these non-cancer breakthrough pain patients will have a greater number of co-morbidities. And associated with those co-morbidities will be the aberrant behaviors that we expect will likely result in non-compliance, as Dr. Vocci just indicated. They're more likely to lose their medication, have trouble with their medication. There may be greater abuse.

And my question is as we go forward and we expect that there's going to be greater non-compliance in this patient population that you're seeking the indication for, what particular parts of your RiskMAP plan will be designed to prevent that particular portion of risk?

DR. MESSINA: So just to clarify, all the patients who would be on Fentora, the intent is for them to be opioid-tolerant, which means they're on around-the-clock opioids, and in all of those cases those patients will already be receiving supplemental opioids as it is, so whether it's

oxycodone combinations or hydrocodone combinations, et cetera.

As far as our tools that we have with regards to educate, it primarily focuses on education both from the patient and understanding about the medication, the risks associated with that, making sure the medication is secure, as well as educating the physician and educating the physician on the appropriate patient selection. We do that through a number of different venues. I touched on some of them, which was the Emergent Solutions in Pain program that we sponsor, as well as our speaker programs where we talk about, through educated speakers, educate prescribers on appropriate patient selection, documentation, monitoring for aberrant behaviors, these types of things.

DR. BICKEL: I think that's helpful, but I guess, if I could push you just a little bit more. A very wise fellow in my field once said that, you know, knowledge is

the solution to the extent that ignorance is the problem. And it's often the case that, with people with psychiatric co-morbidities, which you showed a fair number, that it's not the knowledge that's the problem, it's the problem that they have behaviors that interfere with appropriate therapy outcome. They have made choices that are seemingly irrational. And in that context, knowledge is not going to be an adequate protection from risk. So is there anything else that you would --

DR. MESSINA: What I would like to do is call Dr. Heit up who actually has helped us. He's key in the ESP program, as well as the speaker training. He can discuss about specific tactics that he advises on.

DR. HEIT: Howard Heit, Georgetown University. The one thing I want to make clear as a practicing clinician, I practice in northern Virginia and my patient population is patients who have 100 percent pain or patients

who have 100 percent addiction, and I will see the patient who has both addiction and pain if they're willing to work a program for both. So I'm sort of like the caboose at the end of the train of seeing patients that most physicians don't want to see.

The idea is that if you have a medicine that is approved by the FDA for non-cancer pain, that doesn't mean that I have to prescribe that particular medicine to a particular patient. I evaluate the patient, and this medicine may be contraindicated secondary to my evaluation of the patient, and I wouldn't prescribe it to someone who is in recovery from addiction.

This medicine is reserved for someone who has failed therapeutic trials with other breakthrough medications, whether it be hydromorphone products, oxycodone products, hydrocodone products, and now they have been in my practice for probably months, demonstrated that they're staying within the

boundaries that I set up before writing the first prescription for them. And although they have a co-morbid condition of addiction, psychiatric disorders, et cetera, I have gotten them the proper help during that period of time, brought in the proper consultation for them to work a program.

What I'm saying, in private practice, is prescribing rational pharmacotherapy is just one piece of the pizza pie. If I don't deal with the bio-psycho-social issues of the patient, I could give the patient a bath of opioids. So it's not the molecule of the opioids that's causing the problem, it's the patient could have poor coping skills or have co-morbid conditions. And if I don't address it, it doesn't make any difference what opioid I use. I'm going to have an adverse outcome with that particular patient.

In relationship to a risk mitigation program, I just participated in

developing a slide set with Steve Passik from Sloan Kettering as a form of slide deck which goal is to educate the attendees, the attendees' form of speaking programs in the area to recognize and prevent addiction, abuse, diversion of controlled substance. It's made up of four separate slide decks: patient assessment, re-assessment, regulatory issues, clinical practice and boundary settings, and reducing risks through appropriate pain management. That's the formal slide deck.

But anybody knows when you go to a program to learn is there's an informal session, and the informal session is the Q&A afterwards, the face-to-face meeting, and more important to me in my learning curve of learning to do pain management, and I feel addiction medicine also, is that the education that goes on after the program, independent of the formal program and independent of the pharmaceutical company sponsoring the program,

meaning the exchange of telephone numbers, the exchange of e-mail, the networking of the attendees, the speakers, and the attendees together, all to help to improve the practice of pain management. So the purpose of the risk management program is to facilitate positive changes in somebody's practice that will better the life of the patient, provide information to the healthcare provider, and also protect the community of abuse, addiction, or diversion of these valuable medicines.

So in conclusion, just because we have the medicine to prescribe it doesn't mean that we need to prescribe it to every individual. Each individual has an evaluation, and then we decide what is the proper rational pharmacotherapy, in addition to what else should be part of their treatment program.

ACTING CHAIR SORIANO: Thank you for your comments. We have time for two more

questions from the panel. The first one is from Dr. Paulozzi, and Dr. Anand will have the last question.

DR. PAULOZZI: Thank you. I believe you said, and this is a question for the sponsor, that, as part of the RiskMAP, if a patient has evidence of an overdose or drug abuse that you would get in touch with the physician who prescribed the Fentora to them, talk with them about their prescribing practices and, if they didn't improve by some measure, cut them out of the program. And you said that you would be able to identify these patients, I believe through your surveillance measures. Could you explain how you're getting the names of patients and their doctors through the surveillance system?

DR. SCHMIDER: We would not be getting the names of the patients with the surveillance system. We would be getting reports from individual patients that are participating, spontaneous reports. And from

those, we are able to get the information about their healthcare provider.

DR. PAULOZZI: So the patient who has the abuse or overdose would be reporting?

DR. SCHMIDER: These are spontaneous reports, so either healthcare professionals or the consumer, the patient, reports about adverse events and about adverse outcome or any other question to the company.

DR. PAULOZZI: Doesn't it seem unlikely that a patient who had an adverse event like this, an overdose or abuse, would report that back?

DR. SCHMIDER: We get reports from patients that report that after the fact, and we get reports from healthcare professionals, more likely, to your point.

DR. PAULOZZI: I would imagine it would be a substantial underestimate of the true incidence.

DR. SCHMIDER: That's correct. It's well known that voluntary reports don't

reflect the true incidence of these events.

ACTING CHAIR SORIANO: Dr. Anand?

DR. ANAND: I have a recommendation for the FDA that, when studies are being presented in advisory committees that the sponsors should be required to put out the consort guidelines which account for every patient that was entered in those studies. I'm pretty clearly concerned over here with this pivotal study that was done that recruited 941 patients. And then when you look at the data that is being presented, we have one graph showing placebo and Fentora, which includes only 79 patients, another set of graphs showing Fentora 453 episodes and placebo 226 episodes. It's very confusing to see where did the rest of the patients go. All the other graphs, you know, contain less than a hundred patients. So if 941 patients were recruited, what happened? Where is the data for the rest?

DR. MESSINA: The 941 patients is

the cumulative exposure, the cumulative number of non-cancer patients that had entered four clinical trials. So it's the safety data, when we analyze that, is all the safety data for all of those clinical trials. The graphs you're referring to with the numbers are from the individual efficacy study, which had a smaller number of patients for which, when we did the pivotal time point of assessment, that's the number you're referring to. That's why the numbers are going to change, because we talk about either cumulative studies or independent studies, individual studies.

DR. ANAND: So simply a chart showing that, you know, the data is from this study which included this many patients and so many were withdrawn, which follows the normal consort guidelines for which we're required to present when we publish our randomized trials. We have to show that chart of how every patient is accounted for. So I would recommend that as a uniform requirement for

all studies presented to committees.

ACTING CHAIR SORIANO: Thank you, Dr. Anand. We will now begin the panel discussion to address the charge that Dr. Rappaport and the FDA has given us this morning. That is five questions. And Commander Watkins will be giving us the ground rules for this discussion.

DR. WATKINS: The first four questions that we'll be approaching today for discussion, only there won't be a formal vote. The fifth question, however, will. And if the committee members will notice on their microphone there's a series of buttons. When we get to the fifth question, I will ask you to first push the attend button. Once everyone has done that, then I will ask you to commence with the voting, and I'll go back over that at that time.

ACTING CHAIR SORIANO: Okay. The first question that's being posed to this committee -- would you mind putting this

question on the slide -- is do breakthrough pain episodes experienced by patients with chronic pain that is not related to cancer usually require treatment with potent opioids such as fentanyl, or can they be adequately managed with less potent opioid or non-opioid analgesics? What we'll do is go around the room, starting with Dr. Wolfe. Does anyone have any issues about clarification about this question?

DR. RAPPAPORT: Dr. Soriano, it's me over here. You know, it's okay if people want to have a more general discussion about this first before having to sort of go around and ask everybody.

ACTING CHAIR SORIANO: Thank you. Point taken.

DR. KOSTEN: Just the question of it's got this thing, usually require treatment. It makes a big difference if we say usually or can or sometimes. I mean, usually means most of the time, so can

somebody clarify the question?

DR. RAPPAPORT: Well, I'll just simplify it. What we're just asking is do patients with non-malignant chronic pain who have breakthrough episodes, are there any of those patients who should be treated with potent opioids? And if so, you know, what portion of that population? We're just trying to get at whether this is a legitimate use of the medication.

DR. KOSTEN: Can I ask a follow-up on that? It's a legitimate use for two percent of the patients that have chronic pain is a very different question than asking is it for 98 percent of the people with chronic non-cancer pain that this could, in fact, be a useful thing. In other words, the mechanisms for how you would do this physician judgment seems perfectly reasonable to do off-label things. I'm sorry. Can you hear me okay? Okay. So, again, I apologize if I'm hitting a nail too hard, but I'm just trying to figure

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out what -- if you want to know the answer, usually the answer I think is going to be no. If you want to know the answer that says ever, then the answer is going to be yes.

DR. RAPPAPORT: Well, I don't think you need to answer either usually or ever. I think you need to give us a sense for how frequently this would be appropriate, how common is it. If you have numbers, we'd like to hear numbers. You know, there's some literature out there that says that there is a population of non-malignant chronic pain patients who do have breakthrough episodes that require opioid treatment. But we also hear from people who disagree with that literature, and we're trying to get a sense from the people here who are experts in this area as to what the real patient population is like. Is it a tiny patient population? Is there a significant patient population? We're not looking for an all or none, we're looking for a quantitative assessment of the problem.

ACTING CHAIR SORIANO: Dr. Day has the first question.

DR. DAY: So this is a question about frequency of occurrence, not criteria or conditions under which it would happen; is that correct?

DR. RAPPAPORT: Yes, that's correct.

DR. DAY: So we're not to define parameters, what types of patients, and so on but, on average --

DR. RAPPAPORT: You can certainly do that, as well, if you feel it would be helpful to answering the question.

DR. DAY: Well, I think it would be easier to talk about frequency if we define the parameters under which it happens a little bit.

ACTING CHAIR SORIANO: Dr. Gardner?

DR. GARDNER: Since this is a joint committee meeting, I'd like to give a

little perspective. Those of us who work on risk management usually, often are not clinicians, and so I'd like to ask my clinician colleagues to be very forthcoming about their clinical experience and perspective on these issues so that we can understand what the range of alternatives and options for these patients are. If you were only talking to each other, you might be less likely to do that. But since you have some of us who are not familiar with this, would you be more expansive? Thanks.

ACTING CHAIR SORIANO: Well, maybe a member of the committee who deals with pain treatment. Dr. Anand, would you like to make the first set of comments?

DR. ANAND: Certainly. I don't practice in a pain clinic regularly, but I'm called more often than I would like to to deal with some of these complex issues. I do think that there is a significant proportion of patients who have chronic non-cancer pain that

do have severe episodes of breakthrough pain. And those are unpredictable and, for those patients, carefully selected patients and conditions, it would be a reasonable thing to treat them with a preparation like this or another drug with similar pharmacokinetic properties.

I don't think that of the 30 million or 76 million people who live with persistent pain that there is a huge, sort of, market out there. This is a patient population that is fairly carefully selected and will have gone through the other modalities that are available in terms of biofeedback and behavioral cognitive approaches and are already on around-the-clock opioids. So I think there is a significant population out there.

DR. CORTINOVIS: Having treated non-cancer chronic pain patients for a number of years; I'm both an anesthesiologist and a board-certified occupational medicine

physician, I'm just not sure what breakthrough pain is in this population. It's very clear to me what breakthrough pain is in the cancer patient population. It tends to be agonizing, searing, severe, and most of the time I found it to be related to ongoing tissue destruction.

But when you deal with the chronic non-cancer pain population, when you ask them how they're doing, they typically describe a waxing and waning of their symptoms. The most common response is, I have good days and I have bad days. Typically, they describe their good days as being all day and their bad days as being all day. And when you get into more specifics, these individuals will often describe their acute on chronic discomfort as a catch, an ache, a jab, which really implies an increased pain of very short duration.

Many of these people, as the studies have shown, I have found to have concomitant psychopathology. I'm not sure

whether it's the result of their chronic pain or perhaps a partial cause of their chronic pain. But I don't feel that opiates in this situation would be effective. And listening to the data and the studies, I think, in my mind, what it all boils down to is, how many people are we going to help with the release of this product, and how many people are we going to hurt with this product?

I've heard numbers of approximately 13 to 18 million people would be potential candidates to receive this agent. In my mind, that's very scary to release this amount of very, very potent opiate into the American population. I'm sure that there are some people, we've heard some today, who would benefit from this. But I think that this number in the population would be very, very, very small. I don't have specific numbers. It's just what I've observed, having started my first residency in 1976. I won't tell you how old I am, but I've seen a lot of these

types of patients over the years. And the number that would truly benefit from this very potent rapid-acting opiate would be very small, whereas we really have to consider do we want to flood the United States with this amount of product that is as potent as it is.

ACTING CHAIR SORIANO: Dr. Kosten?

DR. KOSTEN: Again, as another clinician who's a couple of years shy of your years of experience but not many, unfortunately, I see a very special group of patients. I'm an addiction specialist. I see the chronic pain patients who come to me because the primary care doctors or whatever have given up on them. The number of patients who have breakthrough pain is vanishingly small in that group. The number of patients, on the other hand, that have, in fact, under-treated opiates, that is they, in fact, are getting pain because the first thing that goes with opiates is how long it lasts, and so they're getting a medication twice a day that

they need to be on four times a day. They have legitimate pain, and they're being called substance abusers by their doctor who's very tired of them.

I think that the education of physicians around how you treat pain is so far behind, meaning lagging, the group of patients that we're hearing described here, which, in my experience, have been very, very small. I would agree that the patients who are going to get this by GPs and stuff just seems to me is going to be, yes, in the millions, and it's not in the millions of patients that have this kind of breakthrough pain outside of the cancer field. So I completely concur that, if you're talking about frequency, this is an infrequent problem. And if this needs to be treated by off-label use in those infrequent cases, you don't get arrested for off-label use.

ACTING CHAIR SORIANO: I have an observation that, not being a pain specialist

myself, but an observation on the studies that were presented today, particularly the efficacy studies. Many of these efficacy studies have compared Fentora with either placebo, I think hydrocodone, and the lollipop solution, Actiq. However, I know for a fact that there are other drugs that are being used for breakthrough pain, so it's my sense that not enough efficacy studies have been done comparing this new preparation, this Fentora, to other modalities of pain treatment. Am I correct in assuming this? Dr. Anand?

DR. ANAND: I just want to sort of follow up on my comments earlier. The patient population that I'm most familiar with, and maybe my colleagues have seen some of those, are the geriatric patient population who will have acute breakthrough pain simply, you know, transferring from a wheelchair into a bed, and that pain lasts for an hour or so and then they get comfortable. And I've frequently been called to address, because there are

concerns amongst the geriatric specialists who are treating them, that these patients are addicted, that they're doing this in order to, you know, get a high. And that's not the case. You can examine these patients, and they're clearly in pain. Some of them have some degree of dementia, which makes it harder for the clinician to diagnose their breakthrough pain, simply because most adult physicians are accustomed to getting self-report, whereas dealing with the patient population I normally deal with, I look for other signs that are not dependent on self-report. So I do think there is a significant population out there that does have severe breakthrough pain, even when their baseline pain has been taken care of.

ACTING CHAIR SORIANO: The issue is where it's warranted to have Fentora to treat this type of pain.

DR. ANAND: And this is, Fentora is not this silver bullet. There are, you

know, several other approaches. But there are subpopulations of these patient groups that will require acute management of their breakthrough pain.

ACTING CHAIR SORIANO: I'm going to solicit comments from each member of the panel. We'll start with Dr. McLeskey at the far end.

DR. MCLESKEY: Was there a question?

ACTING CHAIR SORIANO: Just addressing this question.

DR. MCLESKEY: No, no comment. Thank you.

ACTING CHAIR SORIANO: Dr. Wolfe?

DR. WOLFE: I was persuaded by both the editorial by John Markman and his presentation this morning relevant to this first question. He said in the editorial, empirical support for breakthrough pain and chronic non-cancer pain has serious limitations, and he pointed out this morning

in some of the slides that there are other alternatives, both pharmacologic and behavioral/non-pharmacologic. And when you look at the reduction in BTP intensity for two hours in the presentation of the company this morning, you see that there's a very powerful placebo effect, not surprisingly. We know that that happens with pain. But somewhere between a placebo, which is nothing, and a whole host of other kinds of things, which I don't believe have been adequately studied in randomized trials, are a variety of things that are likely to be much less risky, subject to abuse than this drug.

So I think that the overall statement that we lack empirical support for this entity, we have it, I think, for cancer pain, but when you see 80-whatever percent of the prescriptions for this going for non-cancer pain, off-label, you see a massive amount of prescribing which would be increased several, if not tenfold, if it actually got

approved for this. So I think that we just don't know is the answer to that first question. Usually require treatment with potent opioids, I would say probably doesn't usually require treatment, and there are a number of other alternatives that have not been subject to randomized control trials.

ACTING CHAIR SORIANO: Ms. Aronson?

MS. ARONSON: I see that Dr. Wolfe and I both pulled out this editorial, which I found very helpful in the information about the definition, the lack of real specifics about breakthrough pain. As well, I found compelling the presentation of Dr. Love as far as the potential for abuse and the DAWN emergency department visits, that it's more dangerous than other opioids. So I just feel incredible caution about just the broad definition of non-cancer patients.

ACTING CHAIR SORIANO: Ms. Krivacic?

MS. KRIVACIC: Having been a cancer patient myself 20 years ago and part of a large support group, I understand the breakthrough cancer pain. And having recently gone through some rehab for an ACL tear with, sort of, the pain that you experience from nerve damage, sort of the neuropathic pain, it's a very different pain. I could basically rip out the tumors myself if I had the chance, if I didn't have the drugs. That's how bad the pain was with tumors. With neuropathic pain, it's a burning, it's an irritation. You know, maybe part of my issue is I'm pretty pain-tolerant as a person overall, but I do know just from my support group, friends that I know, people that I know that have gone through other rehab-type of therapy, the breakthrough pain is very different. It's short. It's not this horrible pain that you feel with cancer breakthrough pain, at least in, you know, the limited experience I have with various people.

I do think when you think about the elderly in the nursing home situation, that's a whole other issue that even in these clinical trials they talked about the elderly on so many concomitant meds. And if you were to give somebody who's non-opioid-tolerant this drug for breakthrough pain it could be very lethal within 15 minutes. So we don't really have a good understanding, either, of how many people out there in the U.S. are non-opioid tolerant, and that could be pretty fatal. I wish we had the proteomics component of that to determine that with this trial. That would be great. Then we could selectively find the right patients. But, unfortunately, we're not there yet. Thank you.

ACTING CHAIR SORIANO: Dr. Vocci?

DR. VOCCI: Leaving aside the issue of the definition of breakthrough pain in non-malignant populations, I don't think we've been given data that would really

address this question. The studies that were done by the sponsor really determine whether or not the drug produces a differential signal relative to placebo. They did not address the issue of the relative merit of using fentanyl versus lesser opioids or non-opioids. I think you'd have to have a different trial design to get at that. The kind of trial design I would be thinking of would be an adaptive trial design where you actually had a population with chronic pain, non-malignant chronic pain, that had breakthrough, and then you would start them out on non-steroidal anti-inflammatories. And whatever percentage were helped by that, you'd keep them on that, and then you'd keep moving up the WHO ladder to the point where your last drug was fentanyl and you'd see what percent of the population actually you could treat without having to resort to fentanyl. If you got 50 percent that you would treat without fentanyl, then you would know that maybe one patient out of

two would still require one of these more potent opioids. So I don't think you've actually got the data to answer this question.

ACTING CHAIR SORIANO: Dr. Nussmeier?

DR. NUSSMEIER: Well, it is likely that there are some patients with severe non-cancer pain syndromes who could be enrolled in some sort of compassionate use program with some very strict controls. I'm not a chronic pain specialist, so I can't, although I'm an anesthesiologist, but I couldn't really define that population. But neither of the vast majority of family practitioners or internists are chronic pain specialists in any sense of the word, so it's very scary to think that up to 30,000 physicians, what one of the sponsors called a core group of physicians, 30,000 isn't exactly a core group, would be able to prescribe the most potent, fastest-acting narcotic to up to 31 million chronic pain patients, potentially for life, and we have no

data or guarantees regarding eventual development of tolerance in the patients who do receive these prescriptions. So I think it's also very likely that prescriptions would be forever increasing dosages, and that whole scenario, going forward five or ten years, is very, very scary.

I know we'll get to it in a later set of questions, but I think some very tight controls and risk mitigation rules will be necessary with regards to whatever is decided today.

ACTING CHAIR SORIANO: Dr. Nelson?

DR. NELSON: I'm not sure we were really given the data either to answer this question, but I'll give you just my clinical perspective. I'm an emergency physician. I practice at a university hospital in New York City and at a public hospital in New York City. My general sense on breakthrough pain patients is that we don't really see them in emergency rooms, at least I don't see them in

emergency rooms, which makes me think about, you know, several possibilities. One of them is that they're so well treated that they don't need to come to the emergency department, and I tend to doubt that's probably true; or that perhaps they're afraid to come to the emergency department because they think it's going to be too much of a hassle; or perhaps the pain goes away in short enough order that they don't need to come into the hospital. I'm not specifically sure why we don't see them. We tend to be, kind of, the last resort for so many other types of patients, it's a little bit, kind of, surprising that we don't see them.

That doesn't mean we don't see chronic pain patients because certainly they make up a substantial portion of our patients, but the reason they come in is typically for perhaps the pseudo-addiction type of problems that Dr. Kosten referred to or, you know, for more typical exacerbation of their chronic

pain syndrome, as opposed to a breakthrough pain syndrome, or, you know, unfortunately, we also see them when they overdose or somebody else overdoses and all of the dark side of medication use that we've discussed today.

But my answer to the question, which is obviously long-winded already, is that I am not convinced, based on my medical toxicology and clinical pharmacology background, that this drug is really going to be the right answer, given the clinical pharmacology of the drug. I just am not convinced that a three or four-minute peak pain syndrome needs to be treated with a drug that doesn't peak for 30 minutes. It might start to work a little earlier.

If we can give them something intravenously at the moment the pain occurs, that would be quite a different issue. Obviously, I'm not saying we should be doing that. But it doesn't totally make sense clinically and pharmacologically that this

would be the right answer.

ACTING CHAIR SORIANO: Dr. Kosten?

DR. KOSTEN: Well, I think I already got my chance, but I agree with Frank Vocci that I think that would be a very nice design that might give you useful information.

ACTING CHAIR SORIANO: Dr. Anand?

DR. ANAND: I'll keep my comments short since I've opined on this issue before. I think there is data out there in terms of doing a medical effectiveness kind of study where chronic non-malignant pain has been treated with this preparation. And for all the patients who have been treated, it may be worthwhile analyzing that data and looking at which populations those patients were drawn from and what are the characteristics that make them eligible for this kind of therapy. So that's certainly something a health services researcher can easily do.

ACTING CHAIR SORIANO: Dr. Bickel?

DR. BICKEL: I concur that we

don't have sufficient information from the sponsor to answer this question. I think the trial suggested by Dr. Vocci makes a lot of sense.

ACTING CHAIR SORIANO: Dr. Prough?

DR. PROUGH: I'm troubled by the fact that, the way the question is worded, it seems to elicit answers that are broader than it seems to me the question ought to be. I think if the question is do breakthrough pain episodes experienced by opioid-tolerant patients with chronic pain that is not related to cancer, but requires around-the-clock opioid treatment, do they experience breakthrough pain episodes, I think that they do and it appears that that population, when they get breakthrough pain, respond to the drug as it was used. I don't think that the population of patients with around-the-clock opioids for chronic non-malignant pain is huge, but I think it's a very tough population of patients to manage, and I think this is

potentially a tool that can provide them with a great deal of benefit.

ACTING CHAIR SORIANO: Dr. Paulozzi?

DR. PAULOZZI: Well, just sticking to the question as worded, I don't think we were shown any data comparing Fentora to other analgesics, and I have no clinical experience relevant to this, so my answer is I don't know.

ACTING CHAIR SORIANO: Dr. Kirsch?

DR. KIRSCH: Nothing really to add beyond what everyone else has already said, but I would like to emphasize a key feature here, which is we don't really have effective risk mitigation programs. It would be awfully nice if what the sponsor has suggested, it would be nice to know whether it's actually going to work before we approve a new indication, assuming that their hypothesis is correct without being tested.

ACTING CHAIR SORIANO: Dr. Day?

DR. DAY: I think this request is premature. I think it's an interesting one. It may turn out to be valid, but, without the appropriate data that's already been discussed, it's difficult. And aside from how to define breakthrough pain, the types of patients and health conditions and so on would be very useful. And it's just very difficult at this time also with the risk mitigation plans looking wonderful but not really put in place. We don't know if they work. So that's my comment.

ACTING CHAIR SORIANO: Dr. Lesar?

DR. LESAR: My only comment is that there's data lacking to give us information related to the incremental benefit of this drug over other drugs, and I think that's a critical point in trying to balance efficacy versus safety considerations.

ACTING CHAIR SORIANO: Dr. Zuppa?

DR. ZUPPA: Trying to stick to the question, I believe that patients with chronic

pain that's non-cancer-related do have breakthrough pain episodes. How to best treat these episodes has not been well defined or presented here today, and I agree with Dr. Vocci that those studies are indicated. While we're trying to figure that out, there are alternatives that are immediate-release formulations such as oxy-IR, which peaks in 45 minutes, that can be used while we try to figure these questions out.

ACTING CHAIR SORIANO: Dr. Cortinovis?

DR. CORTINOVIS: Nothing to add.

ACTING CHAIR SORIANO: Dr. Gardner?

DR. GARDNER: I don't know.

ACTING CHAIR SORIANO: Dr. Maxwell?

DR. MAXWELL: I don't know.

ACTING CHAIR SORIANO: Mr. Yesenko?

MR. YESENKO: I know. The reason

I know is, like Ms. Krivacic, I'm a current chronic pain sufferer. And in answer to the question, I will try to stick to the question. I think I agree that -- one of the panel members said there are good days. Unfortunately, the good days come between bad months and bad years for me. I have cluster headaches. And I think any treatment that makes those bad months into good days I'm all for. I'm going to have a neurostimulator implant done at Hopkins mid-May, and this is after treatment of acupuncture, treatment of opiates, treatment of oxygen.

The cluster headaches I have are also known as suicide headaches. The headaches are called suicide headaches because, oftentimes, patients who have cluster headaches have attempted suicide. And the pain is similar to that of an ice pick slowly being pushed into my temple. There's no way to manage chronic pain such as the headaches I have with the non-opioid analgesic. In

fact, it's an insult to suggest I could treat my cluster headaches with an aspirin or a Tylenol.

I don't think we have, to answer the question, I don't think we have the data, though, to answer the question that chronic pain can be managed with less potent opioids or non-opioid analgesics at this time.

ACTING CHAIR SORIANO: Just to review the comments brought up by the panel, breakthrough pain is real. It's recognized and it's well defined. There's an issue how large this population is. Many members of the panel have suggested it's a small population, small enough not to warrant the release of a drug that has such high abuse potential. However, they deserve to have this type of therapy available to them.

The other point that seems to resonate through the panel is that the efficacy studies that have been shown so far really have compared only placebo to Fentora.

There's a whole list of other alternative drugs, as well as therapies, that comprise a spectrum, and none of these individual therapies have been tested against Fentora and perhaps more studies will be needed to validate whether or not Fentora is a better drug or not.

Members of FDA, is this sufficient for you? Okay. We'll move along to the second question. That is, can Fentora be prescribed to a broad non-cancer opioid-tolerant patient population cared for by a variety of specialists and primary care physicians without a significant increase in morbidity or mortality related to mis-prescribing or misuse of the product? Does anyone need a clarification of this question? Any discussion?

DR. KOSTEN: It seems like we answered it already.

ACTING CHAIR SORIANO: Just for the record, can you repeat the answer to this?

No? All right. Any other discussion points from the panel?

DR. BICKEL: I would just like to say that I was impressed with their risk management plan. It seemed like it was very thought through and very comprehensive, and it was a breath of fresh air. And I would like to see, you know, when there's an occasion that there's an appropriate medication, I would like to see that plan rolled out and tested for the extent that it does manage risk.

ACTING CHAIR SORIANO: Dr. Kirsch?

DR. KIRSCH: I agree. I was also very impressed. I would just like to see the hypothesis tested to see whether it does work.

ACTING CHAIR SORIANO: Any other discussion points? Dr. Gardner?

DR. GARDNER: I agree with that completely, having watched a lot of risk management plans get rolled out and some of them not work. And I wonder if the question

that was raised earlier today with the FDA is whether they would consider the existing Fentora for a similar risk management plan since apparently the one that's going on isn't working as they would like to have it do, and perhaps the additional elements of this one that were proposed today could be tested on the existing Fentora, which I assume would happen if the formulation were approved to go forward.

ACTING CHAIR SORIANO: Dr. Zuppa?

DR. ZUPPA: I don't think we've talked enough about it, but the idea of it being used on a compassionate-use basis for non-malignant pain is something that warrants further discussion.

DR. RAPPAPORT: Can I just make a clarification that there's no restrictions to physicians prescribing this at this time for any patient that they choose to prescribe it for.

ACTING CHAIR SORIANO: Dr.

Gardner?

DR. GARDNER: So that was the question: could there be under the recent legislation?

DR. ROSEBRAUGH: The legislation that we have does give us new authorities to do things. I would just say that you may think that when we get new legislation we know exactly what it means. We really don't until we get a trial case to use it against. And so we certainly appreciate your comments and it is something we will take under advisement. However, to follow up on what Dr. Rappaport has said, what I'm hearing from the committee is, is that we do think there are some patients out there that do not have cancer that are opioid-tolerant that would benefit from this medication, and that's the key about any physician can use it for anything they want. We wouldn't want to hamper those patients from getting it also by having too restrictive of a risk management plan, so we

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always walk a tight rope when we implement those, and we have to be very judicious in how we do it.

ACTING CHAIR SORIANO: Mr. Yesenko?

MR. YESENKO: I just want to clarify the 6,000, almost 6,000 physicians currently prescribing Fentora, is that from a training program that they participated in with the sponsor? I think the FDA mentioned that any physician can prescribe Fentora. I just want to clarify that.

ACTING CHAIR SORIANO: This is a question to the committee, and Dr. Messina will answer it.

DR. MESSINA: Yes. John Messina from Cephalon. The answer is that those are physicians who have prescribed Fentora. They have not been through any special training program. They have just prescribed it since it's been out on the market.

ACTING CHAIR SORIANO: I will not

go through the panel for their individual answers unless someone else wants to bring something up on question two. Dr. Paulozzi?

DR. PAULOZZI: I do think that you would have significant increase in morbidity and mortality, but I have an additional concern in that I'm not sure that we would detect that increase in a timely way in this population. Fentanyl is a fairly stealthy drug, and an opioid-tolerant patient who comes into an emergency department looking like they have an opioid overdose may have some alcohol on-board and a benzodiazepine and the pill has dissolved; and fentanyl is not picked up on routine screening for opiates in emergency departments. It takes a special test. So increase in emergency department visits or even deaths may not be detected in a timely way due to Fentora, given the drugs that this patient population is likely to have on-board in the first place.

Interestingly, in Cook County,

when fentanyl was contaminating heroin and cocaine, they had a substantial increase in their emergency department visits, but they weren't aware that it was due to fentanyl for at least a month or so. The medical examiner wasn't specifically looking for fentanyl in the population that came in with heroin overdoses, and they didn't realize that it was probably the fentanyl that was killing the people.

ACTING CHAIR SORIANO: Any other discussion points from the panel? From my assessment of what the panel's responses to this question, question number two, the direct answer is no. However, they feel that compassionate care should be applied to the patients with real breakthrough pain and be able to use under the laws that are associated with that and best practices.

There are other comments, as well, applauding the sponsor for their risk management plan. However, this hasn't been

proven yet, and perhaps one way to do this is to apply this risk management plan to the existing indication for Fentora, that is the indication for Fentora for cancer pain, and apply this risk management plan to those patients.

Does this satisfy the FDA? Okay. The next question that we'll entertain, it's question number three, and it reads, "Fentora has attributes that make it particularly attractive to abusers and attributes that make it particularly dangerous for those who abuse it. In light of the increasing abuse of prescription opioids and the specific attributes of this particular product, would a widely increased availability of Fentora likely lead to widespread abuse and the public health consequences of that abuse?"

Anyone want clarification for this question? It's fairly straightforward. Anyone want to bring up any discussion points to this? Dr. Vocci?

DR. VOCCI: I'd like to hear from Dr. Comer, who's done some abuse liability studies, whether or not she thinks that fentanyl has any kind of differential abuse liability relative to other Schedule II opiates. And I'd like to hear from Dr. Heit, who's a clinician, I'd like to hear his viewpoint on that.

DR. COMER: My name is Sandy Comer. I'm at Columbia University, and I do abuse liability testing in humans. So we conducted a NIDA-funded trial to examine the relative abuse liability of several prescription opioids, including fentanyl, oxycodone, morphine, buprenorphine, and we compared the abuse liability with heroin. So we measured both drug-taking behavior and subjective responses, and we found that fentanyl, oxycodone, morphine, and heroin showed no difference in abuse liability.

DR. HEIT: Howard Heit, Georgetown University. The disease of addiction is based

on a triangle: a genetic predisposition, a social environment disposition, and a neurochemical disposition. And it's a combination of these three that produce addiction with physical dependence. In the addiction literature, the rate of rise of dopamine or the faster onset and faster fall of dopamine is associated with likeability of a particular drug, but the key in the addiction literature is in genetically-susceptible individuals. So the point being is here, is the likeability or this area of this particular medication in genetically-disposed individuals can raise a risk, but those are the patients where the risk management program that we would not prescribe this particular medication to.

There's evidence in the animal literature but not the human literature that pain attenuates the likeability of medicines that go through the ward and withdraw pathway called the mesolimbic dopamine system. And so

if a patient has pain, the likeability of a drug, even with a genetic predisposition, is much less. So the key in prescribing this particular medicine, we talk about broad-base use, this breakthrough medication is only going to be used for a select population that is much, much, much narrower, much, much less numerically, in numbers, than that was discussed with the committee. This is a medicine that will only be used, let's say, as a clinician, in a very select population, individually evaluated, and prescribed this medicine to help improve their quality of life given the reality of their clinical condition.

ACTING CHAIR SORIANO: Dr. Vocci, I'd like for you to make your assessment of these statements.

DR. VOCCI: Well, it seems like, from the available data in the clinical pharmacological study, that fentanyl does not have any kind of differential abuse liability relative to oxycodone and heroin. So, you

know, I would suggest that it should be considered much the same as those. It may have a slightly more rapid onset, but, aside from that, you know, in terms of its abuse liability, the abusers essentially rated it the same as oxycodone and the same as heroin. So, you know, it doesn't seem to have any kind of a differential abuse liability, so I don't think there's any additional risk beyond that of the other opioids.

ACTING CHAIR SORIANO: How about your response to the second part of this: lead to widespread abuse and public health consequences of that abuse?

DR. VOCCI: I think there's some data that suggests that the availability of an opiate and the amount that's available has a direct relationship to the abuse. It's not a one-to-one correspondence, but there's a certain percentage of individuals, and I think Dr. Heit is correct, that are probably genetically predisposed who will abuse

opioids. And if they wouldn't abuse fentanyl, they might abuse something else.

What I would be more concerned about with this drug is the diversion of the medication rather than the patients themselves abusing it. I think if people were actually using it for breakthrough pain, I don't know that there would be all that much abuse by the patients. But, again, the concern here is that you have a potent opioid that's now in your medicine cabinet and the diversion of this could be uniformly fatal in someone who is non-opioid-tolerant.

ACTING CHAIR SORIANO: Thank you. Dr. Wolfe?

DR. WOLFE: With the limitations that we have heard repeatedly over the last couple of days, it's still worth looking at the data that we were presented this morning by Dr. Shibuya on emergency department visits. And for fentanyl, it was about twice as frequently, adjusted per number of retail

prescriptions, as it was for oxycodone; and about six times more frequent than hydrocodone and combination. So I think that there is, that's all fentanyl, to be sure, but I think there is some concern out there. And these are non-medical use, which is exactly what you're talking about.

I mean, the more stuff that's in there -- I remember the pictures of people, older people who would go in, get a prescription filled for whatever opioid, and they were so poor they would sell it to someone. They themselves were not the usual kind of drug dealers, but I think it's part of this the more that's out there. And there is no question that if this were ever approved for non-cancer breakthrough pain the amount out there would be enormous. I mean, the fact that so much has gotten out there already even with it not approved is extremely worrisome, and we've seen what has happened even with the 20,000 patients or 23,000 patients, depending

on which estimate you use, the adverse events that have already been reported.

ACTING CHAIR SORIANO: Any other discussion points? Yes, Dr. Cortinovis?

DR. CORTINOVIS: I am very impressed with the sponsor's risk management paradigm. It really seems to be a very novel program. But as one of the members of the public said or somebody said today, there's often a disconnect between either clinical trials or risk management programs and how the actual activity plays out. So we wouldn't know how it would play out if this were approved and the product dispensed in the number of people for what's predicted.

One of the items of the clinical trials that somewhat bothers me is that the patients that were selected were specifically excluded if they had any tendency to substance abuse. And even so, there was over a four-percent number of people who were noted to abuse this drug. And all of the people likely

to abuse it had already been cherry-picked away, and you still see approaching 1 in 20 of these people abused it. That's a significant number when you say five percent of 13 to 18 million people in the American population who may be getting this stuff, and that's disconcerting to me.

ACTING CHAIR SORIANO: Dr. Paulozzi?

DR. PAULOZZI: I just want to make one additional epidemiologic point about this particular drug. If you look at the distribution of deaths involving prescription opioids or prescription drugs in general, it's roughly normal with the peak rates in people 40 to 49 years of age. The rates drop off dramatically after that and drop off way down after 65. So it looks like a normal distribution. If you look at emergency department visits for drug overdoses, the rates are also highest in the middle age group. If you look at abuse rates, self-

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reported, they're higher in the middle age group and people 18 to 24. If you look at prescribing, it's probably equal in the middle age group for opioids and for older people.

My point is that the cancer population is probably somewhat older. Somewhere, I would guess, the population using drugs for breakthrough pain for cancer is somewhere north of 60 years of age, on average. But this group we're talking about with chronic pain from other causes is much likely to be younger, much likely to have many more people who are already abusing opioids, and I think that that fact will contribute to a greater likelihood of misuse.

ACTING CHAIR SORIANO: Dr. Nelson?

DR. NELSON: We saw yesterday some slides that showed that the majority of the OxyContin that was available on the street or at least available for abuse was, in some way, derived from doctors' offices and prescriptions. And although I, too, think

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that the risk management plan that has been proposed will have some issues with it, overall it seems like a reasonable, you know, initial start. It doesn't really change the fact that the patients, that some people who will still be able to get this drug for not necessarily personal medical use, and that might still keep that drug available on the street.

ACTING CHAIR SORIANO: Any other comments? Dr. Kirsch?

DR. KIRSCH: I have a question for the researcher from Columbia. I'm sorry, I forgot your name. I, like many people at the table are anesthesiologists, and most anesthesiologists realize that fentanyl is a very high-risk drug in our environment. I've been practicing for 25 years now and have had a number of cases of providers diverting opioids, and they always seem to divert fentanyl, and I've never seen someone divert one of the other narcotics. So how does that

relate to your study? I was just now looking on the Internet to see if I could find a quick publication to support my contention. But it is commonly held that within anesthesiology, fentanyl is the preferred drug, and I'm wondering how that relates to your observation.

DR. COMER: I'm familiar with the thinking that anesthesiologists prefer fentanyl. We conducted our study in heroin abusers who were maintained on morphine throughout the trial. So they were maintained on 120 milligrams per day of morphine, and they lived in a hospital setting, and all the doses were given under double-blind conditions, and so they didn't know exactly what they were getting. IV, sorry. They were all given intravenously. And so, you know, these are a very experienced opioid-using population, and I mean I kind of consider them the connoisseurs of opioids, and they couldn't tell the difference between fentanyl and the

other agonists, except for buprenorphine. That was different.

DR. HERTZ: Can I ask a question, just to follow up on that? Given that, in your study, individuals were dosed parenterally so the pharmacokinetic profile would have been fairly similar for the different opioids, do you think that there would be any impact of the different pharmacokinetic profiles from oral versus transmucosal ingestion in terms of likeability of a product?

DR. COMER: The data seem to suggest, in general, that the rate of drug onset is an important factor in the abuse liability of a drug, and that's been established pretty clearly, I think, for stimulants and for benzodiazepines. For the opioids, the story is a little bit less clear. Dr. Bickel actually performed one of the best studies on this particular issue, and there was another study that was done at Hopkins.

Mary Abru was the lead author in that paper, and the Abru article actually showed that they gave an intravenous dose of hydromorphone to drug abusers, and they infused it over rates of 2, 15, and 60 seconds and found no difference in the abuse liability of hydromorphone, whereas cocaine given under these infusion durations did show a difference as a function of route of administration.

Dr. Bickel's study, he looked at infusions of two different doses of morphine compared to placebo. The infusion durations that he used were 2, 15, and 60 minutes, and he showed that, actually, there is a difference between 2 and 15 and 60. But I thought it was interesting, actually, in your study that there was really no difference between 2 and 15-minute infusions. So it's somewhat consistent, but it's not entirely clear that for opioids there's a rate of onset effect.

DR. SCHNOLL: Sid Schnoll from

Pinney Associates and Medical College of Virginia. I'd like to answer Dr. Kirsch's question because I did a major study several years ago looking at abuse of various compounds by impaired health professionals. The abuse of fentanyl is almost exclusively confined to anesthesiologists. You don't find it in any other group of impaired health professionals except, you know, nurse anesthesiologists may be involved also. If you look at the drugs that are primarily abused by impaired health professionals, hydrocodone among the opioids is number one and, of course, alcohol far exceeds all the other drugs.

ACTING CHAIR SORIANO: The comment I have with that is it's a matter of access, as well. How would you respond to the availability of fentanyl to anesthesiologists?

DR. SCHNOLL: Access does play a role because the anesthesiologists do have access to fentanyl in the OR, and so that's

part of the problem.

ACTING CHAIR SORIANO: Dr. Kirsch?

DR. KIRSCH: And so my point is that with this particular drug, Fentora, everyone would have access to this drug, which apparently has a high addiction problem.

DR. SCHNOLL: I'd like to sort of go back over the risk management plan, because I think that not everybody will have access. I think, as was described, one, only about 6,000 physicians in the first year will be detailed, and those are the physicians who are already prescribing the drug.

But, in addition, any new physician who prescribes the drug will be required to have that access number to get into the system. And not every physician is going to have a card with the number that will allow them to get into the system to prescribe. So there is a limitation on that, and it's not just going to be any physician who wants to being able to prescribe the drug.

And that's very critical here. And so there is limited access in terms of the number of physicians who will be able to provide the drug, and only those physicians will have the cards, the access cards, to give to patients who can then get into the system. So I think that point seems to be overlooked in the discussion, and I just wanted to emphasize that.

ACTING CHAIR SORIANO: Mr. Yesenko?

MR. YESENKO: So the access cards are not, the access numbers and cards are not in place currently; correct? That's frightening. Thanks.

DR. SCHMIDER: This is a system that we're currently developing. It is based on our two pilot programs, NotifyRx and the safety activation card, but they're not in place currently.

ACTING CHAIR SORIANO: Dr. Maxwell?

DR. MAXWELL: Don't sit down. I have a question. Given the large number of physicians prescribing off label, and I think you've heard our concerns both about the large numbers and also wanting to make sure that the drug is available for patients who need it, it would seem to me -- and our concern about not perhaps opening the gate and then finding out later on that the risk management plan doesn't work; is there any reason the company cannot, under the current way in which it's being handled, institute that risk management plan now so that you can come back to us in the future and say we put it in and were able to prevent additional GPs prescribing to prevent the diversion and things that we've talked about so that you would have tested it. Now it's a hypothetical but very, very attractive plan. You could bring us the data?

DR. SCHMIDER: We have designed the system in conjunction with the expanded indication for which we seek approval. Any

other consideration would be subject to negotiation with the FDA.

ACTING CHAIR SORIANO: Dr. Nelson?

DR. NELSON: Yes, can I ask you one more question, as well? Oh, go ahead.

DR. HEIT: Okay. As a clinician, as long as I have a Schedule II registration with the DEA, I could prescribe Fentora to any patient that I think is appropriate, which I do after proper evaluation. Now, let's say I'm not knowledgeable about how to prescribe it. Where am I going to get my education for this? I'm either going to prescribe it with good consequences or adverse consequences. But to me, as a private clinician, you're cutting off an area of education for me by not having this approved by the FDA where they could come into my office and educate me of the proper use of this if I am not doing it in the proper manner, consistent with state and federal regulations and in the best interests of my patient and the community.

So if you want the pharmaceutical company to come in, which we've all stated, with a good risk management program, they have to be allowed to do that. But they're not allowed to come into my office and give me any education because I don't do palliative care or cancer pain, and they'd be coming in an repping it for off-label use, which would be a violation.

ACTING CHAIR SORIANO: You've made your point. Thank you. Dr. Nelson?

DR. NELSON: Well, my question is about the risk management plan, and I don't know if you want to discuss that now or if you want to hold it for the next question. But Dr. Schnoll just made a comment, and it's certainly possible I misunderstood. Dr. Schmider, can I ask you a question? The numbers that we heard before, the 6,000, 6,000, 30,000, that's the number of people that are going to be detailed about the drug, not the number of people that are going to be

permitted to get a number; is that correct? Can anybody get a number or only the people that have been detailed adequately by the company?

DR. SCHMIDER: Well, there are two issues. Primarily, yes, only physicians that have received a number can access the system, so you have to have a number there. That's one of the scenarios that we're currently exploring. It's a very plausible scenario.

DR. NELSON: That I agree with. But who gets a number? Only the people that are detailed by the company, or can anybody apply to get that number?

DR. SCHMIDER: In theory, anybody can apply to get the number. We want only skilled and educated physicians in our database that prescribe Fentora. So anybody applying to get a number will then have to learn about Fentora, will be visited by our field force, will receive educational materials. We have the situation also that

patients will be referred from the pain specialist to their primary care doctor. The primary care doctor will have to continue prescribing the medication. That is a situation that we want to accommodate.

Now, a physician can apply for that in that situation, may be enrolled in the system. However, if the physician may choose eventually to enroll additional patients, he will not be able to do so if we don't provide the physician with a patient kit, which contains the safety activation card that he needs to give to the patients so the patient can enroll in addition to that.

So even if we enrolled a physician, let's say a primary care physician, who has received a patient from a pain specialist for further care, decides to enroll other patients will not be able to do so unless we provide this physician with the patient kit that contains the safety activation card that can be given to the

patient.

DR. NELSON: And that doctor number 6,001 won't be able to get that kit until the end of the first 12-month period is what you're saying? If this new physician is not one of your original 6,000?

DR. SCHMIDER: This is an approximate number. Our experience, from what so far we've seen, is that there is not such a tremendous uptake of physicians. Eighty percent of the Fentora prescriptions are being done by approximately 1,100 physicians out of these approximate 6,000 physicians. So Fentora has been now on the market for more than 15 months, and it's not our experience that this is what is occurring.

Now, should we observe that there is a tremendous request for that, a tremendous, well, let's say a request from physicians to be enrolled, of course we would assess the situation. We'll discuss it with the FDA and see what we need to do to manage

this situation appropriately. But we are able to maintain or keep, for lack of a better word, a lid on it until we have a better solution.

ACTING CHAIR SORIANO: Okay. Just a quick summary for the panel's answer to question number three, we heard from a researcher from Columbia saying that fentanyl is equivalent to other drugs of abuse, other narcotics of abuse. However, the issue about availability will increase should Fentora be approved for this indication and may also increase the abuse potential, and that's certainly been shown in the anesthesiology world. Diversion is still an issue given the increased availability of this drug, and certainly the panel encourages that the sponsor apply this risk management plan that they've suggested for this new application to their current application of Fentora.

Dr. Rappaport, do you need more confirmation from members of the committee?

Okay. We'll move on to question number four.

If there is substantial risk for increased abuse of this product due to greater availability, can this risk be effectively managed? And if so, what specific risk management tools would be necessary to mitigate this risk while still ensuring reasonable access for patients who meet the conditions of labeling? Any discussion from the panel?

Certainly, the suggestion that they apply this risk management plan they have for this application be applied through the current labeling for Fentora is one answer or response to this question. Dr. Gardner?

DR. GARDNER: The reason I asked the FDA earlier about the experience with existing risk management plans was because access sometimes may be significantly reduced when these plans are put into effect. And so if anything is to be done by the sponsor, there's a huge list of items in your risk

management plan. And as we look at it, we think this is wonderful detail and we really appreciate all of it. But my concern for you is that, for all of us, is that if we are to go ahead and a plan is to be implemented that the plan will fall completely if it isn't absolutely well thought through and ready to go from day one.

And, specifically, a place where there's always a disconnect or often a disconnect is in the pharmacy. And I see that there's a lot of dependence on pharmacy and on hard stops and things like that, which can just stop a pharmacy dead. Hard stops are not easy to deal with, as you know. I'm hoping that you have good retail pharmacist representation on your RiskMAP advisory committee. And if you don't, I'm asking you now to get them, get them now, and get them started. And the second thing is to be sure that all the pieces of your registry work together and that they are kept up-to-date.

And if you hire a vendor to help you do this, get them started and get it to work because it can't work if the pharmacist is on the phone or on the computer for 45 minutes to find out that really they don't have that patient registered yet.

I know you know these points, but we have been down this road before with other risk management plans, and yours has a lot of really good pieces. And if you're going to implement it either now or later, please have them ready to go and involve the pharmacists at the outset.

The other thing I think that was brought up today is that piece of yours you mentioned about buyback. And, again, today, as yesterday, we've talked about having a lot of unused extraneous no longer necessary medication in medicine cabinets, and I would like to see you proactively, I don't know what your current buyback plan is, you didn't go into detail today, but I would like to see

you, in managing risk, get very proactive about getting extraneous Fentora out of medicine cabinets and take responsibility for that, not just try to educate through some other group. So those are my thoughts about your risk management plan.

ACTING CHAIR SORIANO: Dr. Day?

DR. DAY: I'd like to echo what Dr. Gardner just said with one minor correction. I think it should be ready from day zero, not day one. But it's very interesting, I think we all, especially those of us with a drug safety and risk management background, are very positively impressed with your risk mitigation plan. Would this just be applied to the non-cancer patients, or would this be for everyone? Would this affect the people who are already receiving it for cancer-related breakthrough pain?

DR. SCHMIDER: That would be for all patients on Fentora.

DR. DAY: All right. And then the

final question is the NotifyRx I'm still very taken with. Would this be a proprietary system that only would be available for this drug through your company, or is this something that's been developed elsewhere that might be shareable across the industry?

DR. SCHMIDER: This is something that we have contracted with a vendor, so it might be available to others, as well.

DR. DAY: You said you've contracted. Has it been written and tested in any way? You said it was going to get started in pharmacies --

DR. SCHMIDER: Yes, there are precedents already.

DR. DAY: All right. Thank you.

ACTING CHAIR SORIANO: Dr. Zuppa?

DR. ZUPPA: I had brought this up before, but I just want to bring it up again in the context of this question. Just for the COVERS program again, addressing the outpatient setting. There are obvious holes

with inpatient settings and other places, just to have those issues addressed.

ACTING CHAIR SORIANO: Dr. Anand?

DR. ANAND: This is sort of to my fellow committee members. It seems we're sort of being asked to make a change in the indications for this drug. And in order for the risk management to be put into place, otherwise it would be illegal, the labeling change needs to occur because Dr. Heit's sort of comment just a few minutes ago points out that if the labeling is not changed to its use in non-cancer pain there would be no legal way in which the company could go and talk to these 6,000 doctors who have prescribed Fentora in the past. So is that --

DR. WATKINS: May I interrupt to allow Dr. Rosebraugh to comment on that?

DR. ROSEBRAUGH: I'm not real sure where this misconception has come up that this risk management plan would be illegal for them to apply to the indication they have right

now. We at the Agency would be more than happy to talk to them about it.

DR. ANAND: Because, by its description at least, and I'm hearing this from every committee member who has commented, is a very attractive risk management plan. It would certainly set the standard compared to various other drugs that are being used and that are at similar risk for diversion, misuse, and abuse. So I think what would be really good to hear is a plan to move forward and to have something like this available and to test its efficacy in the field without changing the label, if that's possible.

ACTING CHAIR SORIANO: Dr. Bickel?

DR. BICKEL: I'm glad I'm following up the comments of Dr. Anand and the prior comments because I just want to paint a scenario or lay out a couple of issues and ask the company to answer a question about the risk management plan, which I generally like. So they had this initial indication and they

had a risk management plan and then they find that 80 percent of their prescriptions are for non-indicated use. And they also indicated they're not allowed to talk to those docs to try to stop them from using it in that fashion.

Now we're going to have another plan with another indication, and what I'd like to hear from the company with risk management plan are they prepared through their COVERS program to stop any non-indicated use through that mechanism? So let's say the docs say, "Oh, now that I've tried it for breakthrough non-cancer pain, I'd like to use it just for pain patients in general," and they find that 80 percent of their market has gone there, will they say, well, we need an indication there to lay it out? So will the COVERS program actually lock it in? That is, any non-indicated use would be stopped through that program? That's the question I'd like to ask the sponsors.

DR. ROSEBRAUGH: I'm going to interrupt just for a second, and then I'll let the sponsor speak. It is not illegal for them to alert physicians about inappropriate use of their medication. That's what warning letters are all about when we send those out. That's the first issue.

The second issue is is that the reason why I've been hedging a little bit about this program they have presented is that if you look at, at least my understanding, we have not had a chance to look at this program. This was proposed for the first time at this meeting. But if you were to apply it to their indication now, then it would be difficult, it seems, the way they have proposed it for off-label use to occur. So for those people that had non-cancer breakthrough pain, like some of the folks we heard at the open public session, I would be reticent to not have a mechanism for those folks to be treated with a physician in an appropriate fashion to get their

medication, and I would want to make sure that their risk minimization plan took that into account.

DR. RUSSELL: If I could just clarify for your question, which I think was, gosh, what next I think is what you were really trying to say. I think the goal of the COVERS program is very clearly to ensure that only opioid tolerant patients with chronic persistent pain get this drug. Its goal is to absolutely try and avoid anyone who isn't opioid tolerant getting the drug because the physician, as he engages and registers into the program, attests that he's going to follow the prescribing information. So the real goal is to ensure use in appropriate patients for which this expanded indication would be clearly opioid tolerant patients with chronic pain. With chronic persistent pain, you also have breakthrough pain.

ACTING CHAIR SORIANO: Dr. Wolfe?

DR. WOLFE: The comment we just

heard about one of the main purposes of this COVERS program to try and ensure that only opioid tolerant people get the drug, I mean the data that was presented today said that that percentage currently is getting worse. It was either, I think if I remember it was 28 percent of the people currently getting the drug under the existing approved indication are not opioid tolerant. So I would just slightly refrain question four that reflects some of the things other people have said.

There is a substantial risk for increased abuse of the product with current availability. All these presentations by Dr. Love and others this morning indicate that, despite the relatively small number of patients that have gotten it so far, most of whom are not cancer patients, there is a substantial increased risk. And I would just reiterate that those parts of that risk management program that are not defacto promoting what would be an off-label use,

namely for non-cancer patients, could be put into place and I think should be put into place because if it isn't capable of deterring the current substantial risk of increased abuse that's going on right now that's been documented, measured, and so forth, there's no way that it would ever work for a much expanded group of patients and doctors.

ACTING CHAIR SORIANO: Dr. Cortinovis?

DR. CORTINOVIS: When I heard the presentation of the sponsor's risk management plan, I said, "Now, how in the world did I miss that in the briefing documents that were presented to me?" The comment that I have is it is my understanding that these advisory committee meetings are supposed to be open and fair, and I was very enthusiastic when I heard you presentation on the risk management program. But why wasn't this presented to the FDA staff prior to this meeting so that they may have had an ability to evaluate the

information and perhaps comment on it?

DR. SCHMIDER: During our preparation over the past months, we met with many advisors. We had a number of discussions with our external RiskMAP advisory board and other advisors, as well. It became more and more apparent that with our current tools, with the tools that we're currently using for Fentora, that this is not adequate enough to address the risk of overdose particularly. This was also then very apparent from the FDA briefing book that you've all received. That triggered now going forward and presenting to you this new proposal.

DR. FLOYD: Hi. Eric Floyd, Regulatory Affairs. There's one other component that you need to be aware of. As we've been working very diligently to try to get the two pilot programs up, you all have to realize that there's a time frame that's required for the sponsor to provide a briefing package. And at the time that we provided the

briefing package, we had went forward and proactively initiated the two pilot programs. There are also additional contractual agreements that have to be put in place for us to be able to link those programs. And at the time that the briefing package was due, we did not have those contracts in place so we were not able to share the information of our final program until such time as we had that in place. When we realized that we were able to move forward and initiate this, we did proactively contact the Agency and made them aware of this.

ACTING CHAIR SORIANO: Dr. Gardner?

DR. GARDNER: I have a question about what the alternatives are here. We've heard that the group of chronic non-cancer pain patients that would fit these criteria is probably very small. We've heard that some people who have been in studies are already helped by this. We've heard a lot of things

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today, and people keep throwing out the treatment IND or Subpart H, and I wonder if we could have some understanding of is it an option for the company to initiate their COVERS program on the current indication while simultaneously continuing on and making the product available through treatment IND? That's not something this committee needs to recommend, but I just wonder. There seem to be a lot of confusing alternatives. Is that one?

DR. ROSEBRAUGH: I'm not sure I really understand that question. Their product is available right now. If they wanted to come in and initiate a different risk management plan, we would be happy to talk to them about it. Their product would be available during those discussions. And, you know, we would be more than willing to listen to their proposals and work with them.

DR. GARDNER: So their risk management plan could go beyond the current

indication to any physician that is -- could they register in their risk management plan a physician who was not prescribing for cancer patients under the current situation?

DR. ROSEBRAUGH: Well, it's a little tough to get into all the nuances of what we would do with the risk management plan, but we have a lot of leeway to discuss things with them.

ACTING CHAIR SORIANO: Dr. Zuppa?

DR. ZUPPA: Forgive me if this is clear to everyone else, but I'm just trying to avoid misconceptions. For a physician that is prescribing a drug for non-cancer pain at this moment in time, exactly what interaction can that physician have with the pharmaceutical company in terms of education, in terms of inappropriate dosing? You had said before that it was a misconception that there can be no education process there. Am I not being clear?

DR. ROSEBRAUGH: Well, what I was

trying to clear up was someone had mentioned that it would be illegal for the pharmaceutical company to talk to prescribing physicians about inappropriate use of their medication, and that is not correct.

ACTING CHAIR SORIANO: Any other discussion points from the panel? Dr. Vocci?

DR. VOCCI: In, I believe it was Jeanine's presentation she actually went over the quarterly report data for the risk, what's been sent into FDA on the RiskMAP, and over 80 percent of the patients that are being prescribed this drug are non-cancer patients. And I think this may be driving Cephalon's program to try to get this indicated. You know, if I worked in a pharmaceutical company and I were faced with the same data, you know, you have a conundrum then. You're actually selling a drug for a population that you have not done studies in. Furthermore, they then did three studies, placebo-controlled studies, and I may be wrong about this but I'm trying

to make the sponsor's case that the FDA believes that the three studies actually show efficacy in breakthrough pain. If that's the case, then I think that what else, the other things they're doing here and what the argument should pivot on is can the risk management plan, if the safety and efficacy data are acceptable to FDA, can the risk management plan actually be performed in such a way that it really does minimize the risk of abuse and diversion?

It seems to me that the FDA has given us a preliminary signal that they believe this works in this indication and that the company is doing something that I would say is the responsible thing to do. I think if a company markets a drug and finds out that the primary indication is only treating 20 percent of the patients it's prescribed for and 80 percent are being treated off label, then they should do studies that actually look at that population. And I think that's what's

happened here.

I'm not an expert on risk management plans. I was impressed with the breadth of this plan. You know, we didn't hear a whole lot about the depth of it and, of course, the devil is always in the details. And I thought Jeanine had some great recommendations that could even strengthen the plan. I think those are the kinds of things that are subject to negotiation between the company and the FDA.

ACTING CHAIR SORIANO: Dr. Paulozzi?

DR. PAULOZZI: I just want to make a comment about post-marketing surveillance. In terms of risk management, I'm concerned that the measures described for tracking the results of the change in indication are not adequate to detect a problem. The systems mentioned sound like they depend heavily on the RADARS system and slide seven in their presentation shows four figures for RADARS

results for rates of prescription opioid abuse. And if you look at that figure, the blue line shows methadone and looking at the three out of the four panels of that slide, it would help if somebody could put that up, you don't see any increase in the methadone line during this time period. The problems that methadone deaths have risen four or fivefold between 1999 and 2005 in the United States and DAWN Live data shows increases in emergency department visits related to non-medical use of methadone during the period of 2004 and 2007.

Looking at the four RADARS panels, the line for methadone is fairly flat except with the possibility of an increase in the drug diversion panel in the upper left. Methadone has a lot more people making use of it. I think you'd have a lot less power to see a difference in incidents for a drug like Fentora, so I'm concerned that an increase would not be detected with RADARS. I'd prefer

that they say that they also would follow the DAWN Live data as an addition to their post-marketing surveillance. I think mortality data is not going to be helpful.

MR. DASGUPTA: My name is Nabarun Dasgupta. I'm at the University of North Carolina at Chapel Hill in the Department of Epidemiology. I also work for the RADARS system and specifically with regard to methadone in the RADARS system. We presented a paper at the American Public Health Association last November and that's in review at the Journal of Pharmacoepi and Drug Safety now, which showed that there are other ways to use RADARS data to detect signals, and we actually looked at mortality from methadone with poison center human exposure calls, and I think you have 14 or 17 states, and we were able to detect the association that you described that we both know very well. And those same techniques can be used for the surveillance data going forward. That level

of nuance analysis is not presented on this slide. This is very rough rates, you know. But there is a sensitivity to detect methadone.

With regard to detecting fentanyl, I think that's a more difficult question, and I'd be happy to look through the sensitivity analyses that would be involved in that. And I believe the company has agreed to look at Dawn Live on a continuing basis, as well.

ACTING CHAIR SORIANO: Dr. Gardner?

DR. SCHNOLL: Oh, I'm sorry.

ACTING CHAIR SORIANO: Dr. Gardner?

DR. GARDNER: Another database we were interested in, several of us are concerned about children, and I think there wasn't any mention of the, I'm probably not going to get this right, but NIDA's survey data on Monitoring For the Future. And I would like us to see if this were going to go

more broadly available. That would be one of the places that would be explored for looking for increases.

DR. SCHNOLL: Monitoring the Future unfortunately does not include fentanyl in the questions. And in order to add a new drug to the Monitoring the Future survey, because they don't want to extend the survey, you have to remove a drug from the system. And so it becomes very difficult to add a new drug to the Monitoring the Future study.

ACTING CHAIR SORIANO: Dr. Rappaport?

DR. RAPPAPORT: Could you put question four back up, please? I'd like to just go back and ask you to focus back in on this question, specifically to the second part of it. What Dr. Vocci was talking about the fact that there is a population that they've established this, there's a difference between showing that there's off-label use in thousands of patients and then expanding the

population to hundreds of thousands or millions of patients and changing the risk/benefit ratio just based on that.

So granted that may be something that's worth doing, and let's say we go in that direction but in order to do that we have to have a tight risk management plan, and I think you've all expressed that opinion. But in order to do that, is it going to limit access to patients? Is there a way to do both at the same time, to have such a quality risk management plan that it's going to avoid the pitfalls but it's also going to allow adequate access to the patients? Remember, you're talking about millions of patients treated by generalists across the country in small towns. How are they going to get their medications with the types of restrictions that are being put into place? I'd just like to hear some comments on that.

DR. WATKINS: Would you like us to individually poll each member?

DR. RAPPAPORT: Not necessary. I mean, if nobody has anything to say, that's fine.

DR. WATKINS: Okay.

ACTING CHAIR SORIANO: Dr. Nelson?

DR. NELSON: That's kind of what I was getting at before with my question about 6,000 physicians perhaps, and maybe that's part of it. If you're going to limit this to 6,000 physicians then clearly you're not going to cover the vast majority of patients if they have to go to one of those 6,000 doctors. Obviously, if you make it so unrestricted that everybody can prescribe that's going to be a problem.

It's very hard to scale up from the, you know, the 1150 current, 80 percent, prescription rate, and the relatively small amount of drug that's given out now by prescription to the population as a whole. And, you know, you can't predict what numbers of physicians are going to ultimately be

involved in this, but it would just seem to me that if you don't keep it restricted to a certain knowledgeable group of physicians you're going to run into problems that we run into now with medication-related errors and other things like that. And, of course, if you open it up too much I think you're going to run into problems with widespread, you know, public health issues in terms of, you know, the availability of the test drug that I mentioned before. So it is definitely a two-edge sword and, obviously, it's something that's going to have to be considered.

DR. RAPPAPORT: Right now, patients with cancer breakthrough pain don't have limitations on their access. But if you expand this to the entire breakthrough pain population, to many, many patients, but with a lot of restrictions, the cancer patients are going to have restrictions on access.

DR. NELSON: Well, the 1150 doctors who are servicing the, you know,

presumably in that group are the doctors who are servicing the majority of these cancer patients, right? So we're looking at a different group of physicians who have to now get certified and involved, so you can't limit it to the 6,000 doctors. You have to open it up to many more. You have to maintain a certain quality control it would seem because, otherwise, when you open it up to the generalists and to the others who are going to be giving it out, just like you did when we spoke the other day about Xyrem and we spoke before about buprenorphine and these other mechanisms, which obviously involve much smaller numbers of patients but also a much less onerous type of system in terms of getting the drug to the patient. You know, it would still be available in most pharmacies with the proper certification of the pharmacy and all.

But, yes, I mean, it's going to be hard to scale it up directly. It's not going

to go that easily.

ACTING CHAIR SORIANO: Any other comments? Dr. Gardner?

DR. GARDNER: I'm having trouble finding in my material how many prescriptions we're talking about. It seems that all the fentanyl has been collapsed in the five and a half million that I can see, and so we've become accustomed today to talking about 80 percent off label, but I don't know how many that is.

DR. MESSINA: John Messina with Cephalon. In 2007, there were 204 million prescriptions for opioids. Actiq, oral transmucosal fentanyl, and Fentora represented 0.2 percent of those prescriptions, or 332,000. So of the fentanyl products, generic Actiq, OTFC, Actiq represented about 73 percent of those 332,000, and Fentora was about 27 percent, which calculates out to about 70,000, approximately 70 to 80,000 prescriptions, somewhere in there. So just

proportionately it's very small. And, again, as we pointed out, 80 percent of the patients who received it had the non-cancer indication.

ACTING CHAIR SORIANO: Any other points to be made by the panel on question four? So as just a review, I think the panel does recognize a substantial risk of abuse for this drug. However, they still suggest that the risk management and mitigation plans be applied and also be proven, as I said before, to be proven with the current labeling for Fentora.

Any members of the FDA have any additions to this? So we'll move on to question number five, and Commander Watkins will let us know how to handle this question. Well, the question is, "Considering your responses to the earlier questions, do you recommend approval of the expansion of the indication for Fentora to opioid tolerant non-cancer chronic pain patients with breakthrough pain?" The members of the panel are asked to

vote yes or no using the touch pad here.

DR. WATKINS: All right. If each voting member of the committee, I'm sorry, Dr. McLeskey, this excludes you, will touch the button on their microphone that says attend. Just working with the technology. Bear with us.

ACTING CHAIR SORIANO: There are also follow-up questions to this. If you voted yes, I guess the FDA would like us to discuss means to mitigate the abuse and diversion that can potentially occur with the approval of this request. And if you voted no, what are some of the additional studies that the sponsor should conduct to address the reasons that you think the drug should not be approved?

DR. VOCCI: Did we vote already?

DR. WATKINS: No, not yet. Just a minute. Okay. At this time, would all members select your choice of either yes, no, or abstain? It's okay? Everyone has voted?

Okay.

ACTING CHAIR SORIANO: Let's make that a trial run because this is new technology, so I think we should let that be a dry run. And now we'll do the real voting, okay?

DR. WATKINS: Okay. One more time.

DR. NUSSMEIER: Do we press the attend button again first?

DR. WATKINS: Not yet, but probably. So we're ready to vote? Okay. Everyone again please make your selection. Has everyone locked in their vote? Okay. Ready? So I can go ahead and display? Okay. Here are the results.

ACTING CHAIR SORIANO: Okay. The results are: for yes 3; for no 17.

DR. WATKINS: Okay. Sorry for the confusion. Now we'll address the second part of the question. For the three of you that answered yes, if you could describe what means

to mitigate abuse and diversion the FDA should consider requiring; and do you require any additional studies?

DR. ANAND: I'm very impressed by the fact that this preparation has indications outside the cancer population for prolonged pain. I think it's a small population, but one that needs a product of this kind. I'm also reasonably assured by the risk management plan that the company has provided. The systematic ramp-up of 6,000 physicians in the first 12 months and 6,000 physicians every year after that to a maximum of 30,000 physicians that this would allow a phased-in introduction of this product to the patient population that benefits most from it where other therapies have not been effective or have not worked.

I do recommend additional studies, and I think the monitoring of those patients and those physicians who prescribe this drug should be intensive. There should be all of

the parameters to qualify physicians and patients for using this product should be in place and that there should be a clear process that is followed, which will allow the collection of data and some measure of how this product is being used. This is in comparison to its current use where 70,000 patients are getting prescriptions for this product, of which only 14,000 have the indication for which this product was licensed. So I think the company has presented a plan but should continue to collect data that would allow the monitoring about the abuse and diversion and misuse of this product after its label has been changed.

ACTING CHAIR SORIANO: Dr. Prough?

DR. PROUGH: I think the RiskMAP put together by the sponsor is quite good. I do think that Dr. Bell's recommendations merit consideration. What bothers me is that, in effect, the proposed RiskMAP, plus some variant of Dr. Bell's recommendations, would

really represent a model program for controlling the utilization of one narcotic, but there still would be 200,000 prescriptions a year for other narcotics that would not be similarly-controlled. And I think that it actually would limit the utilization of the current product in favor of other unapproved drugs.

ACTING CHAIR SORIANO: Dr. Vocci?

DR. VOCCI: I think one of the things that could be done if a physician who was prescribing this to an opioid tolerant non-cancer patient suspected abuse that I would start running urine drug screens on that individual because, if you get a positive urine drug screen for another drug of abuse, most likely they are abusing and/or diverting. I think that that would be a very strong signal, and I would make that part of the risk management plan.

Also, since it suggests to me that, the way they want to set this up, that

there will essentially be a closed distribution system, at least from company to pharmacy, pharmacy to doctor, and patient to doctor, that if a physician again suspected that something was going on you could write the prescription such that even though you gave them a 28-day supply it could be dispensed seven days at a time, something like that, so that you could limit the amount of available drug.

And, thirdly, one of the things that could be done would be to suggest if you have blister packs there is a technology that allows you to know when a tablet was actually punched out of a blister pack. And so that would give you an idea of the timing of the doses that the individual took. If somebody punches out 28 doses all at once, then you know something is going on. It would give you an idea as to whether or not appropriate use was going on or misuse. Even if they punched out two at a time, that might be considered

misuse, something like that. So I think that there are some studies that could be done that could get at certain things.

Also, I think you better define who might abuse the drug, and I think there are hints from the literature on this in terms of people that, there are individuals who have abuse histories of various types. Even if it is an alcohol history, they may be more susceptible to abusing a narcotic than someone who doesn't have an alcohol history. So I think there's some things that could be done to sharpen some things up, but I actually think that the drug could be approved. I would recommend that these be post-marketing studies rather than studies for approval. I still feel that the drug ought to be marketed.

ACTING CHAIR SORIANO: We will now hear from the no. Ms. Aronson?

MS. ARONSON: I guess I would feel better about having some more clinical trials with comparators, as well as a better

understanding about the company's COVERS risk management program, you know, just questions about whether these cards could be reproduced or, you know, where would the checks and balances be in the system.

ACTING CHAIR SORIANO: Dr. Bickel?

DR. BICKEL: I'd like to see more efficacy data comparing to other different agents that are not as high up as on the WHO ladder of interventions and see how efficacious they were and get a better sense of the magnitude of this population in that context.

ACTING CHAIR SORIANO: Dr. Cortinovis?

DR. CORTINOVIS: I don't know of any particular studies that I would recommend that the FDA follow up. I think that I'm still not sure what breakthrough pain is in these patients, but to somewhat paraphrase one of the Supreme Court Justices who didn't know the definition of pornography but knew it when

he saw it. I think that there are patients who, a very small number of patients, who would benefit from this agent. I think that the only way to really, really control distribution, abuse, misuse would be to restrict it to non-cancer patients who are attending defined pain management centers where there are specific protocols in existence to limit abuse and diversion.

I think that Dr. Rappaport has a very good point that there are people who live in rural areas, restricted areas, that don't have access to these fancy centers who would benefit from this agent. In those circumstances, off-label use may be appropriate. In other words, if the label use said you can only use this in non-cancer patients in defined pain centers, it would still be available to people who really need it, although I still feel that that number of patients is probably very, very small.

ACTING CHAIR SORIANO: Dr. Day?

DR. DAY: I've nothing to add to my previous comments. I've made all my concerns known.

ACTING CHAIR SORIANO: Dr. Gardner?

DR. GARDNER: I agree with Dr. Bickel. I'd like to see more comparative data coming from positive comparators. And then I'd like to see, as I said before, the risk management program started with the existing formulation and indication and see if it does anything to help control the off-label use that we're seeing now, which seems to be a cause of great concern for everyone.

ACTING CHAIR SORIANO: Dr. Kirsch?

DR. KIRSCH: As I said before, I'd like to see some cohort of patients subjected to the risk mitigation program and demonstrate that it actually works. If it works, it would be terrific and it would be a big advance in the area.

ACTING CHAIR SORIANO: Dr. Kosten?

DR. KOSTEN: I agree with all the things that have been said. I still think that the adaptive design that Dr. Vocci suggested would be quite helpful to have.

ACTING CHAIR SORIANO: Ms. Krivacic?

MS. KRIVACIC: I also agree with the comparator studies. I think one thing, you know, in thinking about this whole area of opioid abuse and misuse that we've heard over the last two days, one thing we haven't talked about is really more of a public health initiative to get people, younger people, aware of what is going on with these drugs, what these drugs can do to them. And, I mean, I don't see anything on TV. I don't see, you know, what is out there right now is just in public health announcements on leaflets or maybe on some websites. But I think, you know, young people think that they're invincible and, you know, go back to the 60s and 70s and it was marijuana and, you know,

heroin that some could get a hold of, but it was a real controlled, you know, at that time, controlled substances were really controlled. They are not controlled now, not your Class IIs, in the real sense of the term "controlled" where you can only get them at, you know, the clinics.

So I think we really need a real public health effort, and whether that's through maybe the pharmaceutical companies doing some PR, I don't know, or the government to get the information out to young people. I think that's why we're so concerned about getting a lot of these drugs out to patients that need them. Thank you.

ACTING CHAIR SORIANO: Dr. Lesar?

DR. LESAR: I only wanted to add to, my major concerns were that the core definition or the lack of consensus of what breakthrough pain in non-cancer patients are, so how do we educate and how do we measure something that we don't agree upon? And the

second was that there really needs to be both a technical and functional assessment of the RiskMAP before they should really go forward.

ACTING CHAIR SORIANO: Dr. Maxwell?

DR. MAXWELL: Very quickly, in thinking back over what has happened the last two days, I think we are seeing a paradigm shift in that with the great increase in opioid abuse among both young and old, I think we've given a message to the manufacturers that perhaps we expect a much more positive, aggressive stance, rather than a reaction to a problem. We'll see what happens the next time the committee meetings.

ACTING CHAIR SORIANO: Dr. Nelson?

DR. NELSON: Although I'd like to see more clinical efficacy studies, I'm less concerned about putting an ineffective product out or a product that has a very limited audience. I'm much more concerned about putting a safe product out there, one that has

tremendous public health implications, one that is particularly abusable and associated potentially with a fairly high mortality rate, as well. So I think that the risk management program needs to be better defined and potentially needs to be trialed before we implement it.

ACTING CHAIR SORIANO: Dr. Nussmeier?

DR. NUSSMEIER: Well, I remain very concerned regarding the problem of widespread access to the most potent narcotic available, so I would like to see implementation of the described plan or, preferably, an even stricter plan in cancer and carefully-defined non-cancer patients. The neediest of that group needs to be defined for, you know, this initial implementation of the plan. And then I'd like a report back to this committee regarding the results of implementation of the plan.

I'd also like to see at some point

some long-term data regarding patient use, whether dosages need to be increased with long-term use, whether there's eventual ineffectiveness because that leads us down a different path over the years to come.

ACTING CHAIR SORIANO: Dr. Paulozzi?

DR. PAULOZZI: I'm not sure this is possible, but what I'd like to see is a community trial where the company has an opportunity in a state with a prescription drug monitoring program to register physicians, pharmacies, do everything it said it was going to do, and then give it some time and track the prescribing patterns of the physicians enrolled in the system through the state prescription drug monitoring program looking at their use of this particular drug, other fentanyl products, other opioids, and you could even do a comparison in a state without the community trial to see what happens with transfer of Fentora prescribing

there. I think, with a large enough population, it could be powered enough to get a sense of what the impact would be on doing what the company originally proposed doing.

ACTING CHAIR SORIANO: I agree with my colleagues and the committee, and I have nothing to add. Dr. Wolfe?

DR. WOLFE: I would just like to commend the FDA staff for all the work they did. I was quite persuaded by a number of the analyses that were done in terms of the almost certainty of significant increased abuse if this were approved. And I guess one of the reasons why it was much easier for the FDA to approve the breakthrough pain in cancer patients is that part of the definition is objective. You do or you do not have cancer. And having cancer, the occurrence of tissue damage pain and so forth is known, whereas when you start with non-cancer breakthrough pain it is, as Dr. Markman pointed out and as I think other people have agreed, it is very

vague. And so if, you can't define the target population, it's even more difficult to do the kinds of comparative studies that would look at alternatives to fentanyl or opioids for treatment of that group. And, again, as I`ve said several times before, I think that most of the elements of this risk management program need desperately to be put in place with the existing indication because of what is already occurring in terms of abuse.

ACTING CHAIR SORIANO: Mr. Yesenko?

MR. YESENKO: This is giving the sponsor an opportunity to hear what the FDA and our panel has said. I think it's important, as Dr. Maxwell said, to have an action in place, rather than a reaction. It would have been nice today to see a registration system update rather than a registration system preliminary plan. In this fashion, we don't have this yet. I mean, I'm concerned about something like that. When

we're talking about abuse, misuse, and diversion, and we don't have something like that in place from the sponsor, that concerns me.

My second concern came from the FDA, Dr. Shibuya. He mentioned there's been no comparative data, as many other members have mentioned, and some of the safety issues were not addressed and they were not straightforward. So it does give the sponsor an opportunity for some correction and, again, maybe that can be addressed in another meeting.

ACTING CHAIR SORIANO: Dr. Zuppa?

DR. ZUPPA: I agree with a need for comparator studies. I feel pretty strongly that if the risk management plan is instituted for patients with cancer-related chronic pain that it does not limit access for those with non-cancer chronic pain that currently have access to it. And speaking to public health policy, I'm a pediatric critical

care doctor. I don't manage chronic pain. But when these kids do take these overdoses, I take care of them. And I really think that there is a false sense of security in these kids that these drugs are safer than some of the drugs that are illegal because these are drugs that their mothers are using, their aunts are using, their brothers are using. And I think a shift or a new emphasism in public awareness is absolutely indicated.

ACTING CHAIR SORIANO: Dr. Rappaport, I believe that the panel has adequately addressed the five questions you posed to it, and perhaps you can make some closing comments?

DR. RAPPAPORT: I think you've given us some very helpful information both today and yesterday in dealing with this difficult issue. As I think you've seen yourselves, it's a struggle. There's no easy answer to any of these questions, and it's been very difficult for us to sort through

this. But your thoughts and your discussion and this vote and the comments following it have been extremely helpful, and we are very appreciative of this. And we will come back to you with some information regarding our decision, and we will likely come back to you with questions related to this in the future. And, again, thank you very much for your help.

ACTING CHAIR SORIANO: I'd like to thank the FDA for inviting this panel, and I'd like to thank my fellow panel members for a real lively discussion and the audience for being patient with us and listening to what we had to say. Thank you very much, and now we adjourn the meeting.

(Whereupon, the foregoing matter was concluded at 4:23 p.m.)

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