram. That's certainly possible based on some of what we've seen and, if that's the case, then I think that's something that should be considered.

CHAIR FARRAR: Dr. Yesenko.

DR. YESENKO: This is for the sponsor. In answer to question one, I do not think the tools are adequate to address diversion or the use of any reformulation to prevent any problems with children or pediatrics. That really wasn't addressed today.

And in answer to number two, I'm not -- you may want to consider having like active drug addicts on your staff because this is very scientific and wonderful, but if you haven't worked with drug addicts, you know, what I heard so far today is that you made this huge batch of viscous substance and I

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think someone on the Committee asked what about a smaller amount. You didn't have an answer. You know, what about a smaller amount for a syringe? You didn't have that answer.

And as far as the implication for a safe product labeling, I have to agree with it. I think Dr. Nussmeier mentioned not even having 80 milligram on the market. That really is a way to minimize your risk by not having the higher dosage on the market. If you're planning to have something that is tamper resistant, abuse resistant, then have only tamper resistant, then have only abuse resistant, on the market because then if you have 80 -- You know, if you have the 80 milligrams still on the market, aren't you still implicit in something then? I'm not saying what that is, but aren't you implicit in something? You decide.

Thanks.

CHAIR FARRAR: I'm going to actually apologize to Dr. Kosten because you

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were the only one who actually did it question by question. Everybody else just skipped the questions and answered them anyway. We'll come back to you in one second.

I want to -- I obviously have to express an opinion here and what I'd like to do is just summarize the data that we've heard so far. But before I do that, I want to be sure that we hear from Steve Passik in terms of the other two questions because I know he has to leave a little bit early and I want to be sure that we get the full committee opinion.

With regards to -- could the inclusion of data on the physiochemical attributes of the new formulation potentially mislead prescribers, I think you may have answered all that already. I just wanted to be sure I understood your points and make sure if there was anything you wanted to say.

DR. PASSIK: You know, I think the problems with -- I mean I just think there has

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to be a lot of clear education that this will -- that no abuse to turn formulation that comes forward from here on. I mean, there are still pain pills and they're still meant to deliver drug and they always will when taken whole.

So I think there really has to be just a really clear educational piece that will address some of the issues that are raised in number three. I mean, the only way to deal with anything that might be misleading is to make sure that people understand that nothing deters injection of whole tablets. And I don't think that any abuse deterrent related labeling should happen until we have the studies that come up later.

I think if there are liking studies that are done and substance abusers don't like the product as much as manipulated Oxycontin or even IR then I think those kind of data could be presented. I would need to see those data first.

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CHAIR FARRAR: Dr. Rappaport.

DR. RAPPAPORT: Before you summarize, I think we have a clear indication, a unanimous opinion, that the 80 should not be on the market at the same time as reformulated lower strengths. But should the company be able to reformulate the 80 so they have all strengths reformulated to the tamper resistant formulation, I only got a sense from about half of the people on the panel. I think everybody said that the labeling should not change. But I only got a sense from about half the people on the panel whether we should approve it without a label change, whether there is an advantage to approving this tamper resistant formulation without any label change and I would like some discussion on that if possible and is there a reason not to do that and being explicit about what that reason is.

CHAIR FARRAR: So what I'd like to do is we're actually going to start here and go back and in answer to that specific

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question building essentially on question number two, the issue of whether -- I agree that I heard a unanimous vote for not promoting two different formulations, leaving the 60 and 80 without change and approving the 10 through 40.

But I think we should try and answer Dr. Rappaport's question. The issue is if the 60 and 80 are done should this formulation be approved without a label change, I think, is what you said. Correct?

(No verbal response.)

Why don't we start with Mr. Yesenko.

DR. YESENKO: My concern about leaving the labels the way they are is that doctors and patients, everybody who has used this medication thus far will just assume it's the same and will have really no understanding of what's at stake. I would rather not see them on the market.

CHAIR FARRAR: Dr. Sang.

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DR. SANG: Well, if you're -- If the proposal is slide number 51, then I think that -- Is that right? Slide 51, I think, is too broad and doesn't address the wide variability of the data that we've seen. I mean, we have on a prior slide, data that showed that up to 100 -- This may be with the 80 milligram OTR pill, but 103 percent, there's really very little difference at one end of the spectrum.

And so I would say that at best the proposal for the new label is misleading and I would vote to not change the label.

CHAIR FARRAR: The question though is if the formulation is changed for the 60 and 80 into the OTR formulation and they proceed without a label change is that okay from your perspective?

DR. SANG: Proceed without a label change.

DR. ROSEBRAUGH: Let me see if I can help you out a little bit here just to

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kind of clarify things.

DR. SANG: I think my answer addressed your question.

DR. ROSEBRAUGH: With a label change, they would then be able to advertise. That's the reason to do the label change. And so a lot of the concern that we heard here is that the advertising may be such that people don't realize the limitations of the testing or the limitations of the formulation or that sort of thing.

Do you think that the change that they made in this formulation is such that it might be valuable to be on the market, but we wouldn't really change the label at all so that they couldn't really advertise it?

DR. SANG: That's right.

DR. ROSEBRAUGH: That's right what?

(Laughter.)

DR. SANG: The answer is yes. Yes. That is the answer which I think was my

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long-winded answer.

CHAIR FARRAR: Thank you. Okay. No problem. Steve.

DR. PASSIK: The answer firstly would depend on do all strengths do they all perform equally well under the various extraction techniques. If they do, then they're all released simultaneously with no label change and I get the liking data and whatever that I think I need to see to really be convinced that there is a bit more of a resistance here. Then I would say yes that I think it could go forward. I think what we've seen today is sort of the preliminaries leading to the way you would start conducting those further studies.

CHAIR FARRAR: Dr. Maxwell.

DR. MAXWELL: I guess my concern and maybe it's more of a question. If the 10, 20, 30 and 40 were adopted or implemented right now without a label change, would that not lead to save lives, and should that not

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happen immediately, and I think Dr. Sang's proposal of withdrawing the 60 and 80 as currently formulated and then when they come back later look at it. I just would hate to put off the 20, 30, the smaller pills, hoping, you know, because we don't like the others, waiting on the 60 and 80 if we can do the lesser ones now and save some lives.

CHAIR FARRAR: Dr. Gardner.

DR. GARDNER: I think people have raised enough concerns about other issues such as inadvertent or -- assumptions about -- I think you have raised enough other issues that were not tested that I would like to see more data before we went that way even if all the strengths were in the same formulation.

CHAIR FARRAR: Dr. Fleming.

DR. FLEMING: I find this a very difficult question to answer. There is, as my colleague has just noted, still issues that haven't been resolved such as the safety of injection of viscous fluid, etc. There still

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is the possibility of clinical data to feel confidence that this change can be implemented.

If it were implemented, it would be critical that from the time it was implemented there was a very careful scientific plan in place to proactively obtain the most insightful scientific evidence about benefit to risk, particularly safety and there are many critical features that we don't discuss until Section Five on the Risk Management that I would also want to have an assurance in place to justify that.

DR. CORTINOVIS: First, I don't believe there should be any label changes. Secondly, the proposed formulation is to me as a non-chemist, but as a clinician, appears to be so radically different from what is currently marketed, I have not seen any safety studies done in animals, much less humans.

Do we really know what we're getting into with this new formulation? Yes.

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We know it's bioequivalent by FDA criteria and that, of course, is good. But is it still a safe product in the same context that controlled release oxycodone is when used appropriately in the selected patient population?

CHAIR FARRAR: Dr. Zuppa.

DR. ZUPPA: I agree that there should not be a change in the label for the obvious reasons. And I feel pretty strongly that the data that was presented today was inadequate to support bringing the new formulation to the market at this moment in time. I think -- and of too -- and wide ranges, no medians, no really standardized way of evaluating how this drug is acting, requires more studies before it would be brought to market and if those studies did happen and they were in a rigorous way and were reliable, I think it should be brought to market at that point.

CHAIR FARRAR: Dr. Lesar.

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DR. LESAR: I also do believe that this is actually a better sustained release form assuming the toxicology studies work out. However, I think from the standpoint of the downside, it won't be long before people realize this is a different dosage form and that there are some unintended consequences that should be followed up by post-marketing monitoring of use or other types of follow-up on what happens after it's marketed.

CHAIR FARRAR: Dr. Soriano.

DR. SORIANO: I'm most concerned of the fact that there's no scientific data on the safety of this new formulation, the matrix, the polymer that's being used. So indeed there should be a label change and that is what is the effect of this new polymer and this new formulation.

CHAIR FARRAR: Skip Dr. Day.

DR. KIRSCH: So I'm not in favor of allowing it to be changed with or without a change in the printed material. I'm very

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concerned about the safety data that's nonexistent or not presented.

CHAIR FARRAR: Dr. Paulozzi.

DR. PAULOZZI: I still believe that we need to work on developing tamper resistant formulations of opioid analgesics. But I'm not in favor of a labeling change and I think we have to do some more study before approving the formulation change.

CHAIR FARRAR: Dr. Prough.

DR. PROUGH: I'm not in favor of the labeling change. I think the tamper resistant properties of the product are interesting, but I think additional data are necessary on safety and efficacy.

CHAIR FARRAR: Dr. Bickel.

DR. BICKEL: I agree. I think it's an interesting line of study. We need to know more about how to make things tamper resistant. It's very important data to have, but we need to understand also how safe it is not only for the addict who may try to inject

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it but as Dr. Anand pointed out what if kids take a whole bunch of these orally. What happens to that gelatinous mass?

CHAIR FARRAR: Dr. Anand.

DR. ANAND: I do not feel comfortable with this product being brought to market even in the 10 to 40 or even if the highest strengths could be reformulated. I would not support -- If that happens, I would not support a label change based on that. I agree that safety and efficacy needs to be done.

I also believe that in the RiskMAP that the genetic variance and their linkage to mortality must be included. Without that or if that is not done within a specified period of time, then I think even the currently available Oxycontin should be pulled off the market.

CHAIR FARRAR: Dr. Kosten.

DR. KOSTEN: In spite of having answered this before, thank you for the

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invitation to answer it again.

Yes. No.

CHAIR FARRAR: Dr. Nelson.

DR. NELSON: I still stand by my original statement that this new product doesn't bring any solution to the vast majority of deaths that occur from this product which are in people who are taking this pill with relatively more benign intent than those who are injecting it, in other words, those who are taking a pill, a single pill, ingesting it orally.

And I just think no to both bringing the product to market and to the labeling change obviously. And in a way I think we've said this already before, but this is a little bit like the devil that you know and until we know a little bit more about the other devil with some more pre-marketing data about its abuse potential and kinetics, etc., I would not want to see this on the market.

CHAIR FARRAR: Dr. Nussmeier.

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DR. NUSSMEIER: Well, I remain relatively convinced that the new formulation is likely to be an improvement and I actually think it is important to continue to encourage pharmaceutical companies to work to develop novel formulations.

I also think that getting rid of the original 60 and 80 milligram formulations quickly might confer an almost immediate safety advantage for the public. So I'm in favor of allowing them to continue but without a label change.

CHAIR FARRAR: Dr. Vocci.

DR. VOCCI: I think they should one minor label change and I don't know where they would want to put it but possibly in the house applied section to say that Oxycontin is a registered ER, is a registered trademark, of Purdue. It is the following strengths which are in a such and such matrix, something like that, you know, something very -- just a statement of fact without making any kind of

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claim to that and I think that is truth in labeling right there because we don't know anything else.

As far as -- I disagree that you need to do safety and efficacy on this because it's bioequivalent and the safety and efficacy of Oxycontin as in the directions for use in the labeling have been established. So if you bioequivalent product, I don't think you need to do more studies on safety and efficacy.

CHAIR FARRAR: Can I just clarify one point? Do you feel that there's adequate toxicology data on this formulation or did the issue of the gelatinous form other pieces of it that are different? Do you feel that there's adequate data for that?

DR. VOCCI: I mean, I don't know if people are going to ingest multiple tablets. You know, if an abuser does that, they might be able to get away with it. But what the concern is really is what we heard today. You can have several drinks and one

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Oxycontin and die. And so that's something that will not be changed by this formulation.

But I think that the only way you're going to get at those kinds of issues is really through education of the physicians, the patients and the parents. Those people have an underestimated of the risks of opioids in opiate non-tolerant populations. I think the people in the United States do not understand this.

DR. ROSEBRAUGH: But let me just jump in quickly. I see you looking around. It's over here.

Just so that this isn't something people have to worry about, you can assume that the preclinical stuff is clean and that there is adequate animal data and human data to support this formulation. We wouldn't be at this stage if there wasn't. So that's not something you have to worry about.

CHAIR FARRAR: Okay. Thank you.

Ms. Krivacic.

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MS. KRIVACIC: I am all for having tamper resistant opioids. I'm not sure what we've seen today is really kind of ready for prime time with these products. So I'm not real convinced that they should be out on the market given the data that we've seen today and no to the label change.

CHAIR FARRAR: Ms. Aronson.

MS. ARONSON: I find it challenging to answer the question about label change in relationship to the safety data and benefit versus risk in what we've heard today. Also just a question about what happens with the sales force when they go out with the product. That's confusing to me as far as not having specific label information.

CHAIR FARRAR: Dr. Wolfe.

DR. WOLFE: Do you want to go first?

CHAIR FARRAR: No, go ahead. Let her catch her breath. Go ahead.

DR. WOLFE: Whereas technically

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you can't do advertising if it's being enforced by the FDA, that doesn't comport with the label. Not changing the label would obviously stop any kind of formal advertising on this point.

But having said that, everyone knows now and will know via the buzz whether it comes from here or there that the whole intention of this product was to try and reduce the abuse potential and I think that whereas it would be much worse if the label were changed particularly in light of how little we know about too many things now and advertising were allowed, it would still be bad and I think would increase the prescribing even if the label were kept the same way. So I would strongly oppose it coming to market.

And I agree with the other list of things that really have been undone here. I mean, let us assume because we were just told that the animal studies are done. This is not the same. I mean, someone said as long as

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it's bioequivalent. If we're talking about a generic equivalent of a brand name drug, bioequivalent is more than enough.

This is very different because the whole nature of the change is to try and do something about reducing tampering and so forth and it just doesn't look like that's worked.

CHAIR FARRAR: Dr. Day.

DR. DAY: As I understand it, we are discussing whether if all of the dosages came to market at the same time with the reformulation, then would we be in favor of changing the label to make some statement about its tamper resistance? I have not benefitted from my colleagues' comments. So I would say that based on the current data, no. If additional data are collected and analyzed in appropriate fashion, that could be revisited.

Going forward with the formulation without a label change, as Dr. Wolfe was just

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saying, the buzz would be out there anyway. But for those who -- But, if not, then it's like doing a clinical trial on the population without their knowledge. So I would have some reservations.

CHAIR FARRAR: What I'd like to do is to try and summarize some of the comments that have been made here and then we've been asked to look at question five specifically.

My understanding is that there is data on the bioequivalence and safety that the FDA has seen although we have not, that would indicate that this is safe and bioequivalent. But there's a general sense amongst the population that constitutes the Committee, that there is not adequate data either in vitro or in vivo to adequately support the reduction in abuse potential with this drug.

In particular, we think that it's very important that we get a group of people who are skilled at breaking these codes, at breaking this method of trying to make it

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abuse resistant, and getting them to see if they can do it prior to actually releasing the drug on the market and then there are questions about how this drug will actually be used and I think we need to be concerned that people put into dire straits may actually try and inject. There is a suggestion that they may try and inject the gel directly into their system and how would that affect them in terms of potential risk.

There was a clear sense that the 10 to 40 should not be released without the 60 to 80 and that could be accomplished either by withdrawal of the 60 to 80 while the data is being presented and reviewed by the FDA, or waiting for the release of the 10 to 40 until the 60 to 80 are available.

There's a clear sense that no label change ought to be made other than to describe that there's a new formulation until there are clinical studies that go on to support the fact that it's tamper resistant,

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meaning that we're all worried that somebody out there is going to figure out a really easy way to get around all this and that that would be a problem.

The one exception to that which was mentioned by one, but I think would get agreement from all, is that it would probably inhibit the chewing of the Oxycontin tablets and it's very unlikely that anybody would be able to chew it to adequately small sizes to be able to ingest a large dose.

There's a very strong sense that the new product ought to be different in color and/or shape or size so that it could actually be differentiated from the old one and therefore identified by the very -- the systems that we have which are not poorly designed but simply suffer because of the paucity of data that comes from medical records in the current state of the way in which we collect them.

We clearly feel that there's a

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need for a more clear definition of how the surveys and the methodology that would be used in order to understand how this product would be assessed once it's released into the public in terms of understanding whether it actually decreases or increases abuse given the concerns of the panel that a drug that appears to be reduced -- to have a reduced abuse potential may lead to increased use and increased availability leading to more accidental deaths from direct oral overdose.

So I think that's a reasonable summary of what we've heard and what I'd like to do is to move on unless there is anyone that thinks I missed something. Oh, I missed the bezoar. I'm sorry. And actually that's a good point. I did miss the issue that there's a strong sense that there ought to be studies in pediatric populations and I'm sorry. I did miss that. And that that should be conducted no matter what happens with the current formulations.

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Did I miss anything else?

Okay. So just moving on to question five, I'm going to read the question and we'll see how it interprets. You can help us, Bob, if we don't understand it. If you do recommend any of these data to placed in the product label, are there any risk minimization strategies that need to be put in place to support the appropriate use of this product, i.e., additional language in the labeling? Please specify. Education information that will describe proper use and the potential for misuse and abuse of the product, special education requirements, training for the prescribers, limitations on which patients should be treated with the product, formal agreement between the prescribers and patients for proper use, registries for prescribers.

I'm assuming that this is if the formulation were released. Are there anything that we can do in a label to try and prevent the perception that it's a completely safe

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drug and that it can be used more widely? Is that fair?

DR. RAPPAPORT: Not just in the label. This is looking at a full risk minimization plan, what today under the new law is being called a REMS that could encompass all kinds of different things from labeling changes to restricted distribution, restricted prescribing. There are a variety of things.

So what I'd like to hear is since we didn't seem to get the sense today that people think we should put anything, most people think we should put anything in the label at this time even if we were to approve the product. But at the time that we were to approve this type of product, what in your wildest imagination can you come up with that would be good ways to mitigate risk.

CHAIR FARRAR: Okay. Sid, do you want to start?

DR. WOLFE: Well, I just really

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want to raise a procedural question. The way I read question five, Bob, correct me if I'm wrong, is that if we were to agree with (a) there being something put in the label and at least (b) incline in the direction of the product coming on the market, then (c) we would want to give you some input on risk minimization and so forth.

Since we haven't really, at least, most people haven't gone with (a) and (b) on those grounds alone I would think that it would be sort of premature to talk about risk minimization because we just don't know enough about this product, particularly from the standpoint of risk. We just don't know enough. I mean, that was I think the genesis of the answer to the first two questions.

And I can imagine that this group were we to be much more satisfied than we are now at some possible date in the future might have a very different answer to what sort of risk minimization strategies we would go for

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based on one set of facts as opposed to another. So for myself I can't answer that question because it's too abstract. There aren't enough data available.

DR. RAPPAPORT: And that's a reasonable -- I think that's a reasonable answer. If that's the way people feel today, that's what I'd like to hear. However, I'm also using my opportunity here of having you all here and having heard the general discussion over the day to see if you can come up with some ways that would help us as we approach not only this product but other products.

DR. WOLFE: Let me just read. This is a sentence from a memo that was in our CDs from Mary Willy and the Division of Risk Management and she's talking -- this is a memo on risk management and what she said is "we recognize there are many challenges to monitoring abuse particularly when there are multiple versions, generic, old formulation,

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brand and now new formulation and expect the evaluation of the introduction of a newly formulated Oxycontin creative efforts."

And here is her key sentence which I am very persuaded by. "The proposed metrics include new evaluation strategies that have not been validated and in our opinion are not likely to provide clear evidence of effectiveness of the proposed risk management strategy." I would agree with that and again to go beyond that, I would have to know much more than I do about the nature of the risk, the reduced rates, how much it's reduced, and so forth.

CHAIR FARRAR: Okay. Ms. Aronson.

MS. ARONSON: I'm feeling similarly. If we really did have information that there was less manipulation and less abuse, then we could move to the risk minimization strategies and there's a list here in question five that are really terrific. But absent the information that I

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just mentioned, all these risk management strategies would only promote an increased marketing because there just would be incredible opportunities through each of these avenues for marketing.

CHAIR FARRAR: Ms. Krivacic.

MS. KRIVACIC: I agree as well. I do think though, moving forward, if it does get to the point where it is tamper resistant, all the data is here, everything looks clear, maybe one idea at least in terms of slowly rolling out this program would be sort of an idea of compassionate use for non-cancer opioid people, I mean, people that do need Oxycontin pain medication.

CHAIR FARRAR: Dr. Vocci.

DR. VOCCI: Yes. I actually think that all of the opioids should be considered in terms of some type of general advice that the FDA should consider formulating to prescribers in the United States in terms of what the risks are and who might be a possible

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abusers. So I think there are things that can be done now, you know, minus this issue and whether people agree that this goes on with or without labeling, I think you should consider this as a class because the issue is very complex and I liken this to pushing on a balloon. If you can do something that you would essentially depress the prescribing of one opiate, it's just going to pop up somewhere else.

And I think you have to consider this in a global fashion so that you consider prescribing of opiates and most of the physicians that you talk to say, "You know, I never got much of this. I got one lecture in medical school." Some places have more than that now and there is very little -- The doctors basically learn through their residencies or whatever they do, but then they don't learn to manage chronic pain in their residencies which is where we are having the problem in the United States. So I think that

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something like this would be of great public health import, to actually consider what the FDA should be saying to physicians who prescribe opiates.

CHAIR FARRAR: Dr. Nussmeier.

DR. RAPPAPORT: Can I just get a clarification? He was talking about outside of the label.

DR. VOCCI: Yes.

DR. RAPPAPORT: Okay.

DR. NUSSMEIER: Yes, I agree with some of what's been said. I mean, essentially we're talking about another full two-day meeting. The horse is already out of the barn. I mean, all these doses of oxycodone are currently marketed except for the 160 milligram formulation and any of these suggestions in question five may be valuable. Special educational requirements/training for prescribers, limitations on which patient should be treated with the product, formal agreements between prescribers and patients

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for proper use, registries for prescribers, all of those may be good ideas. But I don't think we can solve it this afternoon.

CHAIR FARRAR: Dr. Nelson.

DR. NELSON: Given the proven problems that we've had with this drug in every venue, I think that we should probably back up and take a look at this the way we looked at another drug that came to market not that long ago that got a very comprehensive risk management and a fairly aggressive one that in my mind has a much, much lower lethal risk than Oxycontin does and that is a drug named Xyrem which is sodium oxybate which really came with for those who have followed that quite a full blown prescriber education. You need to get licensed. You need to order your drugs through a specific pharmacy that can be delivered only when you're done with your previous dose of drugs.

I think there is way too much of this drug on the market. It gets to people

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through relatively illegal channels. The only way we're probably going to really reign this in is to make it availability quite minimal and I know that's going to go over poorly with many people in this room. But it's probably the safest thing to do.

DR. RAPPAPORT: Can I just ask you to follow up with after we acknowledged that Xyrem is indicated for a very small, narrow population and oxycodone and other pain medications are indicated for millions of people in this country.

DR. NELSON: Well, you didn't ask me that question. You said what would be my ideal. You know, that's a problem that has to be worked out and maybe it will reduce the prescribing a bit. You know, I guess in -- my perspective on this is maybe different than those that practice pain management.

But there are many, many analgesics on the market out there of which this is one. This probably is the one that

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seems to be most associated with abuse. You compare it to MS-Contin. You compare it to other. You know, even -- I don't want to get -- fentanyl patches, these other things that people are out there using. This one really seems to have a unique position in the market or in the, I guess, the down -- the black market, so to speak, you know the downside of drug use.

And I just think it's something that we really need to look at given the amount we've heard, these terrible stories in the public session. You can open up any newspaper any day of the week and you can read about these problems and I think we need to take a fresh look at this drug and put a fairly comprehensive and aggressive program around it.

CHAIR FARRAR: Dr. Kosten.

DR. KOSTEN: I'd agree that we need to have an example somewhere. I think the example that we might have is how a

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program was developed around the use of bupinorphene or Suboxone for treating opiate dependence in office based practices, an alternative to methadone, that has a whole post-marketing program developed around it.

You might argue to a certain extent that that's what Purdue is trying to do now. That is develop the medication that could be given to people who potentially have had abuse problems with it, but that doesn't mean that their pain is anywhere gone. That is, that it's a tamper resistant. It's in many ways might go into a high risk population because that's what we're all thinking about right now. That is, if you say that this is easily prescribed that you should -- the doctor is not going to worry. He's going to start prescribing a lot of this.

So I would just suggest all these things are of course very useful. I would review the risk management plan which Purdue did present parts of it around what's been

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used with Suboxone already and that is an example.

CHAIR FARRAR: Dr. Anand.

DR. ANAND: I think any consideration of risk minimization, Dr. Rappaport, must include good evidence on opiate-induced hyperanalgesia, on tolerance versus addiction, with studies perhaps using functional MRI to look at the nucleus accumbens in other reward pathways that would predict addiction versus tolerance.

And then to minimize risk, we need to define a length of treatment, a maximum dose that can be used, and clear patient selection in terms of which are the patients that would benefit from this kind of a preparation. So I think those are all important issues to minimize risk.

CHAIR FARRAR: Dr. Bickel.

DR. BICKEL: I want -- First going on by what Frank said, I think this is a global problem with opioids and to treat it as

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we're just dealing with this one little part of the puzzle doesn't make a lot of sense. What I found challenging in listening to lot of the presentations and responses to questions today is what would you do if you found out there was a lot of abuse and all I heard was you would look at some data and think about what we would do.

I'd like to see a decision tree. I would like to see if we see this much abuse we're going to engage in these ten actions or these five actions. If we see this type of abuse, this population, we're going to see a different set of actions. I'd like to see the drug company think through how they're going to control access to the medication, how they're going to educate the population, how they're going to track it to protect us from the adverse consequences of having this medication available in the marketplace.

CHAIR FARRAR: Dr. Prough.

DR. PROUGH: Well, whatever the

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solution is, I agree it can't be a one drug solution. I think the troubling thing is that if you look at the data that suggests that an awful lot of the folks who abuse oxycodone get it from primary care physicians, there is obviously a fair number of people who give out oxycodone prescriptions in quantities that folks even feel comfortable sharing.

On the other hand, you have physicians who are reluctant to treat their real chronic pain adequately and I think one of the most difficult things is going to be to put together a program that discourages use by people who currently over-prescribe and doesn't place further barriers to the use by people who under-prescribe.

CHAIR FARRAR: Dr. Paulozzi.

DR. PAULOZZI: Yes, I agree with treating this as a class. I think that today there are probably more deaths related to methadone being used as an analgesic than there are deaths related to oxycodone or

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Hydrocodone. And it is like a balloon. If you push in one place, prescribing will increase in another.

So I would agree with many of these recommendations and other things. It's like guidelines for chronic non-cancer pain use which include a maximal daily dose and particularly guidelines for use in acute pain because 40 percent of opioids are prescribed in emergency departments in the United States.

CHAIR FARRAR: Dr. Kirsch.

DR. KIRSCH: I don't have anything to add to the excellent comments that have been made.

CHAIR FARRAR: Dr. Day.

DR. DAY: I do agree. It would be very worthwhile to consider the whole class and treat the whole class together and then specify some of the parameters for treatment that people have brought up. But at this point now perhaps something about some educational information about over-prescribing

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and under-prescribing might be useful to the general public and to the prescribers.

CHAIR FARRAR: So I'm going to take my turn this time around. I just want to echo one thing which is as a physician who takes care of pain patients I am strongly in favor of having adequate pain medication to be able to deal with those patients. I'm also very strongly in favor of some efforts towards educational programs that could be substantially larger than they currently are to help physicians understand how to progress with the prescribing of opioids in a safe way.

And we tried this at the University of Pennsylvania. We get as detailed as talking about writing it like a check so that they don't write more numbers in. We tell them to get a safe at home because their kids wouldn't steal it but their kids' friends might steal it. I mean, there's a process that some of us have learned over time and if there was a way to provide that in

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some sort of very comprehensive way, dealing with the group of opioids as a class because I agree absolutely that it's like a balloon.

But I just wanted to emphasize the fact that I'm very much in favor of trying to find new formulations that are less abusable as well as to allow formulations available to treat our pain patients. I think the problem here is that we don't have the data. But in terms of the educational program, I think it's very important that we try and focus on that and how the FDA can play into that, I'm not sure. But it's an important issue.

Dr. Soriano.

DR. SORIANO: It's hard for me to imagine that there are no studies looking at reformulation of a drug, not necessarily opiates, but any drug classes can lead to decreased morbidity. I think we should really look into the pharmacological literature and see what's worked and try to apply it in this application.

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CHAIR FARRAR: Dr. Lesar.

DR. LESAR: You know, just from the public comments, there is certainly a problem out there that needs to be addressed. It's very difficult to sit here though and ask for risk map, things, again not knowing what works and what doesn't work.

But on the other hand, not doing anything is probably just as futile perhaps. But I would definitely encourage trying the development of targeted education and to try to counter act any negative potential from this dosage form.

CHAIR FARRAR: Dr. Zuppa.

DR. ZUPPA: I don't have much to add to the comments that were already made. It's just again hearing the public speak. It's remarkable to me that it's everywhere and a 15-year old, a 12-year old, can get it so readily and so repeatedly is concerning.

CHAIR FARRAR: Dr. Cortinovis.

DR. CORTINOVIS: I don't have the

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data to feel comfortable to make specific answers to these questions that are posed in number five. The information that Purdue has submitted is really observational and descriptive and certainly not scientific.

In an ideal world since Dr. Rappaport said, "Well, in an ideal world, what could be done," one may argue that this agent could be restricted to centers or practitioners who have active surveillance protocols in place. I'm not proposing that. I think there are a lot of suffering people who get adequate relief from controlled release oxycodone and I don't want to see that restricted for these individuals.

The reality is I would love to see Purdue Pharma show us real data, real information, done properly to say that this stuff works because this is a step in the right direction and I'd love to see them have us review this data and have us say that this is a labeling change that they propose that I

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could live with.

CHAIR FARRAR: Dr. Fleming.

DR. FLEMING: For opioids overall and specifically for Oxycontin, I think implementation of many of the features that are listed in Section Five here under Risk Minimization Strategy should be carefully considered. I think it is time for enhanced education, regulation and accountability and that includes enhanced FDA oversight over marketing procedures, and enhanced understanding and pursuit of the use of these agents, particularly Oxycontin, in proper settings, settings such as restricting to severe chronic pain settings.

CHAIR FARRAR: Dr. Gardner.

DR. GARDNER: I think we may be premature on some of the more extensive risk minimization programs that some of which have been discussed today. But with respect to this particular formulation, I have about three things that have occurred to me today.

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First is that the health professional I haven't heard mentioned here at all today is the pharmacist. We're going to educate all these physicians. But I'd like to talk a lot about -- I mean, I'd like you to think about what you already know about how pharmacists can help with this including educating physicians, but more importantly, educating patients and the public and that is, I think I heard Dr. Vocci talk about one of our big problems being that these things are in drug cabinets all over America and some of that is no longer needed by the people for whom it was prescribed.

And the public education campaigns and the pharmacists' education campaigns that can get those brought in to be disposed of when they are no longer needed as opposed to the chronic pain meds that we are so concerned -- make sure that people have I think can help a lot. I'd like to see Purdue Pharma take some positive action in initiating some of

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those programs and gain some positive PR about it.

Secondly, back to the pharmacist and patients, I disagree with Dr. Harris that changing the color or size or look of these products would be a problem for patients. People are very used to having things change now by substitution of generics and therapeutic equivalence in their pharmacy because their health plan changed. And pharmacists who know that they're dealing with something different than they had before, a new formulation, regardless of that the label says are able to then explain to patients why they look different and it may turn out to be a better way to control. This is something else. We have to pay attention to it differently.

So I think that there are things that can be done even in thinking about moving these formulations ahead, before we then move onto the next phase which is with more data

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perhaps we would have a different risk minimization program.

CHAIR FARRAR: Dr. Maxwell.

DR. MAXWELL: At this time it's very interesting in terms of looking at the entire opiate training. I was lucky enough to be at both ASAM and the pain conference last month. CSAT is putting together with these organizations continuing education programs. I sat through the one at the Cleveland Clinic recently.

We have a lot of work to do in educating GPs on how to prescribe and how to translate doses and things that could be done regardless of what drug it is. And I think Purdue could gain a lot of very favorable publicity by jumping into this. Suboxone goes off patent in October. So they are discontinuing a lot of the training they've been supporting.

And if we talk about training doctors on how to prescribe all the opiates,

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it's the same thing in terms of contracts with patients and urines and all these other things that certainly this would be something Purdue could do that would be very, very helpful.

CHAIR FARRAR: Dr. Sang.

DR. SANG: I agree that risk minimization strategies need to be broad and comprehensive and across the class of, in this case, opioids. But we have to start somewhere.

I mean, part of my dilemma today actually is that it's not clear at all what tamper resistance really means to the potential for abuse. It's a methodologically difficult to show and I think that actually in the end, I think that we may get much better handle by using a broader perspective, a broader set of data.

And I agree completely that education is critically important, but I'm also -- I think that registries are critically important and surveillance is critically

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important.

CHAIR FARRAR: Mr. Yesenko.

DR. YESENKO: In answer to number five, I agree we need to treat the class of opioids together.

Education is key in dealing with opioids. And I think, Purdue, this is a wonderful opportunity for you as a sponsor to get an educational packet together, not only about Oxycontin but opioids as a whole. And this could create some type of educational format for docs, prescribers and patients.

And if this does work, I think somebody else mentioned that the data could be renewed and hopefully give the families of people who have lost loved ones hope, because nobody has even really acknowledged the fact that there are people in this room who have lost people to this drug, specifically Oxycontin, the one you produce. So this is really an opportunity for Purdue to look at what they've created and look at opportunities

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for education, not only for the docs but also for patients.

CHAIR FARRAR: So if I could summarize the answers for that portion, I think there is general agreement that continued effort towards working on tamper resistant or reducing the risk of taking opioids is a clear goal that's worthwhile, but that so is good pain management and that we can't lose sight of that and it's a balance between those two that we're struggling very hard to do.

It seems pretty clear from everything that was said that there was clear understanding that the risk management plan for Oxycontin is too narrow and that like a balloon pushing on Oxycontin is going to cause problems elsewhere and that a broader view of that would probably make some sense.

There was a mention that FDA needed to oversee some aspects of the marketing and how that's all done, although

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I'm not sure how that -- It wasn't specified as to how that would occur.

The educational process or the process of training needs to include all people involved in the process of manufacturing and dispensing the drugs including pharmacists, patients, as well as physicians and nurses and others involved.

And that in general there was a sense that there's an opportunity here to make a favorable impact on perceptions about the whole industry that might be worth picking up.

With that, Dr. Rappaport or any of the other FDA folks, are there questions that you wish to keep us here for?

(Laughter.)

DR. RAPPAPORT: No, I want to thank you all. I mean, this was an extremely helpful, extremely enlightening, discussion today and we really appreciate that and, this last question, I'm glad we did go around and discuss this because I think for those of you

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who are going to be here tomorrow it's sort of a good segue into the next discussion. So again, thanks everybody and a particular thanks to our colleagues from SAMHSA for coming in and presenting today and to Dr. Farrar.

CHAIR FARRAR: Thank you all. Have a good night.

(Whereupon, at 5:10 p.m., the above-entitled matter was concluded.)

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