and/or dosage and administration instructions.

Another option is to put requirements around dispensing of Fentora. Pharmacies would have to be enrolled to dispense Fentora. Elements of enrollment may include mandatory training or certification for pharmacists with or without an acknowledgment of understanding of dispensing requirements. Understanding of dispensing requirements could include knowledge that patients must be opioid tolerant, no therapeutic substitution allowed, patient counseling for appropriate use, dispensing and instructing patients to read the medication guide, and knowledge of prior authorization if required.

Prior authorization is used here and not the same as insurance reimbursement prior authorization could be required before filling a prescription for Fentora. Prior authorization could include a qualification sticker placed on the prescription by the

prescriber whereby a pharmacist could not fill the prescription without the sticker or a required patient registry which would require pharmacists to verify patient enrollment before filling the prescription.

In addition, risk mitigation elements that include the patient could include documentation of safe use conditions as a requirement for patients to receive a prescription for Fentora. Patient requirements cannot be considered without also involving the prescriber and/or pharmacy. Patient requirements may include a prescriber/patient agreement for documentation of safe use conditions that include required patient counseling around the key safety messages and receipt of the medication guide.

All of these options have a gate-keeping component for appropriate and/or safe use of Fentora, and all options may require evidence and/or documentation of safe use conditions. Used together, these options may

assure the benefits of Fentora outweigh the risks in the targeted population where the benefit/risk balance is acceptable.

However, there are also challenges with all presented options. Additional risk mitigation strategies may be more burdensome depending on the requirements imposed. And because of the increased burden, some prescribers and/or pharmacies may choose not to participate. This can have an unintended consequence in that appropriate patients could have delayed or no access to the product. And these strategies may have no effect on abuse, misuse, and diversion when Fentora is used for non-medical or non-legitimate purposes. Even if requirements are placed on prescribing, dispensing, and patient use, Fentora will still be available for abuse, misuse, and diversion. As you heard during yesterday's presentation, the usual opioid drug source for non-legitimate users is from prescribed patients.

Finally, we conclude that additional risk mitigation strategies, such as those just mentioned, may assure benefits outweigh the risks in the prescribed population where the benefit/risk balance is acceptable. But they may not prevent abuse, misuse, or diversion, especially in non-prescribed individuals. Expanding the indication even with additional risk mitigation strategies will increase the amounts of Fentora in the community, thereby increasing the risk of misuse, abuse, and diversion.

That concludes my presentation. Thank you.

ACTING CHAIR SORIANO: Thank you, Ms. Best. The panel would like to thank the presenters from the sponsoring institution, as well as the FDA and SAMHSA, for their reports. At this time, we'll provide an opportunity for the presenters to clarify some issues that members of the panel may have. And I'd like

to open this period for questions from the panel. First, we would like to see if anyone has any questions for Dr. Ball from SAMHSA. Any questions? Okay. What we'll do now is -- one question I have for Dr. Ball is do your analyses provide any projections of some of the trends that you're seeing in your report? Because certainly these new drugs have just been available for the past year or year and a half. I was wondering if your analyses also provide projections, as well?

DR. BALL: Our analysis does not do projections, forecasting into the future. And even if it were possible to do that with some drugs, I would say that the amount of experience we have so far with the Fentora data probably wouldn't support such an analysis.

ACTING CHAIR SORIANO: Any questions from the members of the panel for the sponsoring company, as well as for members of the FDA? Dr. Gardner?

DR. GARDNER: I'd like to ask Ms. Best about the experience the FDA has had now with some of the RiskMAPs that contain elements that she mentioned in her recommendations. We now have steps, and we have Accutane and others that have been in effect for some time, and I understand anecdotally there has been significant reduction of access at least to Accutane through the RiskMAP program. Is that the case? Never mind my understanding. Would you just tell us what the experience has been in our thinking about going forward with a RiskMAP?

MS. BEST: Well, basically, the restricted RiskMAPs we have out there are generally used to target the specific population where the risk/benefit has been shown to be acceptable. And isotretinoin or Accutane is one of the largest programs we have, and I think that currently involves somewhere around 300,000 patients.

DR. GARDNER: I'm sorry. When I said my understanding, I'm thinking of for the pharmacist response to difficulties with getting into the registries. And so I just wondered if we're now getting better at making these things more accessible for the providers that, therefore, make them more accessible to the patients.

MS. BEST: I'm going to have Claudia Karwoski address that question.

DR. KARWOSKI: Claudia Karwoski, Risk Management in OSE. I think that, as we gain experience with it, things have been improving. I mean, I can't speak specifically for the pharmacy professionals. I know that these programs are burdensome. They do require quite a bit of time both on the part of the prescriber and pharmacist and even the patients. But what we do know is that they seem to have some effect in prescribing at least more appropriate and safe use and limiting prescribing to a more appropriate

patient. And we've also had experience when there have been some burdens that companies have figured out ways to streamline it, and there's always that opportunity to do that as they learn more when a program is implemented.

ACTING CHAIR SORIANO: Dr. Day?

DR. DAY: I have a question for the sponsor. First of all, I would like to say I was pleased to see the innovative tools that have been developed, especially the NotifyRx, and the sponsor mentioned that there's currently a pilot program where this is being used in almost 41,000 pharmacies. And I would like to know if you can report anything about that? Has the software been installed successfully and there are no incompatibility problems? And then what kinds of outcome measures will you be looking at? And if you could comment on that, that would be great.

DR. SCHMIDER: The pilot program is starting basically as we speak. It starts

this month, so we have no data accumulated yet. We will be looking at data on how frequently on reports that we receive. We will have survey information particularly with the pharmacists that we will be comparing to our previous, our baseline data we have accumulated so far.

ACTING CHAIR SORIANO: Dr. Bickel?

DR. BICKEL: I've two questions for the sponsors. I was struck by the disconnect between the report of the prior RiskMAP results from the FDA and the plans of the sponsor for the future, and I wanted to comment on that. So if I understand it correctly, they had a very limited indication to cancer pain, breakthrough cancer pain, and they have extensive utilization of the drug prescribing practices for non-cancer pain, and their RiskMAP was supposed to protect them from having that excessive prescription to non-indicated use, but there was a whole lot of it. Now they've come back and they want to

expand it, and I was impressed with the list of their items. But I wanted them to reflect on how it is the case that things got so out of hand on the first case, and how are they going to make sure that doesn't happen again? How are they going to be more responsive? Because apparently it wasn't responsive in the first case.

The second thing I wanted to inquire about is I wanted to understand the new risk plan. It seems to me that if a key feature in preventing a sort of a second occurrence of the expansion of prescribing was in there, but I wasn't 100 percent sure if I understood it. So is it the case that you're going to require that every pharmacy that will ever fill a prescription of your medication or a doctor who is going to write a prescription for it or a patient who is going to receive it are going to be signed up in what I think was called your COVERS program?

DR. FLOYD: I will address your

first question in reference to the off-label use, and then I'll have --

ACTING CHAIR SORIANO: Excuse me. Can you just identify yourself for the transcriber and public record?

DR. FLOYD: My apologies. Eric Floyd, Vice President and Worldwide Head of Regulatory Affairs. You posed two questions. Your first question was to get a better understanding of the off-label utilization of our drug currently and which also occurred with Actiq. Your second question was a clarification in our risk management plan, which is currently termed COVERS, and what will be the impact on that plan in reference to the pharmacy, the patient, and the physician. I will address the first question. Dr. Jeurgen Schmider will address the second question.

In reference to the utilization of the drug, unfortunately we have seen more than 80 percent of off-label use of our drug that's

been written outside of the cancer patient population. And the reality and the fact of the matter is, irrespective of that, we have been unable to control it from the mere fact that we don't have the ability to educate and train physicians and patients. We, as a sponsor, are encumbered from actually doing that because we don't have the indication. Therefore, we pursued the clinical development program to address that. And what we presented today was the first evidence of actual efficacy and safety within the patient population.

So the only way for the sponsor to actually address it is to research it. Do controlled clinical trials to address it. So we knew this was occurring within the Actiq. We proactively addressed it and developed Fentora for both cancer and non-cancer. We initially gained the cancer indication. We're here presenting to you today to address this off-label use. There is no other way to

control it than to educate the physician and the patient on it. We are prohibited from doing that without the indication. So that's why we're here today.

I'd like Dr. Schmider to address our COVERS program and risk management.

DR. SCHMIDER: I believe I understand your question is how close is COVERS going to be?

DR. BICKEL: Is the start of the COVERS program a necessary prerequisite and condition of physicians prescribing, pharmacies handing out, and patients receiving this medication?

DR. SCHMIDER: Your understanding is correct. Prescription Fentora cannot be issued if the prescriber or the patient have not enrolled into our registration database. In addition, Fentora can only be obtained from pharmacies that are part of our distribution network, and all these pharmacies will have the electronic link where this check off the

enrollment into the database can be done.

ACTING CHAIR SORIANO: Dr. Francis?

DR. FRANCIS: Again, Dr. Schmider, is a question on the COVERS program. As far as the role of the pharmacy in how the drug is dispensed, I mean there's a number of errors we noted in the FDA data where there's problems with conversions and things like that. Will the pharmacy be an active participant in the hard stops that have to occur to prevent misapplication of the medication? It wasn't clear to me exactly how that process would work. Are they just a pass-through?

DR. SCHMIDER: To address your second question first, the pharmacy is part in providing the hard stop; and if the prescription is being denied, it will happen at the point of dispensing at the pharmacy terminal. The pharmacist will receive the pop-up message saying Fentora cannot be

dispensed and the reimbursement process will not be completed. So that is a hard stop provided there. I'll be happy to walk you again through the functionality of the system if you want me to.

DR. FRANCIS: I guess we can ask afterwards. One other question: in terms of cash reimbursements, how would that fit into the system? Is that a bypass, or is that incorporated somewhere?

DR. SCHMIDER: We are currently looking for solutions for cash transactions. It's still part of the details that we're trying to work out for the system.

ACTING CHAIR SORIANO: Dr. Kirsch?

DR. KIRSCH: I have two questions. First, one way to interpret the data to the sponsor is that you had growth and off-label use. I'm wondering if you have data, maybe survey data, from providers who care for patients with cancer pain as to why they prefer not to use this drug for breakthrough

pain in their patient population?

DR. FLOYD: I'll call Dr. Fine to the podium to address that.

DR. FINE: This is Perry Fine from the University of Utah. I don't have any knowledge of any studies that have ever been done looking specifically at oncology providers or patients, specifically oncology clinics, determining, you know, what's triggering their use or non-use of Actiq and now Fentora for these cancer patients. What we have is the data that suggests that from the original cancer trials that patients have an overwhelming preference. In fact, in those trials, it was greater than 90 percent preference and doubled on the cross-over trials for the oral transmucosal fentanyl product compared with the typical short-acting oral agents.

DR. KIRSCH: My second question for the sponsor relates to the plan to limit the access of sales reps to a limited number

of prescribers. And I'm wondering, during that period, will you limit your advertising so that other providers, or how will you limit your advertising so that other prescribers won't jump on the bandwagon and prescribe this medication to the population that we're concerned about?

DR. FLOYD: Dr. Messina will address that question.

DR. MESSINA: So the only way one can prescribe the medication is through registration through COVERS where we ensure that that individual has attested to understanding the safety messages for that. The advertising details, sort of the broad advertising details have not been worked out with the new COVERS program, etcetera. But the way we intend on ensuring the safety of that is that no one would be able to prescribe it until they've attested to that, which is different than what we have today where someone can provide the prescription whenever

they want.

ACTING CHAIR SORIANO: Dr. Nelson?

DR. NELSON: I have several questions, as well, if I can. In the study, with the double-blinded study that you had done, I guess one of the concerns I had is this must be a very difficult drug to double blind or to blind to the patient because, obviously, it's got a fairly dramatic effect compared to placebo. Was there anything done to determine whether or not the patients knew whether they were getting the placebo or the study drug?

DR. FLOYD: Okay. And your second and third question?

DR. NELSON: I can make up as many questions as you'd like.

DR. MESSINA: This is a typical design that's been done with the cancer population both for Actiq, as well as Fentora, and it was carried over into the non-cancer population. There's no indication that the

patients were able to distinguish between the two. You saw in some of my slides there is actually, at times, it can be a substantial placebo response we know with all analgesics, particularly with an acute pain situation like this, which does indicate that there's unlikely a recognition on the part of the patients of which treatment that they're getting.

DR. NELSON: My second question actually is I know in one of your slides you actually said something to the effect that the, I forget the exact wording, but that the pharmacokinetics or the clinical pharmacology of this drug better approximates the breakthrough pain syndrome, which is a true statement, although it may be a little bit misleading perhaps, I think, because it seems that the peak pain occurs in three to five minutes and it tends to resolve within 30 to 60 minutes or so, whereas the drug's peak onset or peak effect doesn't really occur

until 30 to 60 minutes or so. So, you know, although they do better match, it seems like for the majority of patients the pain syndrome will have been markedly alleviated or gone by the time the drug really kicks into what you consider to be moderately full effect; is that not right?

DR. MESSINA: I don't think it's exactly right, and I think partly because the survey data suggests to us that the median duration is 60 minutes of a breakthrough pain episode, suggesting that for a lot of patients it's more than an hour. We know from the placebo control data that we show a response through that two-hour time period for which we're showing benefit ever increasing. You are correct that patients oftentimes, when they will take this medication, will have already had the breakthrough pain start and, in some cases, it may be at its maximum intensity. But our feeling is that by providing medication that those get on top of

the pain sooner. You can actually provider relief sooner, and that is the objective, as opposed to waiting up to 45 minutes to 60 minutes for something to occur.

ACTING CHAIR SORIANO: Dr. Nussmeier?

DR. NUSSMEIER: Yes. I was pleased to see the clinical studies that were done, the efficacy studies, which my understanding is they were completed through a 12-week period?

DR. FLOYD: Yes, ma'am.

DR. NUSSMEIER: My question is in cancer pain patients and maybe more importantly in non-cancer pain patients, what happens after 12 weeks? What's the likely end point for these patients? I mean, do you anticipate they'll be taking Fentora for life?

DR. FLOYD: Dr. Messina?

DR. MESSINA: The population we have are patients who are already on opioids, on around-the-clock opioids, and in most cases

the patients who have entered the trials have been on those opioids for a number of years. So whether they will be on Fentora for the rest of their life is unclear, but it's likely that these patients will be taking Fentora for a long period of time or opioids for a long period of time. The studies that we conducted is up to 18 months in duration, which are some of the longest studies we're aware of within the opioid arena for treating patients.

DR. NUSSMEIER: Do they eventually become tolerant?

DR. MESSINA: I think tolerance is an issue you see with all opioids. It's difficult to determine tolerance to the around-the-clock opioid versus the supplemental opioid you use for breakthrough pain. It's part of the management that has to be done with these patients either through opioid rotation or through evaluating the effectiveness of the medicine as you continue to use it.

ACTING CHAIR SORIANO: Dr. Wolfe?

DR. WOLFE: It seems from the data presented this morning, particularly by the FDA, that aside, for the moment, of the issue of expanding the use by legitimizing what is already 80 percent of the use right now, which is the off-label non-cancer pain use, that there is a serious problem existing that bespeaks the need for much better risk management. And we heard some very good suggestions by Ms. Best as to what was deficient and what the company is doing now.

The question I have really for the FDA, generally Dr. Throckmorton and Dr. Rosebraugh and anyone else at the table there, is could you consider, even if you don't decide to approve this expanded use, coming down much more hard on the company in terms of better risk management just under the currently approved cancer indication? Certainly, there seems to be every indication that it's needed, and obviously the hook is

different if you are hooking it with the approval of a new indication. But do you not have the authority right now to seriously escalate the requirements that you have for risk mitigation, which I like better than risk management anyway? Could you just answer that, whoever would like to answer it?

DR. THROCKMORTON: We do have new --

ACTING CHAIR SORIANO: This is Dr. Throckmorton.

DR. THROCKMORTON: Oh, sorry. This is Dr. Throckmorton. We do have new authorities on the FDAAA, Dr. Wolfe, as you know. We're in the process of working exactly out what those new authorities mean. As we learn new information about safe use or, in this case, potentially unsafe use, we're going to need to use those authorities to the extent we need to to make changes. In this particular case, what that would mean I wouldn't want to say now.

DR. WOLFE: So no one there has any idea as to whether right now FDA has the authority to force the company to ramp up seriously the risk mitigation? You can't answer that question right now?

DR. THROCKMORTON: There's no question that we understand those authorities to expand what we can work to achieve both in regards to labeling and in regards to more restrictive kinds of risk management. Exactly how that's going to work, exactly how that would play out in this case, you know, that's the thing we would need to work out.

ACTING CHAIR SORIANO: Dr. Zuppa?

DR. ZUPPA: I have two questions, the first of which is for the sponsor. It seems that the COVERS program that you're proposing will really apply to the outpatient setting, and I imagine that patients with chronic pain will be hospitalized in the inpatient setting or in rehabilitation settings. And I was wondering how inpatient

prescribing for Fentora will be addressed?

DR. FLOYD: Dr. Schmider?

DR. SCHMIDER: Dr. Schmider again. This is part of the details that we're currently exploring, and obviously that's also one of the concerns that we're having. We want to cover as many scenarios as possible, including as many pharmacies as possible within the United States but also hospital settings, hospice settings, and other settings.

DR. ZUPPA: Okay. My next question is for Jeanine Best. With regards to the RiskMAP, just from the discussions that happened today it seems that a lot of the medication, the adverse events associated with this drug have to do with the prescriber and conversion from Actiq to Fentora. And I was wondering if there was any consideration of one of the goals of the RiskMAP to be addressing prescribing errors?

MS. BEST: Well, actually, I

think, as the medication errors, and I know Dr. Arnwine can address those better, the medication errors occurred across all levels: prescriber, pharmacists, and patient. And as we look towards revising the RiskMAP, I mean looking at revising the goals is also a possibility.

DR. ZUPPA: I have one more question. I'm not quite sure who to direct it to, but in looking at the trends of opioid use for non-medical indications, there is a rise in the 12 to 18-year-old and the 18 to 25-year-old, and there was no discussion today in looking at how these children are getting the drug. Yesterday, we talked a little bit about getting it from parents or getting it from friends or relatives. Can anybody address how these children are getting the drug?

DR. HERTZ: I'll start.

ACTING CHAIR SORIANO: Please identify yourself.

DR. HERTZ: Oh, sorry. This is

Sharon Hertz, Deputy Director of DAARP. We would think that it would be the same as we heard yesterday, that the primary source for misused prescription drugs is still the medicine cabinet. We don't really have anything to suggest that for this group of drugs, the oral transmucosal fentanyls, it would be different than for the other opioids.

DR. SCHNOLL: This is Dr. Sidney Schnoll. I would agree with what Dr. Hertz said, but what's very important as part of the risk management plan there is information about safe storage and also, as was mentioned, working closely with groups like the Partnership for a Drug Free America and other organizations that are actively involved in providing public service announcements and other information regarding the overall abuse of prescription medications, particularly out of the home. There is that cooperation, so there's a strong attempt to address this situation about which we are very concerned.

ACTING CHAIR SORIANO: Mr. Yesenko?

MR. YESENKO: This question is for the sponsor, specifically the chief medical officer. The patient/physician registries, are they currently in place, or is that something you're looking to create with the new indication?

DR. RUSSELL: Right now, the systems that we have in place are the start up of the NotifyRx, which is the pharmacy type program, and the patient safety activation card. So the approach that we are proposing now for the new indication to link those two systems to provide a complete patient, pharmacy, and physician registration system.

MR. YESENKO: So the answer is no?

DR. RUSSELL: Not yet.

MR. YESENKO: No. Okay. And this is another question for the sponsor. What is the date of the most recent update for your inserts on Fentora, labeling inserts? What is

the date of the most recent update?

DR. FLOYD: The latest update was in February of 2008 in which all labeling was updated based on an agreement with the FDA, and that included our risk management implementation: labeling carton/container and MedGuide.

MR. YESENKO: Thank you.

ACTING CHAIR SORIANO: We have five more minutes until lunch, and we'll have time for two more questions. One is from Dr. Throckmorton, and the next will be for Dr. Maxwell.

DR. THROCKMORTON: Thank you. I'd like to return to what Dr. Day said. I was also struck by the list of tools and interventions that I think Dr. Schmider talked about. One in particular you listed was product returns and disposal. That's a tool I think a lot of us are interested in in this field, but it wasn't clear to me whether that's a part of your proposed risk mitigation

strategy or not.

DR. SCHMIDER: This is a tool that is already available in the current risk management plan RiskMAP.

ACTING CHAIR SORIANO: Dr. Maxwell?

DR. MAXWELL: For the sponsor, I've read all this. There's some very intriguing ideas. One of the things that is currently being done is presence at national meetings to provide in-person educational opportunities, and I have a real question. I was at the American Conference on Pain Medicine April 3rd through 5th, and I picked this up. And, interestingly, the product insert that is encased in here is the first one that was published in June 2006. So I guess my question to the sponsor is if you're providing educational services to people at pain management conferences, why are they being given outdated inserts?

DR. FLOYD: There's a transition

time or period that it takes in order to approve the final label for our product and promotional information.

DR. MAXWELL: No, sir. The first one was June 2006. After that, there was another dated October 2007. I'm not talking about the February one.

DR. FLOYD: And the promotional period, may I see it, Dr. Maxwell?

DR. MAXWELL: Sure.

ACTING CHAIR SORIANO: Can you identify the object, too, for public record?

DR. FLOYD: We can identify a Fentora promotional pen and the prescription information. Now, this was received at which meeting, ma'am?

DR. MAXWELL: American Conference on Pain Medicine, April 3rd through 5th, 2008, New York City.

DR. FLOYD: I can't explain it. All that I can say is when we initiate a new labeling, which has been approved by the

Agency, which was approved in February 2008, there usually is a transition period from which we recall all information and we then reissue all the latest prescribing information that includes all of our promotional material.

ACTING CHAIR SORIANO: And Dr. Hertz would like to make a couple of comments before we break for lunch.

DR. HERTZ: We were just wondering if you have any additional information on the drug return and disposal program on its success and how much it's utilized.

DR. FLOYD: Dr. Messina?

DR. MESSINA: We've had the process in place with the original RiskMAP. It's in the patient materials, as well as in the package insert, but we have not had anyone utilize the system to date.

ACTING CHAIR SORIANO: Okay. It's 12:00. We will now break for lunch, and we will reconvene again in this room for the public discussions at 1 p.m. I'd like to

remind everyone to please take any belongings with you that you may want at this time. The ballroom will be secured by the FDA staff during lunch break, and you will not be allowed back into the room until reconvene. And, panel members, please remember that there should be no discussion of topic during lunch amongst yourselves or with any member of the audience. Thank you.

DR. WATKINS: Committee members, for those wishing a little privacy during lunch, the Montgomery Room has been set aside for you. It's right behind the restaurant.

(Whereupon, the foregoing matter went off the record at 12:03 p.m. and went back on the record at 12:59 p.m.)

ACTING CHAIR SORIANO: Good afternoon. At this point, we will start the public open hearing. The Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such

transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the open public, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, or of direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection to your attendance at the meeting.

Likewise, the FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial statements or relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the Agency and its committee enter consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when you're recognized by the Chair. I thank you for your cooperation.

DR. WATKINS: Our first open public hearing speaker is John Markman.

DR. MARKMAN: Good afternoon. My name is John Markman. I'm a pain management physician and specialist who lives in Rochester, New York, where I practice at the University of Rochester. I run a university-based pain management center and direct

clinical research. I'd like to thank the committees for the opportunity to speak today about this important issue. I would also like to disclose that I've come here today at my own expense, but my research is supported by the federal government, as well as Pfizer Pharmaceuticals and Endo Pharmaceuticals, and I have participated in speakers bureaus for Pfizer Pharmaceuticals, as well.

So I've come here today, as my first slide suggests, to talk about breakthrough and chronic non-cancer pain. And my concern specifically is that the meaning of breakthrough and chronic non-cancer pain is not clear. And my goal is to propose to you the need for further study of this indication.

So I'd like to begin by saying that this is not about whether opioids and fentanyl in particular have analgesic efficacy. I think that's a settled matter, as we've heard this morning. And it's also true that in a patient such as this one, whose

scan, actual CT scan, we see here, that opioids are the mainstay of the treatment of breakthrough pain in cancer. This patient's story, a tragic one, a 34-year-old gentleman with progressive osteosarcoma, there you can see on the left invading his pedicle, as well as his L5 and S1 nerve roots, experienced cancer-related breakthrough pain. And what's important about this case to illustrate is that there's a clear anatomy to what's causing the breakthrough pain and a clear pathophysiologic mechanism. That is a very well-studied phenomenon. There are over 35 original clinical trials looking at the role of opioids in cancer pain.

In contrast, the evidence base for breakthrough in non-cancer pain is relatively limited, the principal setting being a telephone study of 228 patients and the original studies which have been presented today.

And it's important to realize that

many factors can cause breakthrough, even in cancer pain, where this was originally described in the in-patient setting in patients with advanced cancer. It could be related to dosing or pharmacokinetic issues, such as the under-dosing of a long-acting opioid or the end-of-dose effect of an opioid. It could be due to pharmacodynamic issues, such as opioid tolerance or opioid-induced hyperalgesia.

It could be due to incident pain, such as when this patient would get up to go to the commode and there would be some tension placed on his entrapped S1 nerve root or further periosteal invasion of structures by the inflammation associated with a growing tumor. In his case and often in the case of cancer-related breakthrough pain, there's an underlying well-defined disorder as the advancing size of the tumor and the consequences of that structural problem and the pathophysiologic complications and

implications of the inflammation around the tumor, which are so important to understanding breakthrough pain. But even in that specific context, there is a significant amount of debate among self-identified cancer pain specialists as to what breakthrough is in cancer pain, and it's already a complex differential diagnosis.

Now, here is a patient with a transient flare of pain without cancer. He's a 54-year-old gentleman. He, too, has relatively well-controlled background pain on a long-acting opioid, and he has multiple flares per day. It is extremely complex to understand what drives the variations in pain intensity in this particular patient. And it's important to note that breakthrough pain in non-cancer pain, whatever it is, is not acute pain because acute pain goes away and that's not true of breakthrough and chronic non-cancer pain. It always comes back.

And it's also important to note

that, unlike the first patient with cancer, the pain is not tightly coupled to tissue injury or damage. As in this case, where this gentleman has recurrent knee pain, his skin or his x-ray of his knee will never change in that left leg pain, but he will continue to experience this pain at varying levels of intensity. And were we to treat every one of those flares over a lifetime, 2.4 flares of breakthrough pain a day, 24 years, 21,024 rapid-acting opioid doses later, how good would his pain control for these so-called variations of pain intensity be when there are so many other alternatives: behavioral modification, anti-inflammatories, and other strategies that could control his pain because his life is not a series of 60-minute SPIDs all in sequence. His pain is embedded in his biography and his life story, and it's important to recognize that if you just look at the 60-minute outcomes in efficacy you're going to be reinforcing some of the behaviors

which might make this patient lose function over time because he's going to be treating each episode, each variation in pain intensity, as a unique episode of tissue injury potentially.

So it may be that the intensity of pain and the temporal signature may not be enough information for clinicians to make good decisions. And, remember, the patients who take care of low back pain and knee pain and even all-comer type neuropathic pain are, in general, not specialists. They come from widely-divergent backgrounds and have many other issues to take care of in that moment, that 9 or 10 minutes or 20 minutes for a patient. They've got to manage their hypertension, their diabetes, along with this pain complaint.

So I put again this same schema here looking at how we think about pain in this patient. It may be related to pharmacokinetic issues. It may be related to

pharmacodynamic issues, the variation of pain intensity, or it may be simply related to the intrinsic variability of pain intensity throughout the day.

And this is important work by colleagues taken from actual patients in a clinical trial, and it's important to recognize what this suggests because for which transitory flares of pain are rapid-acting opioid treatment indicated? Now, these are patients with postherpetic neuralgia and diabetic neuropathy, and you can see here that their baseline pain is varying. It's varying throughout the day. So baseline pain, which is constant, does not mean unvarying. So which of these spikes are we going to be treating throughout the course of the day? How can a physician, let alone the patient, tell them apart if there's an intrinsic chronobiological variation in pain intensity?

So my simple point is that the unmet need, the definition, and the scope of

breakthrough phenomenon in chronic non-cancer pain still lacks sufficient characterization. And without more information, physicians like myself cannot make good risk/benefit decisions to understand which of the flares that need to be treated.

Now, there are five key areas of further research for the proposed new indication, and many of them have been amply covered today. But I do think that it's important to demonstrate that this can be prescribed safely and that we have chronic pain endpoints to measure patients' function over time. Thank you very much for your attention.

DR. WATKINS: Thank you. Our next presenter is Andrea Cooper.

MS. COOPER: My name is Andrea Cooper, and I'm a person who lives with chronic pain. I'm also a volunteer patient advocate with the American Pain Foundation and chair its Pain Community Advisory Counsel.

I wish to disclose that Cephalon has assisted me with my travel arrangements and costs so that I could be here today.

I have lived with chronic persistent pain in my neck and my back caused by spinal disk disease and a lot of other long words that I'm not going to try to pronounce right now since I was a college student more than 30 years ago. I have fibromyalgia and multiple nerve entrapment syndromes. I was aggressively treated for cancer ten years ago and still struggle with side effects from chemotherapy and radiation.

In order to control my pain symptoms, I now use a regimen that consists of long-acting pain medication, rapid-onset pain medication for breakthrough pain, an antidepressant, regular exercise, and mind/body practices. Singing, creating art work, and patient advocacy also helps me to cope with my chronic pain and allows me to have a more normal life.

Having an invisible medical condition like chronic pain can be extremely frustrating and even demoralizing. People just don't understand it. It affects everything: my family, my marriage, my ability to work, and my self esteem. People say, "Well, you look great. I can't believe that you have such terrible pain." Well, inside my body is screaming. It doesn't show. You can't see pain, and you can't hear pain.

Although I take around-the-clock opioid to control my symptoms, I still experience flares of severe pain on a daily basis. If not immediately dealt with, breakthrough pain can spiral out of control and be difficult to reign in. As I learned over the years, and we're talking about 30 years, the consequences are many: never knowing when or where I'm going to fall apart or for how long; missing ballet recitals, softball games, amusement park rides, and school field trips; feeling so desperately

uncomfortable that I could literally explode, having no other option but to lie down immediately on the floor of a department store fitting room, hotel lobby sofa, public restroom, or park bench because I can no longer stand to stand. And believe me, I've done all of them.

Day after day, the dinner is half made, bread half-baked, and the projects lie in piles around the house abandoned. Constantly apologizing for having to leave early, not showing up at all, or losing my temper because I just can't stand the pain any longer. Episodes like these can add up to big compromises and sometimes have even put my life in danger. For example, one day I was waiting for a train downtown in Baltimore. My pain level was quickly escalating, but there was really nothing I could do to quickly bring it down. I became very dizzy, and I fainted, falling right onto the train tracks. Luckily, the train was late, and I escaped serious

injury.

When pain is not controlled adequately, it becomes physically and emotionally debilitating. According to the voices of chronic pain surveyed by the American Pain Foundation, 60 percent of pain patients said that they experienced one or more spikes of breakthrough pain daily, severely impacting their quality of life and overall well being, and I am living proof of that.

I consider myself fortunate. My doctor listened to me, and we found a rapid-onset med that works well for me and allows me to better control these spikes of pain. Without this medication for breakthrough pain, my life would be considerably more impacted. Adding a rapid-onset pain medication to my regimen has given me so much more control and, in some cases, prevented unfortunate circumstances like the one I spoke of before.

Pain doctors and their patients

should be allowed to decide which medications and treatments are the most effective on a case-by-case basis. We must weigh risk versus benefits, just as we must with any medication that we take. But in my opinion, pain patients need a range of options to augment their treatment and improve the quality of their lives.

Some very effective pain medications are currently approved only for cancer pain. I've had cancer and, to me, unrelenting chronic pain is harder to live with. In my case, the cancer had a beginning and it had an end. For me, I was lucky the outcome was a good one. But chronic pain doesn't have an end. It just goes on and on.

Lastly, when I speak to patients and caregivers I always remind them to keep all of their pain medications in a lock box, as I do in my house. We have to make sure that it's safe from unintentional use. This simple act gives me peace of mind, and I think

it would do the same for others, as well.

I want to thank the panel for allowing me to speak today. Thank you very much.

DR. WATKINS: Thank you. Our next speaker is Art Van Zee.

DR. VAN ZEE: My name is Doug Van Zee, and I have no financial disclosures. I prepared a slide presentation and sent it in a few weeks ago and then kind of realized sitting here through yesterday that I was kind of missing the mark with things, so I wrote up some comments this morning.

I did want to state for today's session and speak to you because I have deep concerns about the public health consequences of an FDA-approval for Fentora for chronic non-cancer pain. I think, if approved, I feel, simply put, that there's going to be a lot of dead young people out there.

This decision comes within the context of an alarming and rising national

prescription opioid problem. We've seen the last two days the various indicators of that. We have an unprecedented number of prescription drug abusers, prescription opioid addicted individuals, unintentional overdose fatalities, and bereaved families. We also have an unprecedented rising availability of prescription opioids this last year from 190 to 200 million prescription opioids out there and 12.4 billion dosage units in 2007. From my perspective, this is not the time to put a lot more opioids out there.

That doesn't mean that there are not people in our healthcare system that have severe chronic pain that could benefit from opioids and are not getting it now. But there is a big disconnect between what we see in clinical trials and what happens when a marketplace healthcare system tries to deal with that. So there's discrimination in the targeted ability to get the opioids maybe to some of the people that do need it, but the

amount of public harm that's resulted from a big liberalization of the use of opioids for chronic non-cancer pain is pretty significant magnitude.

So from my perspective, this is not the time to put more opioids out there. I think Fentora, of course, should remain for patients with cancer-related pain. And I think, certainly, it would be a reasonable consideration to have Fentora under very kind of restrictive compassionate use program for patients with severe chronic non-cancer pain situations.

The remainder of my comments I'd like to address to the broader problems of what can be done about the national prescription opioid problems in general. We've said several times today this is not a one or two drug, yesterday was not a one or two drug issue, and it's certainly my feeling as well. These are suggestions that have been brought up and I think merit some discussion.

Physician mis-prescribing and over-prescribing is part of the problem. As a general internist with an outpatient and inpatient practice, I'm required to do ACLS every two years. And I groan about the time spent and new protocols learned and trying to take the extra time off to do that, but I understand that that's important, and I do it.

I do something every day which has much more grave public health consequences than my ACLS participation, and that's writing prescriptions for controlled drugs everyday. And in the 34 years I've practiced medicine, I haven't been required or expected to demonstrate any competency about my ability to prescribe opioids or other controlled drugs. I think it would be a substantial step forward if physicians were required to demonstrate competency for the prescribing of controlled drugs in order to have a DA license. This could be as straightforward as passing an online examination every few years when the DA

license comes up for renewal. If one didn't pass, further CME could be in order and another attempt at the exam.

Methadone is more complex and somewhat tricky to prescribe at times and certainly is in many overdose death studies in many states the leading opioid killer. So I think a special module dedicated for demonstrating competency in prescribing methadone for chronic pain would be a step forward.

The usual rejoinder to these kind of suggestions is that states regulate the practice of medicine. However, we have a real precedence in buprenorphine, a federally-legislated mandated special training for the use of this Schedule III drug. It's confusing to parents who've lost a son or daughter to methadone or OxyContin that we require special training for a Schedule III that has minimal chance of fatal overdose and absolutely no requirements of education or competency for

physicians to prescribe Schedule II drugs with much more adverse potential.

The second point I want to make and has been made some is to comment on the marketing promotion of controlled drugs. Certainly, the marketing promotion by Purdue Pharma of OxyContin wasn't the only reason for the OxyContin problem, but it was a substantial contributing factor. The public health would be well served by redefinition of acceptable and allowing marketing practices for opioids and other controlled drugs and an empowered FDA to monitor and regulate such marketing.

I'm concerned about the problems inherent in the system that allow physicians to prescribe off-label opioids. Pain is not a rare pediatric disease, and I don't see the rationality of a process in which the FDA, as the insurer of safe and effective drugs and the guardian of public health, would go through a conscientious, laborious, meticulous

process looking at the scientific evidence, come up with indications, and have the drug to the marketplace and prescribed by physicians in any manner off-label. And I'd suggest that the public health implications of physicians prescribing opioids off-label are much higher than, for example, when Gabapentin was prescribed to a great extent off-label. This is a big problem and one that would require addressing the CSA, but it's certainly a problem that can be fixed with concerted effort on the part of many agencies.

And, lastly, I would encourage you to have a meeting with the GDA, all the pertinent committees, and other people at the table to really address all the issues surrounding the opioid problem. I thank you for your time.

DR. WATKINS: Thank you. Our next speaker is Jennifer Bolen.

MS. BOLEN: Good afternoon. My name is Jennifer Bolen, and I am a resident of

Knoxville, Tennessee. I spent many of my years as a federal prosecutor. I am a lawyer. I still practice in the pain community.

I do have disclosures. I am funded by many different pharmaceutical companies for speaking across the United States to teach on legal regulatory issues related to pain management and documentation compliance. Cephalon has paid my travel here today, as they are taking me down to the American Pain Society to work on continuing efforts with emerging solutions in pain, and I think other companies have shared in that effort.

I'm a lawyer that lives with and speaks pain. I don't know if many of you have encountered lawyers like me, but it means something. And I hope that you will hear the words that I'm about to say.

I do live with chronic non-cancer pain. I am a former assistant U.S. attorney. In May of 2003, I founded the Legal Side of

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Pain with the goal to bridge the educational gap that is out there related to regulatory compliance, mind set, and providing quality care to patients. It was very difficult for me, as a prosecutor, to find somebody who would take care of my chronic non-cancer pain, and I'll tell you a little bit more about that in a minute.

I've spent nearly seven years working as an educator in this community, and I have learned a lot from my travels. And I'll share some of those with you in a minute.

I take opioid medications daily. I am opioid tolerant. I am not an addict. I do not seek early refills of my drugs. I go forward every day with my physician in hopes that we'll find a combination that helps me remain active. And without my medications, I would have some severe problems in my life: relationships with my spouse; my ability to do what I love best, which is being around horses; and my ability to travel and do

something that I think I'm very good at and intended for, and that's talking with people and trying to show them, from the courtroom perspective, the end of this line, this battleground if you will, of what happens in a wrongful death lawsuit, what happens in a criminal case involving a physician who has inappropriately prescribed, and what happens before licensing boards when there are allegations of unprofessional conduct.

I have used these medications for quite a period of time, and one of the reasons for it is I'm Factor V Leiden mutated. I've had two pulmonary embolisms and a clot to my brain. I figure that somebody is not done with me yet, and it's one of the reasons I'm standing here. I take 15 milligrams of Coumadin every day. I have a filter implanted. The Coumadin barely holds my INR at two. I'm not somebody that can walk into an interventional pain office and get lots of procedures to help me, although I do get

procedures, SI joint injections, that are of some help. But I don't have a lot of options. And without the medicines that I take, it would be very difficult for me to even handle many of my private bathroom functions, sexual relationships, that sort of thing. And, you know, that's important in my life, and it's important in many others across this country.

I go through urine screens. I go through medication counts, medical supervision. I have no problem with any of that. I think that that's something that a responsible patient should do. I think that the FDA, in looking at the risk mitigation proposals here through the RiskMAP and what was raised earlier this morning, can certainly come up with ways to share responsibility with the patient and the physician, that that much needs to be done. And it also must focus on the insurance companies and their involvement in this, especially with one of the medication errors highlighted earlier this morning.

What happens with me in breakthrough pain, I take breakthrough medicine, and I had a prop over here to show you but I think you can visualize this. I use breakthrough medicine maybe a little differently, and I learned this from the doctors that I've encountered in my teaching careers. I sometimes don't have any breakthrough pain during a particular day or what I would call breakthrough pain, so some days I don't need to take that medicine.

Other days, I have it where it's unbelievably destructive to me and my ability to focus, my ability to travel, my ability to do anything other than sit on the couch. And those days are rare, and I'm fortunate. But I still am thankful that I have a doctor that has believed in me and given me the medications that I can choose from. And I'm an educated patient. I'm not like everybody out there, but I didn't start off this way. And I have learned through the educational

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processes that many of these companies have and bring forward to the physicians that go to dinner lectures, to the physicians that go to booths at conferences, that there is good information out there to be brought to patients; we just need to find that balance.

From 2003 to present, I have logged more than 700,000 domestic airline miles traveling across this country educating clinicians. I have audited more than 800 practices now in this country. Going into the offices of these physicians, doing grand rounds and journal clubs, looking into the faces of the patients in the waiting room, looking into documentation through a business associate agreement that would allow me to audit these records, looking into all of these things.

And I have also seen the eyes of the family members that have lost individuals as a lawyer who has represented or been approached to represent some of these people.

I've seen the eyes of the physician that was defiant to the regulatory requirements in this country, and I have seen the eyes of the physician and their support staff that have really tried to do the right thing but haven't received the education that they need in order to navigate these waters of risk in this whole issue of balance.

There is a tremendous jet lag in this country between what exists as a regulatory requirement. A good example would be some of the FDA's warning letters that have been issued. And when those things end up in the hands of physicians. And that lag must be addressed by you, and you're doing a good job of it by looking at these RiskMAPS and looking at risk mitigation features that can help. But we are getting better, and we've made a lot of accomplishment.

You must remember that we are still in the decade of pain control and research. We started this in 2001, and we've

made a lot of progress. There will always be risk associated with medications no matter what label you give to it. There will always be people that defy the laws in this country. There will always be people that don't listen to their providers and take the medications. But stopping a company from going out and educating or stopping a label that may help some people and may actually imbalance could be exactly what you don't want.

And so I'm asking you in the very end here of my time that you come forward and address this and continue to empower me and others to come forward and educate. Thank you.

DR. WATKINS: Thank you. Our next speaker is James Broatch.

MR. BROATCH: Good afternoon. I'm the Executive Director of the Reflex Sympathetic Dystrophy Syndrome Association, or RSDSA. We're a national organization for people with complex regional pain syndrome, or

CRPS.

CRPS is a neurological syndrome that normally occurs after some type of trauma, surgery, or intractable pain. Our organizational mission is to promote greater awareness of CRPS and to fund research into effective treatments and to a cure.

My financial disclosures are that I was not paid to attend this meeting, but we do receive some pharm and medical device funding from Metronics, Celgene, and Endo, and some others.

On behalf of RSDA and the 7,000 members, I'm speaking in favor of Cephalon's supplemental indication. First, I want to provide you with a snapshot of our constituency.

In 2005, we conducted a web-based survey of people with CRPS in conjunction with Johns Hopkins School of Medicine. An abstract is on our web site at rsds.org. Of the 1359 people who completed the survey, the average

disease duration was greater than three years with an average pain score of 7.9 out of a scale of zero to ten, with ten being the worst. Sixty-percent rated themselves as disabled. Most significantly, 47 percent reported having thoughts of suicide; 15 percent acted on it, sometimes twice.

The rate of suicide ideation in CRPS is roughly two and a half times more than other chronic pain conditions. A pain psychologist at Case Western University stated it well, "Another collaborative truth is that there are no pain conditions so associated with desperation that amputations in an attempt to relieve pain are not unheard of."

Historically, there have been few clinical trials that have included patients with CRPS. Patients with CRPS were excluded from the recent lyric and Cymbalta trials. More and more individuals with CRPS are being denied reimbursement by third-party payers since almost all medications that are used to

treat CRPS are off label. We applaud Cephalon's decision to include patients of CRPS in their expanded trials.

To buttress my testimony today, we conducted an online survey between April 15th and the 22nd of this year regarding the treatment of breakthrough pain in people with CRPS and specifically the use of Fentora. The survey was sent to 3,978 people who have signed up for our electronic listserv. Of the 3,978 invitations, 574 completed the survey, about 15 percent. The survey consisted of 10 questions regarding breakthrough pain, use of narcotics in breakthrough pain, and two specifically regarding Fentora.

Of the 574 responses, 95.5 experienced breakthrough pain defined as moderate to severe, flares of pain that occur when persistent or baseline pain is pretty well managed. During a breakthrough pain episode, the average pain rating is 8.2 out of 10. Again, 10 being the worst possible pain.

And 28.7 respondents rated their pain during a breakthrough pain episode at 10. Of the 65.5 percentage of respondents currently taking opioids for the pain, 52 percent take a short-acting opioid now to manage their breakthrough pain.

We strongly endorse the supplemental indication of Cephalon for the indication of breakthrough pain in opioid tolerant non-cancer patients with chronic pain. Thank you.

DR. WATKINS: Thank you. Our next speaker is Melissa Zuppardi.

MS. ZUPPARDI: I would first like to say I do not have any disclosures from any pharmaceutical companies whatsoever. I would like to first thank you for allowing me to speak on behalf of the victims of opioid-related death and addiction. My name is Melissa Zuppardi, and I'm President of HARMD Incorporated, Helping America Reduce Methadone Deaths, a non-profit organization founded by

surviving family members of loved ones lost to methadone and other prescription opioids. Our objective is to decrease opioid-related addiction, injury, and death.

Although many of us have lost loved ones to methadone, another dangerous Schedule II narcotic that is over-prescribed and under-regulated, the majority of our loved ones who perished at the hands of this drug became addicted to opioid drugs as legitimate patients suffering from moderate to severe pain. Many were over-prescribed and recklessly prescribed such drugs as oxycodone, hydrocodone, Loratab, OxyContin, and fentanyl. Physicians have not only fed their addiction but also initiated the addiction by prescribing these powerful opioids for such things as restless leg syndrome, arthritis, migraines, headaches, pulled tooth, tooth fillings, fibromyalgia, back ache, and knee pain.

I am here, along with Marti

Hottenstein, HARMD National Diversion Specialist, to plead with you to consider the lost lives and the many more to come by allowing yet more drugs onto our street and in the hands of doctors who are uneducated on how to prescribe opioids and on assessing and treating addictive disorders as they develop in their patients.

Severe and chronic pain is a grave concern for all of us. However, we must balance the need for pain control versus the onset of addictive behaviors in patients. Physicians must explore alternatives for those disorders which can be treated without opioids. Before allowing more drugs to filter into society, please mandate education for doctors prescribing Schedule II narcotics.

From September to November, Wall Street Journal articles Cephalon Incorporated, the manufacturer of both Fentora and Actiq, say it doesn't market the drug for unapproved uses. While acknowledging that Actiq is

widely used off label, it says it can't control how doctors prescribe the drug. A spokeswoman for Cephalon, Stacey Beckhardt, said she didn't know what the proportion of off-label use was for Fentora, but she added, "We do know that some of the physicians who are prescribing Actiq are prescribing Fentora in the same way."

Cephalon said Fentora has been linked to a total of four deaths. The company said three of those deaths which appeared to result from respiratory failure were related to inappropriate prescribing of Fentora. Two of the patients were prescribed the potent drug for headaches, even though they weren't on around-the-clock opioid therapy.

The company said it also received a report of a fourth death, a person who committed suicide while taking the drug but wasn't prescribed the drug by a doctor. In that same article, Connecticut Attorney General Richard Blumenthal has initiated

investigation in 2004 and has found that Cephalon promoted Actiq off label to neurologists to treat headaches, set unrealistically high sales quotas for its drug representatives, and pushed larger prescriptions at higher doses.

In relation to this admission and the Connecticut Attorney General's investigation, I would like to know why the FDA would consider expanding the uses of this drug when we already know of deaths that have been prescribed off label. Physicians' liberal prescribing practices and the myth concerning the safety of opioid drugs have led to unnecessary deaths of trusting patients. This is another reason for the immediate need for mandated physician education and licensing of Schedule II narcotics.

People are receiving opioid medication who do not meet the criteria, yet are being prescribed it anyway. This type of reckless prescribing leads to these

medications being diverted, resulting in instantaneous threat to the community. The FDA should have complete control over prescription drugs. They are not being manufactured in someone's kitchen or smuggled into this country. They are coming from a doctor's prescription pad. It is time to get this prescription drug epidemic under control before more lives are needlessly lost to so-called controlled drugs.

I would like to give you some examples of poor prescribing practices that led to addiction and death. In 2004, a HARMD family member lost her brother and his girlfriend to fentanyl, the preparation is unknown, overdose. Both were discovered dead by their landlord covered in inches of maggots. This drug was diverted to them by a so-called legitimate pain patient.

A family member was prescribed OxyContin for a tooth filling. A 22-year-old man was given 30 Percocets after having a

tooth pulled and then physician continued to rewrite script. After losing her daughter to methadone, a HARMD family member's doctor tried to prescribe it to her for arthritis.

Another HARMD family member was prescribed 200 oxycodone every three days, and she eventually died when the doctor attempted to switch her to methadone. My fianc,, who later succumbed to methadone taken exactly as prescribed by an ASAM physician, began his 14-year battle with addiction as an 18-year-old who needed knee surgery after a sports injury and was prescribed high doses of oxycodone and OxyContin.

A successful businessman was injured on the job and was prescribed OxyContin and, after three overdoses, he finally died. After an auto accident at 22 years old Carl Hottenstein was prescribed oxycodone and was taking up to 15 a day and later died after attempting to use methadone given to him by a methadone clinic patient in

an attempt to be weaned from the medication. If approved for chronic and breakthrough pain, you will see Fentora being prescribed for the above conditions, and you will hear the same outcomes from the same family members coming here.

If time would allow, I could tell you at least 700 more stories of addiction, dependence, and death I personally know of. Addiction does not discriminate. It could be your mother, father, child, husband, or wife; and contrary to popular belief, all of those addicted to pain pills do not rob, steal, and break the law. They simply fill a prescription written by their doctor. They do not have to crush, snort, inject, smoke, or chew these pain medications to abuse them.

How do you prevent abuse, death, and addiction for those doing exactly as directed by their physician? We believe the answer is in mandatory physician education and licensing of these powerful narcotics, as well

as them being strictly reserved for severe cancerous pain. When making this important decision, I implore you to consider those who have been lost to these drugs and learn from their deaths. I also would like you to think of their families that suffer from a chronic debilitating pain for the rest of their lives that no pill can fix. They do not enjoy the simple life activities of other people.

When is enough going to be enough? We are now a pill-driven society with pharmaceutical companies dictating medical practice with their marketing techniques. When are we going to value human life over the financial influence of pharmaceutical companies?

DR. WATKINS: Thank you. Our next presentation is a group presentation by Kristen Thacker and David Larson.

MS. THACKER: Hello. I'd like to start off by saying thank you to the ladies and gentlemen and honored guests and

distinguished members of the FDA for allowing us to be here today. I'm here with my husband, David Larson, who also has something to say about chronic pain. Today I'm here to tell you about my experience with chronic pain and explain how Fentora changed it.

For several years, I have been battling a unique chronic pain disorder called RSD. RSD has many unusual symptoms. It can spread to different parts of the body. In my case, it has spread from my left foot to the right, into my ankles and part of my calves. At night, I am often awakened by pain that is almost impossible to describe. It feels like an ice pick that is working its way into the sides of my feet, twisting back and forth, distorting and breaking all tendons and bones.

More often the pain is different, though no less troubling. The skin on the top and bottom of my feet feel as if they are engulfed in fire. It feels like the red hot grill is pressing against my swollen skin.

Even the softest sheets, the lightest touch are unbearable.

This has occurred countless nights with multiple occurrences during the night to which to keep from waking my husband I try to shuffle into the bathroom and shut the door before the tears overwhelm me. My inability to keep the pain under control has left my life in shambles. From disuse, I have developed osteoporosis in both feet. I have become depressed from radicalized changes. I had full blown anxiety attacks between three and six times a week. I had suffered extreme mood swings, self loathing, and anger. This has led to stress among relationships with my families and friends.

I have trouble doing things that many normal adults take for granted, such as cleaning, bathing, cooking, walking my dog, and shopping. At 32 years old, I needed a cane to go even short distances. Doing the work I was trained for was impossible.

This is normal for chronic pain sufferers. This was my life until I was accepted into a drug study for Fentora.

Pain is often measured from a scale of zero to ten. Much of the day before the study, I felt around a six or a seven. Within the first months of the study, with the use of Fentora, I was able to bring it down to a three or four. With the aid of my physical therapist, Brad Jordan, walking without the constant use of my cane became possible again.

Eventually, the osteoporosis was reversed. Better pain management has lifted much of my depression. I feel that I have a lot of my life back. Although I still suffer from chronic pain, Fentora is one reason why I was able to physically fly across country to speak with you today. Another reason is my doctor's willingness to prescribe an off-label medication. Many pain sufferers are not so lucky.

I also benefit from the excellent

health insurance that covers off-label medications. Many pain sufferers are, again, not so lucky.

I hope you will approve Fentora for chronic pain for all the people that suffer and cannot use it today. Thank you.

MR. LARSON: I have to mention that our expenses here were covered by Fentora for our travel to talk to you today. Ladies and gentlemen, I'm here on behalf of all the loved ones and caregivers of chronic pain sufferers. Specifically, I hope to enlighten you as to the effects chronic pain, and the breakthrough pain in particular, have on those people. I found a definition for breakthrough pain on Wikipedia, and here it is, "Breakthrough pain is pain that comes on suddenly for short periods of time and is not alleviated by the patient's normal pain suppression management."

Breakthrough pain is pain that comes on suddenly as in it comes on

unexpectedly. In other words, it happens at the most inopportune times. It happens while one is doing their day-to-day work. It happens while grocery shopping. It happens in the middle of the night.

Kristen went to school and received a vocational technical degree in machining. She started her own successful business as a machinist doing custom titanium jewelry. When she experienced chronic pain, when she experienced breakthrough pain, it made her work dangerous. She was operating powerful and dangerous equipment, and when she had breakthrough pain it made it so she had to stop work because, otherwise, she would be hurting herself. She might damage herself permanently.

That was before Fentora. After Fentora, she was able to resume full-time work. Fentora allows the pain to be under control quickly, which enables her to function day to day, to shop, to enjoy, to cook dinner,

to sleep at night.

Breakthrough pain is pain that is not alleviated by the patient's normal pain suppression management. For Kristen, that was a variety of medications, including oxycodone. Because her medication did not adequately suppress the breakthrough pain, she did what all chronic pain sufferers do. During breakthrough pain episodes, she increased the dosage of the fastest-acting medication she had available to her to get it under control. In her case, it was oxycodone.

This led to a very terrible cycle. I would see her sitting on the couch in terrible pain. I would plead for her to increase the amount of medication she was taking to get the pain under control. She would often refuse. She hated the way the medication made her feel. She hated the way that it made her less cognizant, less able to think clearly, less able to carry on conversations clearly. So she would choose to

suffer instead. When she did take more medication, she felt lonely and then unable to operate medically. This led to more severe pain episodes because she was constantly cycling back and forth between not taking the medication because she didn't like the effects and taking the medication and suffering the effects of the medication itself. That was the affect of oxycodone.

Another outcome of that was that we had in our house large quantities of oxycodone to handle these episodes. With Fentora, we don't have any. So Fentora broke the cycle. Fentora gets the breakthrough pain under control, which means she doesn't need to fight the losing battle.

The right medication for the right person in the right circumstance is always the best policy, and that's what we're trying to suggest that you do today. It also results in fewer drugs distributed and lower doses taken. Fentora breaks the cycle of suffering for the

chronic pain patient, and it also breaks the suffering that her family and friends feel also. Thank you.

DR. WATKINS: Thank you.

ACTING CHAIR SORIANO: The open public hearing portion of this meeting is now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to the task at hand, and that is careful consideration of the data that has been presented before us, as well as the public comments.

Before we do that, there are a couple of housekeeping items that we need to clear up. Dr. Floyd wants to make a point of clarification in one of the FDA presenter's slides, and the FDA has agreed with this and it will be a brief clarification. And that will be followed by seven questions from the panel that were held back so we could have a timely lunch break. So Dr. Floyd?

DR. FLOYD: Yes. I just wanted to

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provide a clarification to our proposed indication. I believe there's a disconnect in one of the Agency's presentations that we wanted to clarify for post-indication. We are seeking an indication for Fentora as an opioid analgesic indicated for the management of breakthrough pain in patients who are taking around-the-clock opioid medications for their underlying persistent pain. So what is key in this indication is that we are mandating that the patients must be on around-the-clock opioid medications.

ACTING CHAIR SORIANO: Thank you, Dr. Floyd. Now we will continue with questions from the panel. The first one will be from Dr. McLeskey.

DR. MCLESKEY: It wasn't a question. Actually, I was going to make a comment to a question that Dr. Maxwell raised right before we broke for lunch. I was trying to get your attention, but I realized everybody wanted to go to lunch, so I didn't

try very hard. But it was just in response to your comment or question to the sponsor as to why they might have distributed a package insert that was at least not the latest package insert at a conference you recently attended and I just wanted to say from what my understanding is, and the Agency can correct me if my understanding is wrong, my understanding is that when a label change is made, and they're made frequently, depending upon the magnitude of the change and the importance of the change and whether or not patient safety is related to it might determine the speed with which a label actually needs to be replaced in the marketplace. If there's something that's extremely substantiative, then the sponsor may be asked to replace existing package insert materials that are in the marketplace or about to be sold.

Whereas, if it's more of a normal package insert change, in that case the

sponsor is asked to replace the labels but maybe in a little bit more relaxed time frame. And I don't know this to be the case, but I would suspect that probably the latter explains why in a meeting you might have seen a package insert that might not have been the most recent one.

DR. MAXWELL: No. If you'd like to come look at them, the one that should have been in there was the major revision that was approved in October 2007. It was a significant difference.

ACTING CHAIR SORIANO: Dr. Floyd, do you have a response?

DR. FLOYD: Yes. I spoke with Dr. Maxwell during the break, and let me provide clarification. There were two handouts that were issued. One was a manuscript publication by Russ Portenoy, and within that publication there was a replacement of the actual package insert with the latest package insert which was done by the sales reps and it was placed,

so the latest information was included in that. The package in which it was promotional which the pen was included is a third-party vendor packaging, and that's done externally by a third-party vendor. So there was a lag time between our ability to be able to get the final package out and that being presented at the convention or the presentation.

Now, that being said, could we have manually pulled that out? Yes, but that did not occur. So there was a disconnect there.

ACTING CHAIR SORIANO: Okay. I'll take the Chair's prerogative and go ahead with the questions. We'll let this issue go to rest, and maybe you want to discuss it outside the panel setting. Our next question goes to Dr. Anand.

DR. ANAND: Thank you, Dr. Soriano. I wanted to ask a question from Dr. Fine where he had presented the rationale for an indication for breakthrough pain in non-

cancer patients. Given the spread of the standard deviations on those bars, was there any difference in the SF-36 between the chronic non-cancer breakthrough pain patients versus the other conditions that were listed? And I didn't see any bar that relates to cancer patients with breakthrough pain.

DR. FINE: Is the question is is there a meaningful statistical difference?

DR. ANAND: Yes.

DR. FINE: Actually, I don't know precisely. I don't know what the statistics actually are on this.

DR. ANAND: Were we to do this on cancer patients who had breakthrough pain, would they have similar findings as the non-cancer?

DR. FINE: You know, the studies that assessed cancer pain patients did not include this type of data, so I don't have a way of answering. I can give you my clinical impression, which, of course, is that there's

an extraordinarily sort of importance. In fact, we do have one study that we put up on the main screen that actually did look at functional component scores. This is from the cancer trials. It's a different tool. It's not the SF-36, but it looked at activity, mood, walking, working, social, sleep, and enjoyment of life. It comes from a brief inventory and other types of functional outcome assessments showing the difference in patients untreated and then treated with breakthrough pain. It sort of leads me to conclude the same type of clinical outcome.

DR. ANAND: Thank you.

DR. FINE: I'm not sure. It's the same issue. I don't know, actually, going back to this if this was also statistically analyzed or not.

DR. FINE: I had a couple of questions for the sponsor, if I may continue. The FDA had presented some data regarding the theft of more than 8,000 doses of Fentora,

totaling, if I recall correctly, 4.3 grams, etcetera. My concern is once this drug becomes more easily available and more widely prescribed, what is the company going to do to ensure that doesn't happen again?

DR. MESSINA: The clinical trial setting in which this occurred is different than how the drug is necessarily stored in the post-marketing setting. The clinical trial setting is that the drug is at a drug center, a doctor's office, following the various DEA regulation. In the post-marketing setting, it's in a pharmacy, in a locked pharmacy with many other opioids, etcetera. We continue to monitor through our RADARS system and other post-marketing things to ensure that this does not occur and do what we can to provide the education necessary.

DR. ANAND: The other concern that I have is that, although the drug was approved by the FDA for breakthrough pain in cancer patients, yet when the specialists are broken

down it seemed that most of the people who were prescribing this drug are anesthesiologists. So how did that happen? Was the drug marketed to anesthesiologists rather than oncologists, as it should have been?

ACTING CHAIR SORIANO: Please introduce yourself before --

DR. MESSINA: I'm sorry. John Messina from Cephalon. With the approval of Fentora with the cancer indication, the marketing was to individuals skilled in the use of C2 opioids who treat cancer patients, and it was marketed to oncologists, as well, as well as pain specialists and those individuals of those specialties.

DR. ANAND: And then I have one last question. There is a high prevalence of application site events or application site sort of side effects. Those were not described. Could you tell us what were those side effects?

DR. SCHMIDER: That is correct. All these events were grouped together, and I have an un-grouping of these events here for information, so you can see that there's irritation, all local events, irritation of the oral mucosa, pain at the site of the application, or an ulcer occurring, erythema reaction.

DR. MESSINA: With regards to the application site adverse events, when we have analyzed not only the types but the severity, the majority are mild to moderate. They tend to have a very short duration and only two percent of the patients discontinued the trial because of this.

DR. ANAND: Thank you. Those were all my questions.

ACTING CHAIR SORIANO: Dr. Vocci has the next question.

DR. VOCCI: The clinical trials that were described today were all done in opioid tolerant patients, and the risk

management plan also describes the fact that all the patients are going to have to be certified to be opioid tolerant. And, yet, the indication that the company is seeking does not have the words "opioid tolerant" in it. I find that to be a disconnect, and I'd like to hear the company's logic why they wouldn't put that in the indications for use.

DR. RUSSELL: I think there's an oversight. We clearly mean for the patients to be opioid tolerant, and that would be in the indication.

DR. VOCCI: Another question. The people who exhibited what might be aberrant behaviors and said they lost their medication, which is what a lot of substance abuse patients say, or the medication was stolen from them or people who exhibited what you might call misuse or abuse, was there any follow-up with those patients? Did they have a history of any kind of substance abuse? I know the trials stated that you couldn't have

a history going back five years, but was there any follow-up on those patients to see if they had actually had any kind of substance abuse problem even anti-dating the five years?

DR. MESSINA: In between the five years?

DR. VOCCI: No, not in between. Prior to. They couldn't have any kind of substance abuse history apparently five years before enrollment in the trial, but beyond that, in their total medical and psychiatric history, was there any evidence of substance abuse?

DR. MESSINA: In the analysis that we ran with the aberrant behaviors, we looked at those people who did have a history previous five years, five years prior, and we were able to get in this study, and there did not appear to be any increased risk of those individuals actually displaying aberrant behaviors. That was not something that was predictable.

With regards to these things indicating abuse, in some cases that's always a potential. But in this specific situation, we have no information to say that those were definitely abuse. We use these merely as, we did not use these as diagnostic criteria for abuse and addiction. These are aberrant behaviors which are signals usually requiring additional follow up.

ACTING CHAIR SORIANO: Ms. Krivacic?

MS. KRIVACIC: Thank you. I think he just asked the question that I was going to ask.

ACTING CHAIR SORIANO: Thank you. Ms. Aronson?

MS. ARONSON: I'd like to follow up on the question of tolerance and the understanding. Through the sponsor's information, we were given information about the drug acted two hours, and then the recommendation is for four hours. Just

wondering about the sentence in the background information that fentanyl has a profile of pharmacological activities similar to that of morphine but with greater potency and a shorter duration of action. Could you respond to this greater potency and shorter duration of action?

DR. MESSINA: The potency part of that refers to the fact, essentially, that we had dosed this in micrograms versus milligrams of morphine. So because it is more potent, we dose it at lower doses.

With regards to its duration of action, the duration of action is primarily literature based. The information that we would have with Fentora is going to be related to breakthrough pain. Now, breakthrough pain is a fleeting condition. It goes away on its own. So the assessment of duration within this specific clinical condition is somewhat difficult to do given the fact that the pain does go away.

ACTING CHAIR SORIANO: Dr. Lesar?

DR. LESAR: I have two questions related to trying to assess risk/benefit. First of all, it has to do with the fact that the efficacy studies were done versus placebo, which is really not a reflection of reality in real practice. I have a question related to in those studies in those patients was there some assessment or summary of what rescue therapy they were being given and any other assessment than a post hoc, apparently post hoc, questionnaire about the desire, the efficacy of Fentora versus their existing therapy? And that's just to try to, what is the incremental benefit of Fentora to other standard therapies, just like one has to do with assessing potential risks. It has to do with the COVERS program of where it is in terms of development. There's a plan to have it implemented prior to marketing. How would it be assessed? And at assessment, if it's not successful, will the approval not go

forward?

DR. MESSINA: So if I understand your question correctly, the medications for breakthrough pain that patients were using when they came into the study. The two most frequent ones were oxycodone and hydrocodone in the immediate-release formulations, followed by fentanyl and then morphine were the most common ones. But the hydrocodone and oxycodone represented over 70 percent of the patients, so they were the most frequent ones for which that assessment was compared back to. And I'll let Dr. Schmider answer your second question.

DR. SCHMIDER: So the question related to where are we with regard to developing COVERS and what is our intention with regard to the new indication and when do we have it ready for implementation. So as we are currently exploring multiple options still to enroll as many pharmacies as possible within the United States and make it as widely

available to the patients in need, as well as how to deal with cash transactions and hospital settings and hospice settings. These are the things that we still need to work on and need to clarify how we can close the system completely on those.

Our goal is to have it available with the expanded indication. There will be a transition period prior to that where our goal is to enroll all the currently prescribing physicians, approximately 6,000 prescribing physicians, so that they're all registered in the database, as well as give them an opportunity to register the patients that are already on Fentora into the database, as well, so their supply will not be disrupted and they will be treated and get the medication they need.

ACTING CHAIR SORIANO: Dr. Bickel?

DR. BICKEL: Thank you. I have a different question for the sponsor. If I understand correctly from their presentation,