DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANESTHETIC AND LIFE SUPPORT DRUGS

ADVISORY COMMITTEE

Wednesday, September 10, 2003

8:00 a.m.

Holiday Inn Bethesda
Bethesda, Maryland

PARTICIPANTS

Nathaniel P. Katz, M.D., Chair
Johanna Clifford M.S., RN, BSN, Executive Secretary

MEMBERS:

Solomon Aronson, M.D.
Madelyn Kahana, M.D.
Steven L. Shafer, M.D.
Mary Beth Bobek, Pharm.D., Consumer Representative
Vera Bril, M.D.
Bhupinder Saini, M.D.
Carol Rose, M.D.

VOTING CONSULTANTS:

Louis E. Baxter, Sr., M.D., Drug Abuse Subcommittee
Domenic Ciraulo, M.D., Drug Abuse Subcommittee
Stephanie Crawford, Ph.D., M.S., Drug Safety and Risk Management Advisory Committee
John Cush, M.D., Arthritis Advisory Committee
Robert Dworkin, Ph.D.
Jacqueline Gardner, Ph.D., M.P.H., Drug Safety and Risk Management Advisory Committee
Jane Maxwell, Ph.D., Drug Abuse Subcommittee
Gregory Skipper, M.D., F.A.S.M., Drug Abuse Subcommittee
Brian Strom, M.D., M.P.H., Drug Safety and Risk Management Advisory Committee
David J. Wlody, M.D.
James Gillett, Ph.D., Voting Patient Representative:

Charles McLeskey, M.D., Industry Representative

NON-VOTING PARTICIPANTS:
Mary Jeanne Kreek, M.D.
Laura Nagel
Terrance Woodworth, M.D.
Judy Ball, Ph.D.,, M.P.H.
Joe Gfroerer
Arthur G. Lipman, Pharm.D.
Elizabeth Willis, Ed.D.
Deborah Trunzo

FDA STAFF:

Robert J. Meyer, M.D.
John Jenkins, M.D.
Bob Rappaport, M.D.
Sharon Hertz, M.D.
Deborah B. Leiderman, M.D., M.A.
Anne Trontell, M.D., M.P.H.

C O N T E N T S

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. KATZ: Good morning. Once again, this is a meeting of the Anesthetic and Life-Support Drugs Advisory Committee. My name is Nathaniel Katz.

I wanted to make brief opening comments. First of all, in terms of committee discussion and in terms of speaker presentations, the ground rules for today will be the same as yesterday. If anybody around the table feels that they want to direct any questions to anybody just raise your hand and we will recognize you, and those would go through me. Speakers will get a yellow light two minutes before the end of your presentation and then a red light at the very end of your presentation.

There will be some periods of time for discussion this morning. We are going to follow the same schedule as everyone has received and as is out there on the table. There have been no changes to this point in the schedule so we will start out with about a half hour or so to continue some discussion from yesterday, then we will have presentations from our sponsor at 8:45 and the

schedule will continue like that.

Today is nominally a day to discuss the Palladone risk management program, however, there are still general issues from yesterday that need to be discussed so I will try to be clear during the discussion period, and I think the questions are clear enough themselves, as to whether we are talking about general issues on risk management programs or the Palladone program in particular. I have no other general comments. Bob Rappaport or any of the folks from FDA, anything to add? If not, Johanna Clifford will read the conflict of interest statement.

Conflict of Interest Statement

MS. CLIFFORD: Thank you. The following announcement addresses conflict of interest issues with respect to this meeting and is made part of the record to preclude even the appearance of impropriety at this meeting.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their own or their employers' financial interests. All participants have been screened for conflict of interest in the product, competing products and firms that could be

affected by today's discussions.

In accordance with 18 U.S. Code Section 208(b)(3), the Food and Drug Administration has granted waivers to the following individuals because the agency has determined that the need for their services outweighs the potential for a conflict of interest. They include Dr. Nathaniel Katz for consulting on an unrelated matter for the sponsor. He earns less than $10,001 per year. Dr. Robert Dworkin for consulting on unrelated issues for three competitors. He earns less than $10,001 a year from each firm. Dr. Steven Shafer for consulting for a competitor. He earns less than $10,001 per year.

A copy of the waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A-30 of the Parklawn Building.

We would also like to disclose that Dr. Charles McLeskey is participating as a non-voting industry representative, acting on behalf of regulated industry. Dr. McLeskey is an employee of Abbott Laboratories and a shareholder.

In the event the discussions involve any other products or firms not already on the agenda

for which an FDA participants has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon. Thank you.

Committee Discussion

DR. KATZ: Thank you. Now we have about 40 minutes of time to continue our discussion from yesterday. If everybody around the table could return to their list of questions, we will be continuing our discussion of question one which we were able to begin very briefly towards the end of the day yesterday.

I will read the question. Please discuss the role of the potent modified-release opioids in the management of chronic pain. We can just begin a general discussion or continue a general discussion of that issue. Does anybody from the FDA side want to add any clarifying comments to that question, or are you satisfied with beginning a general discussion?

DR. RAPPAPORT: Why don't we just begin with a general discussion and if we feel the need to jump in, we will?

DR. KATZ: We are open for comments. Yes, please, Dr. Rose?

DR. ROSE: Yesterday you had asked several questions about certain types of patients, certain patients at high risk for adverse events, etc. and I wanted to put my two cents in on that.

I felt that when you talk about types of patients we should also talk about the physician doing the prescribing who needs to identify and document, if necessary of patients who in the past, when they have cared for them, have been unreliable and non-compliant. I think that is the issue. Cases that I have seen can kind of tell you in advance that these patients are going to have problems with the type of drug that we are talking about today. So, I think it is very important for the physician to actually evaluate the patient for their reliability. That was one issue that I wanted to make a comment on.

Then the other, when you are going to say about the duration of treatment--you are going to be getting to that, I know--in the past there have

been issues of putting a time limit on certain types of care that we give to patients who are considered to be terminally ill. There is, for example, the issue that hospice is only for patients who you expect not to live more than six months but, as was mentioned yesterday, many times if you appropriately treat a terminally ill patient you can actually extend their life and make their life more comfortable for whatever time they have left. So, I do think it might be inappropriate to put a time limit or to say if you don't expect the patient to live more than a certain period of time that this patient is a candidate for this drug and not otherwise. So, I don't think that we should put a time limit for terminally ill patients.

DR. KATZ: Thank you. So, if I take your two points, you are suggesting that, number one, in assessing the appropriateness of long-term therapy one factor is assessing the likelihood of patient compliance with that therapy.

DR. ROSE: Correct.

DR. KATZ: One element in that assessment is history of compliance or non-compliance.

DR. ROSE: Thank you.

DR. KATZ: Then, the second point that you

are suggesting is that in the course of appropriate medical practice artificial limitations on the duration of therapy are not part of normal medical practice with opioids.

DR. ROSE: That is correct.

DR. KATZ: Other comments? Yes, Dr. Baxter?

DR. BAXTER: Thank you very much. I am glad to see that on my first attempt today I am in, not that I am still thinking about yesterday--

DR. KATZ: God forbid!

[Laughter]

DR. BAXTER: But I think that it is important from an addiction standpoint that part of the appropriateness that should be considered by physicians if in fact, number one, that there is a history of addiction or use disorder and, number two, what is the current status of that medical problem. It is my belief, and the belief of many addiction specialists, that people who have histories of addiction are not automatically excluded from use and benefit of opiate medication, but it is very important to be able to ascertain that person's recovery status.

DR. KATZ: That is very helpful. So,

again, you are suggesting that an addiction history should be a standard element and in good practice is a standard element of assessing a patient for the appropriateness of opioid therapy. I wonder if you could expand on that and maybe give us a little bit more information on what physicians do to get an addiction history and the accuracy of those office-based methods in obtaining an adequate addiction history.

DR. BAXTER: The first thing is that the questions have to be asked. Unfortunately, I know that many times an addiction history is not taken. So, one would minimally need to ask if, in fact, a person has ever had any problems with drugs and/or alcohol. If the answer is yes, well, then further information needs to be gathered in terms of what substance was the drug of choice; what measures in terms of treatment were employed; and what the person's current recovery status is.

DR. KATZ: What if the answer is no?

DR. BAXTER: Well, then you have to figure out how far you really want to go with that line of questioning. As an addiction specialist, of course, you know that I would go much further but I think that in terms of primary care or general

practitioners who, we all know, prescribe a lot of these medications we have to at least get them to start asking questions.

DR. KATZ: Thank you. Dr. Dworkin?

DR. DWORKIN: I have a question about the question. The question seems to emphasize the word "potent" and I don't think we have discussed that. Given a range of potency in the available modified-release opioids is the potency, meaning the milligrams needed for an equianalgesic dose, relevant in any way at all or not to clinical practice of these modified-release opioids. So, I guess my question is about have we really discussed potency variability among these drugs? And, I don't think we have, and should.

DR. KATZ: So, are you asking the question about whether the word "potent" changes the answer here?

DR. DWORKIN: Yes, whether the potency of the drug change has any impact on the answer.

DR. KATZ: Or, are we just really discussing about opioid therapy in general? Well, that is a question and that is open for commentary. Is the standard of practice different for opioids depending on their potency? Dr. Saini and then Dr.

Shafer?

DR. SAINI: I think the WHO letter was made on an arbitrary basis. There is really no difference between a weak opiate and a strong opiate. You can give enough of a weak opiate and get the same effect as compared to giving a smaller amount of a stronger opiate. So, the main question is should the opiates be used in pain. And, the answer is, yes, if appropriately used they are the gold standard for moderate to severe pain while NSAIDs should be used to control mild to moderate pain.

Having said that, the risk of addiction should be assessed and at the same time the adverse effects of narcotics should be assessed also as the therapy is going on. While you are assessing these risks, when you see these drug addicts nobody will divulge a history that they have been in a drug rehab program. It is usually later on that you find that these people have been in a drug rehab program and you have problems. So, assessing the history and if they are prone to becoming an addict is important. Family history of drug dependency, history of anxiety, depression, psychiatric disorder and previous history of drug abuse makes

them more prone to become a drug addict.

DR. KATZ: Thank you. Dr. Saini, your answer to Dr. Dworkin is no. You are saying that the word "potent" could just as easily be taken out of this question and that the standards of care and medical practice are the same for all opiates, regardless of their potency or their release. Am I understanding you correctly?

DR. SAINI: That is correct.

DR. KATZ: Dr. Shafer?

DR. SHAFER: Dr. Dworkin's question is a good one. I think it relates to the fact that there are two definitions of potency that are used. To the lay public potent just means strong and the strength has two components. One, from a pharmacological perspective, is the concentration associated with 30 percent maximum drug effect, which is the definition you are thinking of, and that is absolutely irrelevant to the utility of the drug provided you don't have to eat, you know, bricks of the stuff to get a drug effect. The other is the intrinsic efficacy, the maximum effect the drug can produce, and all of the full mu agonists are thought to pretty much go to the same maximum drug effect.

From a pharmacologic perspective, I think what we are talking about is the full mu agonists. If we want to be true to what we are talking about here pharmacologically, we should perhaps talk about full mu agonists and leave potency out of it. I think potency is being used in a colloquial sense.

DR. KATZ: So, your answer is also no to Dr. Dworkin?

DR. SHAFER: Yes.

DR. DWORKIN: Can we ask the Division whether potency is being used in a colloquial sense or in a pharmacologic sense in this question?

DR. KATZ: Yes, you can.

DR. DWORKIN: Thank you.

DR. RAPPAPORT: Thank you. This question refers to the use of the high dosage, extended-release opiate products that are under discussion as a general topic of the meeting.

DR. KATZ: Maybe I can clarify that. Correct me if I am wrong, I think the question was worded this way because that is what we are here to meet about and it doesn't in any way mean to exclude other forms of opioids or get into the issue of whether the practice standards might be

different. Is that fair enough?

DR. RAPPAPORT: Yes, although we would like to have some focus on that particular group of drugs as it applies to this meeting and also as it applies today to the ensuing discussion of Palladone.

DR. KATZ: Yes, I think what we are hearing, so far anyway, from the group is that the practicing patterns and standards are the same regardless whether the opioid is more or less potent or modified release or not modified release, if I am hearing the committee correctly. Does anybody think I am hearing wrong? Dr. Bril?

DR. BRIL: My comment was more in the form of a question to individuals running pain clinics; as I say, I run a more general clinic. This applies to opiate therapy and disclosure with the patient and exactly how the therapy is phrased to the patient. I think it is important, in chronic pain particularly, that the patient really be aware of the class of drug they are taking. I mean, opiate may mean a lot to us and so may pain killer but to the patient I think even being very blunt and telling them they are taking a narcotic, with all the implications that has, is something that

may be considered because a lot of patients won't really know what you mean if you just say opiate and if you say pain killer, there are so many it is a non-specific term.

So, for me, when I start a patient on this, because there is no definitive way that I have of knowing who would be addicted, if I select the patient and think that they are safe candidates for this kind of therapy I do warn them about the class of drug I am using with them. I just think that caution and full disclosure in a way that patients will truly understand are necessary.

DR. KATZ: So, you are suggesting that in prescribing these medications to patients, just calling them pain killers without being more specific about their class and their potential risk is not sufficient.

DR. BRIL: True. I mean, a nonsteroidal is a pain killer, or aspirin is a pain killer if we use it in certain ways, which are quite different from opiates. And, using the word opiate isn't necessarily enough either, although you might think it is.

DR. LEIDERMAN: First a comment and then a question. I think that it is important when we

talk about pharmacologic potency to think about the multitude of effects that drugs have, and equianalgesia does not necessarily equate to equal effects in terms of psychic effect, euphorigenesis, reinforcing effects. We will come back to that with some data to be presented later this morning, but that is a part of the very complex concept of potency and I think that that is part of what we mean.

The question part, I would ask the pain doctors here, I mean, do you prescribe Dilaudid in the same way that you prescribe a codeine 30 mg? I would suggest not and it doesn't have to do just with the different dosage strengths available. So, that is sort of my comment.

My question is about something touched upon yesterday that I would like to have a little bit more input on. What does the committee think is the role of physician-patient care contracts in the context of chronic, non-malignant pain treatment with high dose opiates?

DR. KATZ: Let's leave that question in the air. I want to make sure that I am not missing people who are on line for comments. Dr. Gillett, you are next.

DR. GILLETT: When you are a layman this whole business of indication is a very difficult proposition. After you have questioned your patient and discussed their addiction, what choices do you have? Do you withhold from a patient who has gotten squamous cell carcinoma as a consequence of alcoholism? You are going to withhold a pain killer like one of these medications during radiation therapy when they elect not to have surgery because their physician had a TV show and testified in court about drug addiction and alcohol and drug-driving cases? In other words, a friend of ours down in Greenville, South Carolina is faced with this and he receives OxyContin.

DR. KATZ: It sounds like you are agreeing with Dr. Baxter that one needs to do a risk assessment and that some patients may be at higher risk for complications, but that doesn't necessarily equate with withholding therapy. Maybe what we will get to in some point of our discussion is, well, what does that equate to? What does one do in that situation? Let's see, Dr. Skipper, you were next.

DR. SKIPPER: Because we are here primarily, in my view, to talk about the risk of

these drugs and the primary risk that we are concerned about is the spiking epidemic abuse and the recruitment of new addicts who take these drugs, some of whom die from overdose, going back to the end of the day yesterday when you asked about mild, moderate or severe and I was looking toward possibly encouraging a change in that terminology, which I have now decided maybe to give up on, I would subsequently like to see more of a move toward restricting the use for severe pain, if we define severe pain as significant impairment of function, because I think we need to decrease the amount of these drugs on the market because that will decrease the epidemic of abuse.

DR. KATZ: Won't you expand then on how you would propose implementing that sort of an approach?

DR. SKIPPER: Well, I would suggest that the package insert say that these drugs, these potent extended- release opioids be used for severe pain, and then define severe pain as significant decrease in function associated with pain.

DR. KATZ: Of course, we have an ambiguity because most practitioners/researchers use the term mild, moderate and severe as a measure of pain

intensity on some sort of scale, so you would introduce the term but then redefine it in a way different from its customary use, focusing more on impact. But I still would, you know, be interested in hearing you expand more on this notion of impact on function as being a marker of the importance of the disease to the patient and the importance of treating it aggressively.

DR. SKIPPER: Well, as I said yesterday, I think the way we monitor whether these drugs are effective is by looking to see if function improves. If function is not impaired, then I am not sure they should be used. So, I would like to see movement towards some kind of policy that function be assessed. Because that was not received well, then I am thinking that to redefine mild, moderate and severe so that that it be associated with significant decrease in function may restrict to some degree the use of these, which would decrease the problem of substance abuse.

DR. KATZ: So, just to clarify what you are saying, it sounds like--correct me if I am wrong--is that even somebody whose pain intensity level was rated using the word moderate but, yet, that pain still had an impact on that patient's

ability to function they would be a candidate for opiate therapy in your mind because they would be reclassified as severe based on your impact definition.

DR. SKIPPER: I guess that is correct.

DR. KATZ: Thank you. Dr. Ciraulo, you were next.

DR. CIRAULO: Yes, Dr. Leiderman had addressed some of the issues that I wanted to raise but I wanted to go back to the issue of potency. I think that what we are really talking about is abuse, liability and concerns about that and I think that, yes, it is correct that most of the drugs we are talking about are full mu agonists. We also have to think about the pharmacokinetics of these drugs. If you look at abuse liability across substances of abuse, you know the drugs that are more rapidly absorbed and reach higher peaks are subject to greater abuse liability.

I think there are differences among the opioids. Certainly, in the days when I did physician management of addicted physicians there were patterns. There were certain drugs that were preferred, and I think they correspond with a lot of the PK of the full mu agonists and I think we

have to keep that in mind as we look at the data.

I just wanted to add that I certainly support the use of these drugs in recovered substance abusers. I think you should do an assessment. You will make mistakes. I want to emphasize that when mistakes are made people should not be prosecuted for these mistakes; this is going to be part of the practice, but denying substance abusers who are in stable recovery adequate pain management is inappropriate.

DR. KATZ: So, you are then joining those who have said that while risk assessment, including a substance abuse history, is important. That doesn't mean that the patient should necessarily be excluded from opioid therapy as a result of that assessment. So, what are the implications then for the use of opioids in such patients? If we are taking their history and identifying their risk level are there any implications for management?

DR. CIRAULO: Yes, definitely. I think you have to step up surveillance. I realize that this would be a problem in some rural areas, and I don't work in a rural area so I don't have specific suggestions for that, but in areas where there are specialists I think with more frequent visits, good

contact with pharmacy, single-source prescribing, and a lot of the things that we can do to monitor we can build in good surveillance programs so that even if a substance abuser does end up having any problems initially, I think it is inappropriate to say, "okay, you're out." I think there should be an algorithm to step up the surveillance.

DR. KATZ: So, you are saying that patients who are identified as being at higher risk, even if they are prescribed opioid therapy, need to be prescribed it in a different sort of program than somebody without those red flags for risk.

DR. CIRAULO: Exactly. What we have done in the past--and I am not saying we want to do this in the future but in the past we have put such patients in methadone clinics. I am not sure I would do that now; I think there are better ways to do it.

DR. KATZ: Thank you. Next was Dr. Strom.

DR. STROM: A couple of related comments. I am a general internist; I am not a pain expert and I certainly have no problem with the clinical recommendations I am hearing and referring my pain patients to colleagues. But as an epidemiologist,

my role is to be a curmudgeon, and part of my concern about what I am hearing is that I would ask my fellow committee members to differentiate when what you are saying is based on data versus when it is based on opinion. It is not clear to me virtually any of this is based on data and I think it is important we make that clear when we give this advice to FDA because FDA is a science-based agency and needs to make its decisions according to that, and that ranges from clinical recommendations to recommendations about risk assessment to try to predict addiction and thinking we really have the ability to do that to recommendations about even restricting use and that that would in any way affect the amount of addiction in society. I am not sure we have heard the data to underlie any of that.

DR. KATZ: Thank you. I think that is a very important point and I want to get back to it but first Dr. Jenkins.

DR. JENKINS: I would like to offer the committee some clarification on what the intent was of this question because I think you are verging into a much more general discussion about the role of opioids in treatment of pain. We were really

focused on what is the role of sustained- release or modified-release opioids in the treatment of chronic pain. There have been some, for example, who have argued that these products are simply convenient dosage forms and, therefore, the abuse liability and the abuse potential and the actual abuse we have seen negates the value of these products to the patients. So, our focus of this question was not to get into a general discussion of when should you use opioids in the treatment of chronic pain. It was more to ask you to talk to us about the role of sustained- or modified-release opioids in the treatment of chronic pain. So, hopefully, that can help you focus your discussion so that we can get back from you all that we are looking for.

DR. KATZ: Thank you for that clarification. Let's then look at the discussion in a different way and open up the floor for comments on the particular role of modified-release opioids in the opioid management of patients with chronic pain.

Actually, as long as we are pausing for a moment, Dr. Leiderman did put this question in the air about the use of patient care agreements. So,

in light of this refocused discussion, does anybody have any comments on patient care agreements? Go ahead, Dr. Rose.

DR. ROSE: I get to look at liability insurance claims and sometimes I see anesthesiologists or other physicians who have had problems where there are not contracts. I can see situations where had this physician used a contract and insisted that the patient comply we wouldn't have the problems. I am very much in favor of physician and patient contracts.

DR. KATZ: For medical-legal reasons, it sounds like you are saying.

DR. ROSE: Yes, for medical-legal reasons and also I think it helps the physician to help the patient. I think that contracts are very, very important.

I would like to make a comment about this issue of the concept of sustained release. The concept of sustained release I think is great. If we were talking about a drug for sustained-release management of hypertension I think all of us around the table would think that is great because if you want someone to take a pill four times a day to manage their hypertension, that is a problem

because it is just hard to do. The issue here is sustained release for opioids, and then the reason why we are looking at that in a more focused way is because of the problem of abuse and inappropriate use of the drugs. So, I think that really our focus needs to be on how can we handle that abuse because underlying it all I think most of us would agree that sustained release anything is a good idea because it helps in better patient care.

DR. KATZ: Dr. Kahana?

DR. KAHANA: I would like to reiterate from a non-epidemiologist what Dr. Strom had said because I feel like I am in a very awkward position of trying to come up with recommendations with remarkably little real data. I guess the question I would have is would we be better off trying to define the patients who are not good candidates for these drugs rather than the ones who are, and to define a subset of patients who might be better off referred to people who are specialists, either by direct referral or by telecommunication. We certainly have the ability to encompass an enormous geographic area with expertise, if not by direct patient contact at least by telecommunication with someone who is an expert. Could we not provide a

mapping system for people who would have the ability to access the experts in this kind of drug dispensing? Because the restriction of this class of drugs to those who really have chronic and sustained pain, malignant or non-malignant in its origin, I think would be a real serious error based on at least the data we have seen, which would lead me to believe that 50 percent of perioperative patients are getting the sustained-release preparations which, I must say, I am a little skeptical to believe. So, even the data I think we have seen is questionable at best.

DR. KATZ: Yes, Dr. Ciraulo?

DR. CIRAULO: Since you have redirected that, I would like to re-approach the issue of the addicted patient. I have two comments and questions. One is if we believe--and this is a question--if we believe that these drugs, these long-term and immediate-release drugs are different in their abuse liability, if we say the drugs we are evaluating have higher abuse liability, would the pain people feel comfortable saying that this would not be a first-line drug for pain management in someone with a history of substance abuse? That is part one.

The second part is if you use these drugs, do the pain experts have an idea of what the risk is of creating a new addict in the patients they treat?

DR. KATZ: That was a complicated question and comment but it sounded like the first part of it was sort of a question about whether the modified strong-release opioids have a higher abuse liability than the immediate-release opioids. Was that the first part?

DR. CIRAULO: Yes, the extended release, for example, can be chewed and has a very high abuse liability. It wouldn't be a drug that I would be inclined to prescribe for someone with an addiction history.

DR. KATZ: So, maybe the first part of your question or statement is worth discussing, which is whether the modified-release opioids have a higher abuse liability or risk of harm should they be abused, or something like that. If so, does that imply some differentiation in how they should be used? You are suggesting perhaps in high risk patients that is one area of differentiation and maybe there are other areas of differentiation as well, but it seems like in either case it hinges

on the notion of whether these medications do have a higher abuse risk than the immediate-release dosage forms.

DR. CIRAULO: Yes.

DR. KATZ: Maybe we should discuss that. That seems to be a relevant issue to the current question. Do people have comments on whether these modified-release dosage forms have a higher abuse risk than the immediate- release forms? Dr. Maxwell?

DR. MAXWELL: Well, yesterday we had a significant amount of data presented showing increases in the emergency room episodes and treatment admissions with the introduction now at least of OxyContin. I think some of these increases are due to that.

What we haven't talked about, which concerns me, is not the pain patient who, I agree, needs the medication but the unintended consequence of creating another pool of patients who are addicted drug users who previously were not addicted until they used OxyContin. So, I think we need to look at what are the unintended consequences. It is not just a new and better medication for patients who need it, but we have

created a whole new population of users and we are paying the cost because we are now having to provide drug treatment to this group. So, there is another aspect to this.

DR. KATZ: So, there is one question in the air, which is are these modified-release forms a higher abuse risk than the other forms? You have also echoed another of Dr. Ciraulo's questions, which is what is the incidence of creating new patients with the disease of addiction based on therapeutic exposure to these drugs? I think both of you were asking that question and implying that these are important things we need to know in order to create appropriate standards of practice. Dr. Strom?

DR. STROM: I think it is important, looking at the data that we saw yesterday, that we realize that almost all of it was numerator data. We saw a lot of increased abuse, illness, admissions and so on, but the denominator data were increasing equally dramatically. There was also a lot of increased use of these sustained-release drugs and it is not at all clear to me from the data that we saw that that indicates a higher abuse potential. In fact, OxyContin represents a very

small proportion of all of the abuse that is out there. So, it is important to look not just at the numerator data but also denominator data before drawing any conclusions.

DR. KATZ: Dr. Dworkin?

DR. DWORKIN: It seems to me there is another way of addressing Dr. Jenkins' question in relation to whether the modified-release opioids are associated with greater abuse liability, and that is whether there are any data in head-to-head comparisons of modified release with immediate release to suggest a benefit on any endpoint of the modified release.

I have been perseverating on that issue because I don't know, other than a kind of broad overview of the data, the real results. It seems to me those must be incredibly difficult studies to do because if you do it in a double-dummy way you lose the convenience of the modified release because every patient is taking both drugs p.r.n. or q.i.d., and if you don't do it in a double-dummy way and patients and investigators know whether they are doing b.i.d. dosing or q4 or q6 dosing, it is not a double-blind trial. But it seems to me that that would be a very important set of data to

know about, if it exists, and if we could get over these methodological issues because I hear your question as asking are there any benefits in the literature of modified release versus what we had before in 1995. And, I just don't know the answer to this question but I despair that the studies can be designed in a way to really answer it.

DR. KATZ: So, you are asking yet a third question which we are getting on the table. We are getting all these questions and no answers from this committee. But your third question is what is the evidence base for the benefit of the modified-release opiates over immediate-release opiates. Dr. Shafer?

DR. SHAFER: Thank you. Let me just read here from Jim Zackney, "Drug and Alcohol Dependence," 2003, this is a consensus statement from the College on Problems of Drug Dependence: At present, it is almost impossible to separate the risk of abuse from the therapeutic action of opioids. So, hopefully, there is one answer.

By the way, I put the same question to Art Lipman yesterday, is there any difference between the therapeutic action in terms of potency and abuse potential, and he also said absolutely not.

So, the answer to that question by two people who are quite expert and publish here is, no, there is no difference in abuse potential related to the molecule per se. Now, there may be differences in prescribing patterns, variability and things like this and, you know, street fads but the pharmacologic answer appears to be no.

DR. KATZ: As you said though, that doesn't really get to the question of if there are any differences in the abuse liability of the modified, high potency formulations we are talking about. It is the molecule part of the question that that seems to be addressing.

DR. SHAFER: Interestingly, as you pointed out, people have associated rapid blood-brain equilibration with abuse potential. People like the sense of giving a drug and, whoosh--you know, you are high immediately. I infer from what I have read about these drugs that they are intended to get around that, to not have this rapid onset. Actually, they have lower abuse potential. The fact that these drugs appear to have been abused more is in line with their overall properties rather than their pharmacokinetic profile suggests, that there is no difference one way or the other.

Certainly, the benefit that was envisioned for slow onset was not appreciated.

DR. KATZ: It is time for our sponsor presentation but just for me to wrap up our collective wisdom for the moment, it seems that in attempting to discuss the role of modified-release opioids as distinct from other opioids at the moment we have basically three questions on the table and we have constant pressure, as we should, to make sure that our answers are evidence based or at least that we should understand the difference.

One question is whether the modified-release opioids have higher abuse risk, abuse liability, and I am deliberately being vague about what term I use, than the other opioids and that seems to be still a question on the table which, hopefully, we can get back to later.

The second question is what is the incidence of new addictions based on medical exposure to these medications, and that remains a question.

The third is an even larger question perhaps, which is what is the benefit of these medications over previous forms and what is the evidence base underlying the notion that there is a

benefit?

Those are questions that the committee has not gotten to trying to answer yet. Any FDA comments prior to moving on to the sponsor presentation?

[No response]

Well, our first presentation then, if everybody is ready, will be from Dr. David Haddox who will be speaking with us on Palladone capsules for the management of persistent moderate to severe pain in opioid-tolerant patients. Dr. Haddox is a long-standing contributor to this field and is currently vice president of health policy at Purdue Pharma L.P.

Sponsor Presentation

Palladone Capsules for the Management of Persistent Moderate to Severe Pain in Opioid-Tolerant Patients

DR. HADDOX: Thank you very much, Mr. Chairman. Members of the committee, the members of the agency who are here, thank you for the opportunity to address you this morning.

[Slide]

I want to go over some of the highlights of our risk management program for Palladone capsules and sort of bring to focus some of the

issues that are in your briefing document. It will come as no surprise, given the discussion yesterday, that we, at Purdue, believe that we have some considerable experience in risk management with modified- release opioids and I would like to share how our thinking is evolving there.

[Slide]

The speakers in this one-hour session will be myself, Dr. Sidney Schnoll, who is a noted addiction expert and researcher, and Dr. Herbert Kleber, who is also a noted expert in substance abuse treatment and research and is also the former deputy director for Demand Reduction in the White House Office of National Drug Control Policy.

For those of you who don't know me, just a moment about myself. As you can see, I started out my professional life as a dentist. I then went to medical school. I have done combined residency in anesthesiology and psychiatry with the idea of becoming a pain physician. I have also received certification in addiction medicine along the way.

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In addition to the three speakers, we have three of our consultants with us, Dr. Theodore Cicero, who is vice-chancellor for research at

Washington University and one of the principal investigators in our signal detection component; Dr. James Inciardi, from the University of Delaware, also a principal investigator on another component study; and Dr. Richard Dart, from the University of Colorado and the Rocky Mountain Poison Control and Drug Center, who was another principal investigator.

[Slide]

You have been exposed to a lot of material. I heard some comments during the discussion yesterday that it seems to be somewhat overwhelming; I hope you have had your coffee this morning. I will try to pace you through this and, hopefully, keep things on track.

I am going to make a few introductory comments and then I am going to briefly review Palladone capsules as a specific drug product for you, then go through the risk management program, highlighting our goals and objectives, some of the elements, and giving you some examples of some of the tools that we are using. Then Dr. Schnoll will talk to you in some detail about the surveillance component, the RADARS system and, finally, Dr. Kleber will end with his observations from his

35-plus years of drug abuse treatment and drug control policy, and make some observations for you.

[Slide]

Our position on risk management programs for opioid analgesics is that, first and foremost, they must protect patients. We must try to mitigate the risk of using these medications in the specified population for the specified indication. We must always balance the legitimate needs of patients against the risks posed to abusers.

We believe that risk management programs are needed for all opioid analgesics. We believe that they must be consistent within a schedule of the controlled Substances Act. That is, Schedule II risk management programs should have certain common elements and Schedule III programs should have certain common elements.

It is extremely important in contemplating this, given the environment into which new opioid analgesics will be introduced, that we think about three distinct populations, patients who have a need for and deserve good pain care; abusers who need to be prevented, if at all possible, before they become abusers and certainly need treatment once they become abusers; and criminals who prey on

the abusers who need to be stopped.

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We further believe that no single group can implement an effective risk management program for opioid analgesics that addresses all three populations. This is a shared responsibility that requires a multifaceted effort of coordination, cooperation and consistency from industry, from regulators at the federal level and also at the state level as in licensing boards, and all the other stakeholders here. Part of what I would like to do in the presentation is show you how we have worked thus far with our ongoing risk management program with some of these various stakeholders.

[Slide]

Now let me briefly review for you Palladone capsules.

[Slide]

You have heard the discussion today and yesterday that oral opioid analgesics are an effective therapy for appropriately selected patients; that modified-release opioids have been proven safe and effective in those patients. However, due to variability of response to opioids and the need for individualized treatment

strategies, healthcare professionals need a variety of opioid formulations.

[Slide]

Palladone capsules, in our approvable letter of September, 2002, were deemed to be safe and effective by the agency. They contain lots of little hard pellets, each of which has hydromorphone hydrochloride embedded in an extended release matrix. That is, if you pull a capsule apart and these little pellets fall out, each of those is its own extended release delivery system, in contradistinction to OxyContin for instance.

Hydromorphone is a full mu agonist with reported equianalgesic potency compared to morphine, ranging from 1:3 to 1:10 by the oral route. There is a great deal of variability. It is formulated for once-a-day administration and it is going to be launched in a variety of strengths to allow easy titration for the physicians.

[Slide]

The benefits of Palladone capsules provide the healthcare professionals with an important therapeutic option. It will be the only extended-release hydromorphone in this country. The once-a-day administration is for the

convenience and compliance, for instance, the elderly patient who might have difficulty remembering when to take medications and needs, like my mother, to have my sister call her and say, "hey, mom, did you take your medicines this morning?" For analgesia she just needs that one phone call.

It provides a choice among extended-release opioids. You have heard some comments today and pain clinicians on the committee know that when we are treating patients, as I did for much of my professional life, not everyone responds to everything the same way. We need to have a large pallet at our disposal to make sure that we can optimize care for a given individual.

The contents--as I mentioned before, the capsules can be pulled apart and the contents, little pellets, can be sprinkled on soft food. Think of the advantage in the case of a person with swallowing difficulty, a person with scleroderma for instance, or a person with esophageal stricture or radiation results from head and neck surgery, this is going to be a real advantage for these people.

And, it may just simply be the best choice

for some patients, as was validated in our clinical trials where we had a number of reports from the investigators saying that this was really the right drug for that patient.

There is less fluctuation in blood levels compared to immediate-release hydromorphone and I will show you a PK slide.

There is no food of pH effect, which is a distinct benefit. We have studied this in cancer and non-cancer pain in doses ranging from 12 to 500 mg/day.

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At steady state Palladone, which is in the yellow here, compared to the equivalent daily dose of immediate- release hydromorphone given, of course, several times a day, you see lower peak-to-trough variability, essentially a smoother curve as one would expect from a modified-release formulation.

[Slide]

I now want to talk about the risk management program itself. It is important again to remember the thesis, that we want to have the benefits for the intended patient population for the intended indication balanced against the risks

not only for the intended population but also for these unintended populations.

You will also notice as I go through this, keeping in mind those three groups, patients, abusers and criminals, that there are Palladone-specific elements to this risk management program even though there are also common elements with our OxyContin risk management program because the common elements are to address the abusers and the criminals because these are system-wide problems; they are not limited to a single drug or formulation. The Palladone-specific elements are to address the intended population for this particular formulation.

[Slide]

As was mentioned yesterday, Research!America has come up with a pool very recently showing that despite the fact that we are in the congressionally determined decade of pain control and research, if you look systematically at the surveys of pain prevalence, particularly under-treatment of pain in this country, not much has changed in the last 15 years. Yet, while Palladone will be one of the tools to help meet this need in appropriately selected patients, it

will be entering into an environment that we have already heard a lot about yesterday.

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These are the number of new or first time non-medical users of pain medicines. You can see here that from 1980, just in five-year increments, there was a significant problem in the '80s, that the problem doubled between '90 and '95 and doubled again between '95 and 2000.

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It is also known from these data that, if you look, there is not one single opioid that seems to be the problem, or even one single formulation of the branded hydrocodones compared to other hydrocodones.

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It is also critical, when you are looking at these data in your briefing document, to make sure that you follow the somewhat peculiar or at least particular way that these data are presented and that lifetime prevalence is in response to the question "have you ever, even once in your lifetime used a drug that was not indicated for you or wasn't prescribed for you or for the feeling it caused?" "Past year" gives you an example of sort

of point prevalence over a year and "past month" is defined or is thought to be the proxy for current use. So, these are very different figures and I just want to call that to your attention because it is easy to get lost in these data.

[Slide]

As part of our risk management program, in addition to reviewing these various surveys, we have also done some analysis where we asked for specific data runs. I just want to share with you this analysis looking at the people who admitted to any lifetime non-medical use of hydromorphone compared to those who said, "no, I've never non-medically used hydromorphone."

What you see here on three parameters over three years, '99 to 2001, is the percent using multiple prescription analgesics non-medically--and multiple means two or more--is about twice that in the group who admit to non-medical use of hydromorphone than those who do not admit to that use. Likewise, the percent using cocaine or heroin is about twice as many. If you look at the percent using needles, it is about 12 times as many people who say that they have any lifetime use of hydromorphone admit to needle use as opposed to

those who do not have any lifetime use of hydromorphone.

I believe that this is describing a distinct population that is very different from the patients that most of us are treating in a pain setting. These are people that are hard core drug abusers.

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Let's talk about the pharmacological considerations for abuse liability of hydromorphone. When you look at the pharmacological profile, the propensity to induce tolerance, the propensity to develop physical dependence, it looks like morphine. When you look at the human and animal abuse liability studies, hydromorphone looks like morphine. There is no evidence in the scientific literature of differential abuse liability among full mu agonists and potency. As has been discussed this morning and a little bit yesterday, it is really irrelevant to abuse liability because the abuser will take the dose that they want, whether they take a little or whether they take a lot.

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Specifically hydromorphone abuse

liability, if you look in patients there is really no evidence in the literature of differential abuse liability compared to other full mu agonists. If you look in the abusing population there is no evidence of greater abuse liability compared with morphine. In fact, Preston and Jasinski, in a 1991 review article of this literature, stated "in all of the studies the profile of subjective effects of hydromorphone were similar to those previously reported for morphine." Of course, hydromorphone is a full mu agonist and in the abuse setting has all the risks of abusing any other full mu agonist, especially the risk of overdose and particularly when the abuse involved multiple drugs.

When studying drug abuse deaths it is imperative to remember the caveat in the DAWN medical examiner's report that states "when multiple drugs are involved in a single case, the cause of death cannot be attributed to any particular substance."

As our recent study in the Journal of Analytic Toxicology earlier this year showed, in 919 drug abuse deaths where oxycodone was detected, 96.7 of them involved multiple drugs, with a mean of 4.5 drugs of use per decedent and a range of

1-14 drugs.

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These data are combined from two separate studies that we have done. One was an intravenous study and one was oral immediate-release hydromorphone single dose versus Palladone single dose. For the immediate release study, I want to call your attention to this, this part of the curve is missing. That is because in this particular study design, because of what we were looking for, the data point was at 30 minutes so, obviously, this peak was much higher in the first few minutes but that is why the data point starts right there. This is the immediate-release and this is the extended-release hydromorphone.

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In the risk management program our goals are basically three: to ensure proper use, that is the patient population; to reduce abuse in the abusers and potential abusers; and to minimize diversion and the attendant criminal activities that go along with that.

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I would like to review for you the objectives of each of those goals. To ensure

proper use, proper patient selection is one of the key objectives. We want to make sure that physicians know who is right for this drug and who is not. Once they have made the selection, we also want to know that they actually know how to use the drug, and we want to make sure that they know how to prevent unintentional exposure.

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As far as reducing abuse, we are involved in a number of community-based interventions, which I will share with you, and healthcare professional education. We need to make sure that our healthcare colleagues understand the signs, symptoms and indicators of abuse and how to assess for abuse before putting a person on this medication.

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To minimize diversion we are supporting law enforcement in some ways that I will give you some examples of. We have a very active supply chain integrity program to ensure that the program integrity is what is supposed to be as it leaves us and goes to the distributor. Again, healthcare education to help the healthcare individuals who are prescribing and dispensing these medicines

understand what the criminal element is up to so that they can, hopefully, not fall victim to the scams.

[Slide]

These are some of the key elements of the risk management program. You have heard about Schedule II restrictions. I have mentioned briefly the supply chain integrity. Because this is a public hearing I don't want to talk in any more detail about that because I really don't want to tell people how to try and compromise our supply chain integrity.

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So, let's focus on communication of key safety messages. There are a number of things that I want to highlight for you in this regard--

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--the package insert for the prescriber or dispenser, the patient package insert for the patient or caregiver, medical communications that are outside the package insert and our promotional activities.

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Let's focus on the proposed package insert. These are some of the key elements in it.

Again, in the interest of time I am just going to highlight three. You heard about the CII designation yesterday; you know what that involves. I want to walk you through the boxed warning that we have proposed to the agency because I think this is the first thing the practitioner is going to see; this will be in the ads, etc.

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Palladone, or hydromorphone hydrochloride extended-release, capsules are indicated for the management of persistent moderate to severe pain in patients requiring continuous around-the-clock opioid analgesia for an extended period of time. Palladone capsules should only be used in patients who are already receiving opioid therapy and who require and can tolerate a minimum total daily dose equivalent to 12 mg of oral hydromorphone.

Thus, the practitioner has to meet a four-tailed test for the appropriate indication for Palladone. The pain must be moderate to severe. It must require continuous around-the-clock opioid analgesia because there are moderate pains that may not require that. And, it must require that for an extended period of time, and the patient must be able to tolerate and require 12 mg minimum of

hydromorphone.

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The boxed warning goes further to say that Palladone capsules are not intended to be used on an as needed basis or as the first opioid product prescribed for a patient.

Palladone capsules are only for use in opioid-tolerant patients. Therefore, they cannot be the first opioid product prescribed for a patient. Use in non-opioid-tolerant patients may lead to fatal respiratory depression. This is very clear, right up front.

We also go on to state that Palladone capsules contain an opioid agonist that is a Schedule II controlled substance with high potential for abuse, similar to morphine, oxycodone, oxymorphone, fentanyl and methadone. In addition, the high drug content in the extended-release formulation may add to the risk of adverse outcomes from abuse.

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We then go on to tell the prescriber or dispenser that Palladone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or

dispensing Palladone in situations where the physician or pharmacist is concerned about increased risk of misuse, abuse or diversion.

Lastly, the admonition against compromising the delivery system, taking chewed, dissolved, or crushed Palladone capsules or its contents can lead to the rapid release and absorption of a potentially fatal dose of hydromorphone.

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In the indications and usage section we reiterate the fact that it is not to be used as a first opioid or on a p.r.n. basis and we emphasize the need for physicians to individualize therapy in every single case.

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Let's talk briefly about the messages in the proposed patient package insert. Again, the admonition about intentional or unintentional compromising of the formulation, keeping Palladone away from children to avoid unintentional exposures; letting patients know right up front that this is an opioid or narcotic pain medicine; letting them know that these are not for as needed use; and cautioning them to prevent against theft

and misuse.

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Our medical communications--we have a single telephone number, staffed around the clock by trained healthcare professionals to provide product information for other healthcare professionals, to receive adverse event information and put that into our pharmacovigilance system, and to address product inquiries and complaints.

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Let's talk about the promotion. We have had discussions with various groups and individuals and we have decided that we would launch Palladone in a phased manner. It will initially be promoted by a subset of the sales force to a limited group of healthcare professionals for approximately four months. During that time there will be an ongoing evaluation of promotional message retention and understanding by healthcare professionals by an independent third party that we will contract with. Based on what we find from that, the introduction of the drug will gradually be expanded based on that experience and any modifications that derive from that experience.

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What will we be looking for? We will be looking for the evaluation of messages; understanding patient selection criteria, did the practitioner get who is an appropriate candidate for Palladone or not? Understanding dosage and administration, did they understand this is not a p.r.n. drug; this is not the first opioid and things of that nature? Understanding what CII designation means and understanding how to recognize abuse and institute practices and procedures in their practice to minimize diversion.

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In summary, our phased launch program, we believe, will help ensure that healthcare professionals understand our messages. It will enhance the quality of our promotional activities, and we believe that this current environment dictates that all future approvals for CII opioid analgesics should be launched in this manner.

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I want to briefly go over a few examples of interventions that we have done of educational nature, community outreach nature and law enforcement support.

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Healthcare practitioners learn by a variety of ways. Therefore, we have a variety of tools available to help them learn, including teleconferences and distance learning for the rural practitioner who may not be able to leave her practice to get to a CME event somewhere. We also circulate guidelines from the federation of state medical boards and from individual state medical boards in those states to help practitioners do a better job of complying with prevailing rules.

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Here is an example of another intervention that we did. The need was this, practitioners were telling us "I want to use urine testing in my practice to screen for illicit substances and also to ensure adherence to the treatment plan but, you know, this stuff is not in a textbook anywhere; it's not in one place." We made a grant to the California Academy of Family Practitioners. They put together family physicians; they put together a group of experts and assembled this monograph.

What were the results of this? By request we have now distributed over 100,000 copies of this, not to mention the downloads from the California Academy's web site and this is, in fact,

our most requested piece of enduring material. It has such pearls that one might not find in there that, for instance, hydromorphone is an active metabolite of hydrocodone. Many physicians don't know that in a clinical setting if you have a patient on hydrocodone and you order a GC mass spec of their urine and hydromorphone comes back you might misinterpret those results and think that they are being non-compliant when, in fact, you are giving them hydromorphone; you are giving it to them in the form of a hydrocodone.

Likewise, in a medical examiner setting this is important because in a postmortem assay, if you get hydromorphone, you might attribute the death to hydromorphone when, in fact, hydrocodone was the cause.

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Slide kits of lawful prescribing, what are the principles of lawful prescribing and how do you prevent diversion, a very popular thing. Here, again, with an external advisory board of experts we have produced over 10,000 of these.

Then in our second edition, which is shown here and copies of these are available if you wish to receive them from the secretary of the

committee, we revised it with images based on feedback from the physicians--"gee, I want to know what track marks actually look like." So, we now have pictures of track marks and skin-popping scars.

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What was the need here? Mr. Joranson talked about this yesterday to some extent, a joint program with the National Association of Chain Drug Stores, NADD, National Association of Drug Diversion Investigators and the Pharmaceutical Security Institute where there is an internet clearinghouse where police officers and pharmacists can go and find out about pharmacy robberies one by one to compare MOs and patterns and, hopefully, spot the patterns and stop the perpetrators.

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Tent cards with the DAMMADDs and MAAD moms against drug dealers. We have provided seed money for their web side, tent cards with a phone number and the URL that are placed in pharmacies. What are the results of this intervention? To date, 21 convictions of pharmacy robbers.

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Law enforcement support, the need--law

enforcement said, "gee if we stop someone on the street and we see a bunch of pills in the car we don't know if they're blood pressure pills or asthma pills or something they shouldn't have." So, we were approached by NADDI and we gave them a grant. They have now distributed over 100,000 of these photo ID cards, and Commander John Burke who, by way of disclosure, is a consultant for us, said "these brochures were one of the hottest projects we've ever done."

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The need--how to stop altered, forged and counterfeited prescriptions. The solution--security paper. This paper has a number of security features, including "void" appearing, as you can see faintly here. It shows up better in real life; it doesn't project well but no matter what you have your scanner set on or your photocopies set on, you are going to get a line of "void" across there. It is also watermark paper. It is also sort of a water colored pattern like your checks so if you try to smudge or alter a prescription it will be very obvious. We have now been distributing these free of charge.

The results of this--a lot of physicians

are using them and, secondly, a number of states have now recommended this to physicians. Some states are contemplating making it mandatory.

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Public service ads, the Household Survey data and also alerting parents to the fact that, you know, kids find drugs in lots of places and the street is not the only place. Know what is in your medicine chest.

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Communities that Care is a structured planning system that is based on 20-plus years of NIH-funded science research that provides strategic consultation; working with communities to provide an integrated approach to diminish these kinds of problem behaviors in communities. The reason is that research has shown that these are linked. If you just go after teen pregnancy and that is all you do, you are not likely going to make a dent if there is violence in the school, high dropouts, etc. Likewise for drug abuse. The CTC program which Michelle Ridge, Tom Ridge's wife is the national spokesperson for, is working with this and we are supporting this in a number of communities right now.

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The need--young people. The Household Survey data showed that the 12-17 demographic are the ones who are the most frequent new initiates of pain reliever non-medical use. Targeting middle school students, the strategy was to make these so-called "tweens" feel sorry for people who abuse prescription drugs because they have no self-respect and dignity. The key message is if you abuse prescription drugs you will lose your dignity; trying to resonate to what is important to this demographic, if you use drugs you are not cool anymore.

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We have done it in a way that resonates, this sort of gross-out humor: "picking your nose at lunch does not count as dessert" and "spastic shaking caused by prescription drug use is creepy"--painfully obvious is the conclusion, hence the tag line for the program. We have a web site. There have been over 300,000 hits on this web site and over 4,000 copies of this material downloaded in addition to the ones we have distributed in hard copy form.

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Does this work? We are not really sure but there was last week, at the Household Survey press conference, an encouraging comment by John Walters, the current director of ONDCP, that said that the data suggest that youth who have heard anti-drug abuse messages have lower rates of abuse than those who have not heard the messages--not a huge difference but if my kids are in the 11.3 percent, that is where I want them to be.

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Multi-faceted surveillance, this is a key tenet of any risk management program. You have heard things about that.

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Again, monitoring for patient safety, pharmacovigilance, including a structured, regular ongoing review of scientific literature; monitoring for other populations I mentioned; national surveys, as I have mentioned, the ones we have looked at and it is not passive monitoring, as I have shown you from the special data we have from the Household Survey; also monitoring the future. Some of our consultants met with the people who do monitoring in the future and actually got them to modify this high school-based survey to include

issues about prescription drug abuse and remove things that probably didn't have very high abuse prevalence, such as laudanum.

Media surveillance--we have an active sample through one of the clipping services where we look at media surveillance to find out if there are reports of abuse or diversion around the country.

Then, the RADARS system. This is an evolving system but it is innovative. We are very excited about it. We think we have some very good data. Of course, we fine-tune as we go along, but I think it is something that you will find interesting and for that I would like to introduce my colleague, Dr. Schnoll.

RADARS Surveillance System

DR. SCHNOLL: Thank you very much.

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I am going to be talking to you this morning about the RADARS system and I would like to reiterate something that Dr. Haddox said to you already, that this is an evolving system. As you heard yesterday from Dr. Winchell, there are no guideposts for how to run this type of surveillance; there are no data out there. We have

some clues from research that has been done in the surveillance of altram and Meridia but we felt we had to expand this system. You will be seeing some data today that were sent to the FDA but they have not had the opportunity to comment on those data at this time.

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We had picked up the media indicating that OxyContin abuse was becoming a public health concern. We recognized that we did not have the expertise to deal with this on our own and so we put together a panel of outside experts to assist us in dealing with this situation. This external panel, the external advisory board, was formed in June of 2001, and part of what they did was to review existing databases. They recognized from these reviews that the data in these databases was often not timely, being published or presented sometimes a year or more after the data had been collected, and the data were not necessarily geographically specific. What we were hearing and seeing was that the problems of prescription drug abuse were not uniform nationally but seemed to have specific target areas around the country.

So, the programs that were developed in

RADARS were developed to provide geographically specific and timely data. The question came up yesterday about whether or not these data were presented to the FDA, and I would like to mention that on June 23 we had a meeting with the FDA to present RADARS data and the FDA, and other federal agencies, do meet with the external advisory board on a quarterly basis to review what is happening with the RADARS system.

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These are the members of our external advisory board. As you can see, there are many well-known researchers in addiction, people who are in policy positions regarding prescription programs and law enforcement.

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The goals of the RADARS system are primarily to study the nature and extent of abuse and diversion of scheduled prescription opioids, and you see the drugs that we are studying here. These are major and important Schedule II and III prescription opioids. In addition, the goal of the external advisory board and the RADARS system is to develop and suggest to Purdue interventions to reduce both diversion and abuse.

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The objectives are to proactively collect timely and geographically specific data on the abuse and diversion of the drugs you have previously seen.

In addition, as has come up here already by Dr. Strom this morning, there is a need to develop rates and we need to develop these rates both on a national and a local level because, as I mentioned, problems do not exist uniformly across the United States.

In addition, we have to develop interventions and these interventions are suggested at times by the EAB and are done in collaboration with Purdue to reduce the diversion and to monitor the outcomes of these interventions.

In addition, we review existing databases, such as you have seen with the National Survey of Drug Use and Health, to do some other analyses of these databases and review the literature to look at new data as they are emerging. We see what we are doing with RADARS as complementary to these existing programs.

[Slide]

There are several levels of activity

involved in the RADARS system. Signal detection is the first one we do, and I am going to go over some of the data from our signal detection systems.

From signal detection the data are then taken and merged and they are sent to the Johns Hopkins University where relative rate determinations are done, and I will discuss that a little further later on.

When we receive a signal that we feel is at a level that requires something to be done, we go in and investigate that signal and do verification as to what that signal means. We may get data from other sources at Purdue which will launch a signal verification.

The three bottom items, the focused studies, interventions and outcomes, will depend on what happens with that signal verification and so don't always occur.

[Slide]

The signal detection component functions as an early warning system. As I have mentioned already, the data are timely and you will see that as we already have second quarter data from 2003. They are geographically sensitive and we can break the data down to the first three digits of the zip

code. This makes it very useful for monitoring localized outbreaks of an event that may occur with a newly approved drug. The threshold we have set for signal verification is five or greater cases per 100,000 population in that three-digit zip code. We feel that that is a very sensitive level and this may be from a single detection study or from a combination of all of the signal detection studies.

[Slide]

The signal detection studies are funded by Purdue. The studies, as you will see, are conducted at major universities under the direction of a principal investigator, and the data are independently housed at those universities and reported to the external advisory board and Purdue on a quarterly basis.

[Slide]

Through the signal detection studies we have covered a wide area of the United States. If you look, there is the Key Informant study with the stars; our Drug Diversion Network, with the diamonds; and DENS Network, with the yellow circles and these are the states that are either wholly or partially covered by the Poison Control study. So,

we have a rather significant area of the United States covered with these studies.

[Slide]

The principal investigator for the Key Informant Network is Dr. Ted Cicero who is with us today. The key informants are made up of pain specialists, NIDA grantees, drug abuse specialists and others who can provide information to us in their local area about what is going on. We have picked one three-digit zip code to present some data to you to show the kind of data that we can collect.

[Slide]

As you will see, the data cover a range of drugs and I think it is important to point out that this is a very sensitive system and we are able to detect already abuse of buprenorphine, a drug that does not have a lot of prescriptions at this time. But we can see changes over time in what is happening with the various drugs on which we are collecting data.

[Slide]

The law enforcement drug diversion signal detection study is under the direction of Dr. James Inciardi, at the University of Delaware, and he is

collecting data from drug diversion units around the United States. As you can see, we are continually trying to increase the number of key informants and units from which we are collecting information.

[Slide]

These are the sites that have responded in each quarter. These are the number of cases that they are reporting. We have consistent response from about 85 of these sites each quarter, and there is a group of about 85-90 key informants who respond to us each quarter.

[Slide]

In each of those cases there may be several drugs mentioned. Here is the data from the four quarters of 2002 and up to 2003 second quarter, and you can see there is wide variation in the diversion of different prescription drugs, and we have some benzodiazepines included here. Hydrocodone is the most commonly reported. OxyContin, which is separated from other oxycodone products, appears to be dropping a little bit over this time but, as has been reported in the press, we are beginning to see some increase in methadone mentions.

[Slide]

Yesterday you heard Dr. Winchell mention the Drug Evaluation Network System that is under the direction of Dr. Tom McLellan at the University of Pennsylvania. The important part of this system is that it collects data on a real-time basis. In some of the other systems you have heard about the data are collected, say, once a year and then the report may not occur for some time.

[Slide]

These are data on 11,000 consecutive admissions to the programs in the DENS system. There are about 80 programs nationally, some in urban areas and some in rural areas. As you can see, again hydrocodone is the most frequently mentioned drug. There are specific questions asked about these drugs in the DENS interview, and hydromorphone is also picked up.

[Slide]

As you see again, we can plot over time what is going on with these drugs. This is lifetime reported use of hydromorphone and this is past 30-day use, as Dr. Haddox mentioned, which is a surrogate for recent current use. I would like to point out the scale here. This only goes up to

3.0 so this is not a major rise in the problem.

[Slide]

We are also collecting data from poison control centers. One of the most important things about the data from the poison control centers is the fact that the people who are collecting the data give very specific information about what the tablet is. They ask about what the markings are on the tablet, the size, the shape, and they can then look at a book that gives them specific information and say precisely what branded or unbranded drug was being reported.

[Slide]

This is a map showing, in our pilot study, the coverage we have from the poison control system. It covers over 25 percent of the United States and, as you can see, covers some of the states mentioned yesterday as areas with high problems, Kentucky, Virginia, Maine, and we are trying to expand this system gradually to include more of the United States.

[Slide]

There are two types of calls that come in to the poison control centers. One is an information call where somebody may have forgotten

what their pills are. As you know, many people will put all their pills into one little box and then they can't remember so they may call to find out what a specific pill is, or somebody found a pill. But the ones we are most interested in are the intentional exposure calls. These are the calls when somebody has taken a drug either for abuse problems or for suicide.

As you can see, these are data from all of the poison control centers from which we collect data combined and we have worked at a rate per 100,000 based on the population covered by those centers. Again, you can see hydrocodone here, oxycodone--this does not include OxyContin which is covered separately--and the other drugs involved.

[Slide]

Now, the data that are collected from these signal detection studies are then sent to Washington University where we have a central database housing all these data. The data are collated and then specific data fields are sent to Johns Hopkins University where rates are calculated.

Now, as I mentioned earlier and Dr. Strom has brought up, the denominators are very important

in calculating these rates. In looking at this, it is clear that there is not one simple denominator to use to provide us with the information we need. If you are going to look at patients you have to look at patient day exposure. A short-acting opioid may only be used for 10, 11 days. An extended-release opioid, such as OxyContin, may be used for 24 days so you have more exposure and you may have a higher dose.

You also need to know how much drug is out there, kilograms sold. If you are just looking at prescriptions you may get data that are biased because IMS data provides prescriptions mainly from retail pharmacies and currently, for a drug like hydromorphone, there is a significant portion of that drug that is being dispensed in hospitals and long-term care facilities those are not included in the IMS data. So, unless you are aware of that you can get a skewed rate so there are many different types of denominators that we have to look at to find out which is the most appropriate to provide us the information that we need.

Using these denominators we are trying to calculate relative rates of abuse and diversion of the drugs that we are investigating, and with this

we can compare one drug to another and compare a drug to itself over time to look at changes in the rates.

[Slide]

To give you an example, we have looked at DAWN data and created a rate based on total kilograms sold. This is not just the kilograms dispensed in retail pharmacies but the total kilograms including hospital and other sources. As you can see, there is some consistency of those rates. OxyContin has gone up. This is morphine, in the purple. We do not have the 2002 OxyContin data yet since the DAWN data were just released and we have to obtain the specific data from SAMHSA to get that.

[Slide]

Once we pick up a signal, as I mentioned five or greater cases per 100,000 population in a three-digit zip code, we have our field researchers go in using a questionnaire that is structured to try to verify the nature of that signal. This is very important because we are finding that there are different problems going on in different parts of the country. We have recently investigated a problem in a tribe of native Americans in the

northwestern part of the United States where the problem appeared to be drug being smuggled in from Canada. In another part of the country we found that it was a city, 20,000 people, a lot of nursing homes and assisted living facilities and 18 pharmacies for 20,000 people. In a third area we discovered that river boat gambling had moved into the area and brought in a lot of outsiders who were using drugs.

If you look at these differences, it tells you that there is not one single approach that can be applied on a national basis for these various problems, and that is why we need geographic specificity in terms of what we are doing. As mentioned here, the results of these interviews are presented to the EAB for suggestions on where to go.

[Slide]

I mentioned the focused studies. We have two focused studies that are currently going on, one in southwestern Virginia under the direction of Dr. Janet Knisely at Virginia Commonwealth University, one in Maine under the direction of Dr. Heimer at Yale University, and we are soon to implement a third in eastern Kentucky under the

direction of Dr. Carl Leukefeld at the University of Kentucky.

So far, information from these studies has pointed out that, one, it is very difficult to collect data from people in rural areas. They are very reluctant to talk to outsiders who come in to try to gather information from them. But we are also discovering that prescription drug abuse has been endemic in these areas for a long time and people go from one drug to another. So, we are getting some very important information.

[Slide]

Based on the information we get, we will be developing, in conjunction with the external advisory board, interventions that are specific to the area. In one case we found a physician who was performing some illegal activities and that was reported to the local authorities. As I mentioned, the interventions are specific. Dr. Haddox has gone over some of the interventions that the company is already doing.

We need to look at outcomes for these interventions, and we will monitor carefully with our signal detection studies to see if there is a change but we will also look at other indicators.

[Slide]

So far, we have learned something about prescription drug abuse from the RADARS system. One, that abusers of a given opioid drug are similar to abusers of other prescription opioids. There seems to be no specificity in terms of the abusers. These individuals are typically individuals who have abused other prescription drugs as well as illicit drugs. This is not a problem of ethnic minorities and, as mentioned, the problem seems to be endemic in some of these areas.

[Slide]

We feel, in summary, that the RADARS system establishes a standard for proactive collection of data on abuse and diversion and provides relative rates of abuse and diversion for the drugs of interest. We are able to detect abuse and diversion of the drugs that are infrequently prescribed, as pointed out by buprenorphine, and the data are generated in a geographically specific area and in a timely fashion.

I would like to now turn the microphone over to Dr. Herbert Kleber.

Prescription Drug Abuse

DR. KLEBER: Thank you for the opportunity

to meet with the committee today.

[Slide]

I would first like to point out this is not a new problem. Prescription drug abuse has been with us for a very, very long time. The under-treatment of pain has been with us for a very, very long time and the question is always the tension between these areas. How do we keep effective pain relievers available for appropriate medical use while decreasing abuse? If I stood up here and said we have the answer I think you would all get up and walk out, and rightfully so. This is an evolving area. There is no one answer yet. We are improving what we do; we don't have the answer.

[Slide]

At the turn of the century we had an enormous problem with patent medicines. They were often unlabeled. One of the favorites was Mother Winslow's Soothing Syrup which was rubbed on the gums of teething babies and also taken by the mothers when they had trouble dealing with the teething babies. Finally we had the Pure Food and Drug Act in 1906 which at least required that these patent medicines be labeled as to ingredients. It

certainly did some good. On the other hand, it left a lot of openings. You still had doctors and pharmacists who were basically willing to sell these medications to whoever wanted them, and you had mail order catalogs. So, there is really nothing new under the sun, today we have the Internet drug sales; in those days you had mail order catalogs.

Then, in 1914 the Harrison Act tried to close some of these loopholes and you needed prescriptions by physicians for reasonable treatment of pain. At the same time, as often happens with unintended consequences or maybe intended, basically between the Act and the Supreme Court interpretations, it ended the involvement of the general medical system in the treatment of addiction. It stayed that way really until methadone came along, and you will hear more about that from my colleague, Dr. Kreek, this afternoon.

[Slide]

The Harrison Act did not solve the problem of prescription drug abuse. We keep trying to do it by coordinating things better. The last bullet there, ONDCP, is one that you have heard. I had the honor to serve as the first deputy director,

back in 1989, under Bill Bennet and the first President Bush.

We keep trying to improve things, not just with coordination and with laws regulating prescribing, but with enforcement activities so the Bureau of Narcotics morphs into the Bureau of Narcotic and Dangerous Drugs, which morphs into the Drug Enforcement Administration. Each probably is somewhat of an improvement over what came before but is clearly still problematic.

[Slide]

Who are the abusers? I have been in the field for between 35 and 40 years and it has been my experience that there are really four groups of people that we need to talk about. We need to talk about addicts. We need to talk about pain patients. We need to talk about addicts who have pain, and we need to talk about pain patients who become addicts. Each of these is a different category. They need to be approached as individuals, as is beginning to emerge from the discussions this morning, especially as Dr. Baxter pointed out that we need to keep in mind that there is no one approach that is going to work for all of these, but most non-medical users of prescription

opioids are polydrug abusers. These are not people who just abuse these medications; they also tend to abuse alcohol, marijuana and other drugs. Most pain patients do not abuse these medications nor do they become addicts. There aren't as good studies as we would like, especially prospective studies, but most studies of the few that we have suggest that it is less than five percent of people who receive legitimate medications for pain end up addicted--not dependent, a different term, but addicted.

[Slide]

Since the patient is not the key person at risk for prescription drug abuse, how much legitimate medical need needs to be tolerated to reduce abuse? Again, it is that tension that we have talked about that there is no easy answer to.

[Slide]

So, let me wrap it up in the next minute or two. Quick fixes do not work for complex problems. I wrote in an op ed in "The Times" 15 years or so ago that we should leave the quick fixes to the addicts. There is no easy solution.

There are often unintended consequences of good intentions. The concern over OxyContin led

many physicians to stop prescribing it and many pharmacies put signs in their windows saying "we don't prescribe OxyContin" and it led, instead, to a marked increase in prescribing of methadone for pain relief and more diversion of methadone, which then has also the unintended consequence of casting disrepute on legitimate methadone maintenance programs.

So, when you squeeze the balloon in one part it tends to pop out in another, often in areas where you don't expect it to. The patterns of drug abuse continually shift and preferences change. In the '70s Quaaludes was a big problem and we haven't heard about that for quite a while. PCP was also a problem and this stayed with us.

We continually search for technological fixes. One of my favorites was paregoric, which was camphor with a tincture of opium. The camphor was put in to deal with abuse. One of the first things my addicts taught me, when I was at Lexington treating patients there in the early '60s, was you simply take the paregoric, put it in the freezer, the camphor freezes, the tincture of opium doesn't. You throw away anything that freezes, boil what is left and you now have opium.

So, the addicts are very good at figuring out whatever system we come up with. Likewise, the Addiction Research Center which is now the intramural branch of NIDA, was really set up in the '30s with one of its major missions to come up with a non-addicting analgesic, a strong analgesic, and we are still at it, guys. But, hopefully, maybe before the Red Sox beat the Yankees and win the pendant--remember, I spent most of my years in New Haven so I am a Red Sox fan, not a Yankee fan.

So we continue to search for technological fixes. We have certainly come up with better ones but I have great faith in the ability of true abusers to get around it. So, I expect evolutionary, not revolutionary, changes.

[Slide]

We have a number of strategies that have we have gone over. I am not going to reiterate them; you have heard about them. I have been associated with the RADARS program since its inception in July of '01, and in my experience in treatment of addiction, treatment of pain, the risk management strategy that is used for OxyContin and Palladone and the RADARS part of that strategy is one of the most comprehensive I have ever

encountered. Is it perfect? Absolutely not and that is why they have all these experts on the committee to try to keep tweaking it to improve it.

[Slide]

Secretary Thompson has just recently commented on the need for treatment. "There is no other medical condition for which we would tolerate such huge numbers unable to obtain the treatment they need." Again, if many of these people who cycle through the system could get adequate treatment for their opioid problem there would be much less of a difficulty out there. With heroin, for example, less than 20 percent of the individuals who need treatment are getting it.

[Slide]

Last slide, and this I think is a really important take-home message I want to leave you with, the past decade has witnessed the pendulum swinging toward adequate pain relief for patients. This has occurred under the impact of legislation, of lawsuits, of reports from learned societies. My own feeling--hopefully I am wrong--is that this pendulum swing is still very superficial; it is skin deep; it is easy to reverse and I think we need to pay attention to that, and it is important

that any strategies that we come up with do not reverse the trend toward adequate pain relief for that segment of the population that needs it. Thank you.

Questions from the Committee

DR. KATZ: Let me thank the speakers from Purdue and from Columbia for their comprehensive presentations. Of course, it is always tantalizing because there are so many issues that we would all like to discuss in depth and we never seem to be able to satisfy ourselves there, but I am sure people around the table have questions for the sponsors and we have 15 minutes allocated for that. So, why don't we go ahead and take that. Dr. Dworkin first?

DR. DWORKIN: I think this is a question for you, David. It seems to me, in thinking about risk management programs, that the extent of how widely the drug will be used is a consideration so that a risk management program for buprenorphine or transmucosal fentanyl might need to be different than for more widely used drugs like OxyContin.

So, I guess I would like to know--and I hope this is not an unfair question--by any measure OxyContin is a block-buster drug. looking down the

road four or five years from now, how does Purdue view Palladone? Is it going to be another block-buster drug like OxyContin or do you view Palladone as being a more niche-limited used drug? There must be projections of this that your marketing projections have done.

DR. HADDOX: There are marketing projections but we don't discuss commercial information in public, but let me see if I can answer your question in a way that satisfies the need. If you look at the indication for OxyContin and indication for Palladone, they are fairly similar with the exception of that fourth test, that is, the opioid-tolerant individual who needs and requires 12 mg minimum of hydromorphone. So the estimation would be, I think logically, that it is going to be a smaller subset of patients than those who are taking OxyContin. Now, there are some five million patients in the entire country who might be appropriate candidates for opioids that are high potency. So, you know, OxyContin has a share of that. Maybe about 1.7 million patients in a given year have been exposed to OxyContin. My guess is that Palladone will be smaller than that, but I really can't give you a scale of marketing

projections.

DR. KATZ: Dr. Crawford?

DR. CRAWFORD: Thank you, Mr. Chairman. Dr. Haddox, thank you for the presentation. I have three very quick questions, at least there could be very quick answers.

First, slide 30 with the boxed warning part of the indication states use for an extended period of time which, of course, could be subject to interpretation. What is the intent of the sponsor?

DR. HADDOX: Well, this is a claim originally negotiated with the agency. It requires clinical judgment. Certainly, it is not appropriate for a day or two but it might be appropriate if the pain is going to last for a few weeks. It is somewhere in that range and we and the agency I think agreed, certainly with the labeling for OxyContin, that you don't want to, you know, draw a line in sand. You want clinicians to use their judgment and individualize therapy.

DR. CRAWFORD: Thank you. The second one, slide 32, the capital letters with the boxed statement not to compromise the formulation, one thing that is very important in my opinion for us

to understand is can you describe and quantify the potential or the likelihood of adverse effects if the formulation is compromised, as well as what the appropriate use is because we didn't see any figures on fatalities or other serious adverse events that may occur with the formulation?

DR. HADDOX: I think you asked two questions there.

DR. CRAWFORD: That was my second question. Can you describe and quantify what are the adverse effects, what is the likelihood of that occurrence if the formulation is used appropriately and if it is compromised?

DR. HADDOX: That is what I meant by two questions, two conditions. If the formulation is used appropriately the safety profile in all of our studies we submitted to the agency is comparable to the safety profile of any other opioid. We, obviously, don't try to compromise the delivery system and give it to people and see what happens. So, we can only guess that it would be what the warning describes, which is why we and the agency agreed to put that in the proposed label.

DR. CRAWFORD: Okay, and the last very quick question, the tamper-resistant pads, do they

come preprinted with the product name or indication to the prescribers?

DR. HADDOX: All they come preprinted with is the prescriber's information they would normally print--name, address, that sort of stuff. In fact, we actually encourage prescribers, based on advice from law enforcement, not to preprint their DEA registration number either. So, you know, just your name, your phone number, your address, what you would normally do. Then, because they are distributed in different states, the vendor goes to the state board pharmacy with a prototype and says does this meet your requirements for prescription in this state? And, we have had to tweak that a few times so that it would be state specific.

DR. KATZ: Dr. Ciraulo is next.

DR. CIRAULO: Dr. Crawford asked one of my questions but I just would like to expand on that. Do you have data on how easy it is to compromise the formulation to make it from a modified release to an immediate release? Do you have PK data or toxicity data either in animals or humans that would give us some information on what we could predict might happen if it is easy to chew and get this into the brain more quickly?

DR. HADDOX: There has been some work done on that. We don't do this in normal volunteers, as you might imagine. It is harder than some and it is not impossible but, again, being a public hearing here, I don't think it is prudent for public health to discuss ways people might compromise the delivery system.

DR. CIRAULO: Sure, but the FDA, you have that data?

DR. KATZ: But, Dr. Ciraulo, is your question what would be the likelihood of harm to some sort of person, say an opioid-naive individual, should they be able to ingest a compromised dose or an immediate-release dose of whatever is in one of these Palladone pills?

DR. CIRAULO: Yes, that is my concern.

DR. KATZ: So, if someone, for example, were able to compromise the 12 mg tablet, just to pick a dose, and ingest that, in opioid-naive people what is the likelihood of harm? That is your question?

DR. CIRAULO: Yes.

DR. KATZ: Are there answers to that?

DR. HADDOX: Well, I think, you know, the likelihood of adverse events is pretty clear.

Which adverse event would occur I am not certain. I am not aware of people who have done that, who have given 12 mg of IV-push of hydromorphone to opioid-naive volunteers to see what happens to them. Even where I trained you wouldn't get too many medical students to volunteer for that study. So, I think the warning is appropriate. It says what we all believe in my clinical experience, that if one were to compromise this, this is very risky behavior.

DR. CIRAULO: I think my problem is I can't advise anybody--I can't advise the agency without knowing the toxicity data, but you have it.

DR. RAPPAPORT: We will have the data, we do have the data and are able to review that but to some extent Dr. Haddox is correct, we would expect certain severe adverse events to occur, but there is not a lot of clinical work you can do to study that.

DR. CIRAULO: Yes, my concern is when this medication is on the street and gets diverted, as it will get diverted and as addicts begin to tamper with it, what are we going to face from a public health standpoint?

DR. RAPPAPORT: Theoretically there could

be people dying from taking these products and abusing them, but I don't know that we can say any more than that.

DR. KATZ: Dr. Haddox, correct me if I am wrong, but it sounds like we should assume for the purposes of this discussion that the likelihood of harm for an opioid-naive individual ingesting an immediate-release formulation of any of these dosage forms of hydromorphone would be very high. Is that a fair assumption?

DR. HADDOX: I think that is a fair assumption with any equivalent dose of hydromorphone, regardless of formulation.

DR. KATZ: Dr. Aronson is next.

DR. ARONSON: Thank you. I have a number of questions. Let me ask you, Mr. Chairman, if you wish for me to ask them all. Some are directed to Dr. Haddox and others are directed to some of our other speakers.

DR. KATZ: Any questions to any of the sponsor representatives is fine.

DR. ARONSON: Okay. This is an operational question that I would like to direct to you, Dr. Haddox. You mentioned a number of risk management tools that you are going to launch or

implement as you phase your launch of Palladone. Other than just telling us that there are guidelines and brochures and CDs, etc. that you wish to promote in an educational process, what is the metric that you are going to use to judge whether or not that message was received, and what is the threshold that you would use to determine whether or not you are going to accelerate your launch beyond your first phase?

DR. HADDOX: Let me answer that in two parts. Number one, it is clear, as I said before, that there are some elements of this that are Palladone specific--the phased launch, the labeling for Palladone, etc. But the big difference between Palladone and OxyContin is that all of these things that I have talked about, except for the phased launch which hasn't occurred yet, are already in place. Practitioners have gotten the tamper-resistant pads. They have been educated on abuse and diversion. Those things are out there.

RADARS is up and running and that is the second part of the answer. I believe that one of the major mechanisms we will use in the evaluation of the message will be those four points that I talked about. The threshold is still being

determined because it is an evolutionary process. We are still trying to sort out how to do that best. But the big metric will be will RADARS pick up something early on and allow us to do targeted interventions to try and suppress the issue.

DR. KATZ: Does that answer your question?

DR. ARONSON: I think so. I think the point is, is there a threshold whereby you would just sort of delay or stop your process of evolving the launch?

DR. HADDOX: I think it would be premature for us to try and determine threshold until we try and get some data back from that message evaluation to see what it looks like. I think at that point we will get a sense of what should be the cut-off or what we should do differently.

DR. ARONSON: The segue to that--and I would firstly say that the RADARS program, in my opinion, is responsible and you ought to be commended for the effort, but as was pointed out by this committee, the problem of clearly defining the denominator still persists despite your best efforts and so I raise the question is more incomplete data better than complete data? I suppose we are having to confront that.

The part of this equation that I think we need to consider, and I am asking if you have attempted to do that, is the mirror graph, if you will, the decrease in the number of patients that need to be treated for pain. As that decreases, as that tendency would drop we would expect the adverse mirror curve to increase, and at one point do the lines cross and is that the point that we find acceptable? Is there any data to show the benefit, improvement?

DR. KATZ: Can you clarify that question?

DR. ARONSON: I will try. We conceptually appreciate that the reason we would consider, if you will, approving another drug is because we wish to do good for those people who deserve to have good done. Are we measuring the impact of how much good we are doing and comparing that to the potential harm that may come of it? We have only seen the absolute increase in harm but we haven't looked at that in a comparative way to the absolute good that we have done. Are there any data to show that?

DR. HADDOX: Well, as I have said before, if you look at survey data, survey data have not really changed substantially in the past 15 years

in terms of the prevalence of under-treated pain. I think, however, that the denominator issue that you raised in the preamble is important because, as Dr. Schnoll pointed out, we don't anticipate a single denominator. We think that this is a complex issue and to really understand this we may have to look at multiple denominators, some of the ones that he pointed out, so that we can look at what is the relative risk of abuse or diversion of one formulation to another, those sorts of questions. It still begs the question how can we measure the benefit to the populace and that is a tough question. Outside of survey methodology, I don't have any suggestions right now but I would be willing to entertain them.

DR. KATZ: I want to make sure we are getting to the core of your question. Are you suggesting that a risk management program such as the one that is being proposed for Palladone should incorporate a component that measures the societal benefits of the approach as well as the risks so that we can have a complete picture? Is that your question?

DR. ARONSON: Absolutely. What we are confronted with is a balance of most good for least

harm, and we need to have that side of the equation in order to make that decision and I do not see that side of the equation. So, yes indeed, I am asking that.

DR. KATZ: And how would you suggest that be done?

DR. ARONSON: Give me a moment.

[Laughter]

DR. KATZ: There is a long list; I will put you at the bottom so you will have some time. Dr. Cush, you are next.

DR. CUSH: I have two questions, one for Dr. Rappaport or the agency. Could you just generally state what your requirements for manufacturers as far as pharmacovigilance are and what you want them to do in their program? Some of the agency requirements for pharmacovigilance for a product like this?

The second part is going to be to Dr. Haddox. Could you tell us why you chose four months and to what selected health professionals will you be targeting initially, and is that the appropriate population, meaning is that the population that has also been shown to be guilty of improper use of these agents in the past?

DR. KATZ: So, first question first.

DR. TRONTELL: I will comment first on the regulatory requirements for pharmacovigilance. The regulatory requirements in that arena are uniform across all products and require reporting to the agency of adverse events that come to the attention to the sponsor spontaneously. They are mandated to send those to the agency and those in a certain category deemed serious by regulatory definition are, in fact, required to be sent to the agency on an expedited basis. I will defer now to Dr. Rappaport to talk about this particular class of drugs.

DR. RAPPAPORT: We have been asking for some extra pharmacovigilance with this group of drugs, asking for expedited reports that are expedited on a faster basis, and following carefully indications of abuse, overdose and such. So, we are doing a little bit extra here but the general requirements are what we follow for all drugs in all areas of safety.

DR. CUSH: So, is this risk management program we are talking about here part of the pharmacovigilance effort?

DR. RAPPAPORT: Yes.

DR. KATZ: The second question was on the specialists that are being targeted in the initial phase.

DR. HADDOX: The intent is to have that portion of the sales force which calls on physicians who are likely to have patients for which Palladone would be an appropriate option. So, people like anesthesiologists, pain specialists, oncologists, that is the intent.

As far as the four months, we had to start somewhere. We just decided we would collect the information. We will be looking at it as it comes in but four months is where we will sit down and really try and make a decision point.

DR. KATZ: Next was Dr. Shafer.

DR. SHAFER: Thank you. Three questions. I think they will all be pretty straightforward. The first is a simple pharmacokinetic question. In looking at the data on drug administration over the first 24 hours the peak concentrations are reached at 24 hours, suggesting you have done a very good job on the sustained release part. But that also suggests that over the first week of therapy there is the potential--not a potential, the drug will accumulate until you reach your steady state. How

much more does the drug level rise over the first week of therapy until you reach steady state?

DR. HADDOX: Two to three days to reach steady state.

DR. SHAFER: And how much has it risen? Has it doubled over that period of time?

DR. HADDOX: No, I don't think so. Let me ask my clinical experts here.

DR. KATZ: Could you come up to the microphone, please?

DR. SHAFER: I was impressed that the peak was reached at 24, which means that you are then adding your next dose on top of that.

DR. APFEL: David, if you could go back to the slide showing the steady state?

DR. SHAFER: But we are really talking about the rise to steady state, not the steady state exactly.

DR. APFEL: My name is Dr. Stuart Apfel.

[Slide]

DR. SHAFER: That shows the rise and what I am referring is the peak at 24. So, the question is how much accumulation will you get on top of that over the first week of therapy?

DR. APFEL: We see that the levels continue to remain pretty much at that same level with continued exposure. As the drug is continued to be administered, once it reaches steady state the levels of the drug in the serum remain approximately the same. You can see it a little bit better here where you see very little variation.

DR. KATZ: I think the question was what is the ratio of the blood level at day three to the blood level at day one. Is that right?

DR. SHAFER: That is right. If we could go back because it is not in the handout that we received. The question is how much higher is this than the level at the end of the first day of treatment.

DR. HADDOX: That is why I went back to this. There is the metric, right there. It is a little less than 2 ng/ml with a 12 mg capsule.

DR. KATZ: But this is a 24-hour slide.

DR. HADDOX: This is steady state. This is steady state and I am going to go back to the single dose to answer the question.

DR. SHAFER: Let's go back to the single dose if it is the same dose.

DR. HADDOX: The single dose was actually twice as high I believe.

[Slide]

This is 24 mg and there is the 2 ng/ml.

DR. SHAFER: So it is approximately doubling.

DR. GOLDENHEIM: Paul Goldenheim, Purdue Pharma. I think the answer to your question is it is a little bit less but we will get the precise answer for you, but steady state is achieved after two to three doses.

DR. SHAFER: I have two other questions, quickly. One is, the question was posed yesterday to what extent is theft and criminal activity versus diversion from patient activity responsible for the misuse of drugs and diversion to addicts, and has your RADARS system been able to give us more information? We did not learn an answer yesterday when I posed that question. Have you learned anything from your RADARS system?

DR. HADDOX: Well, certainly, the diversion study is showing what the police are intercepting either in undercover buys or busts. So, that is some idea of what is on the street. It does not tell us necessarily how it gets to the

street. There are people who are feigning to be patients, who are scamming physicians. There are people who just take the easy way; don't have to worry about learning new symptoms to fake or getting fake medical records, they just go in with a gun or, you know, roll the place at night. No one is quite sure that the DEA does collect that theft and loss data and does categorize it, and I believe Dr. Willis made some reference to that in her presentation yesterday but those data reside at the DEA.

Even so, that only gives you one piece of the question that you asked. That might give you a sense of what is from theft and loss, and that sort of thing, but it doesn't say what the doctor shopper, who in fact is not a patient, is getting on the street, or particularly,, the bad doctor who is indiscriminate and doesn't really care who they are writing prescriptions for.

DR. KATZ: Dr. Schnoll, do you have a follow-up?

DR. SCHNOLL: Yes, we don't have at this point specific information to directly answer that question. Most of the abusers get the drug from the street. I think your question is how does it

get to the street.

DR. SHAFER: Exactly.

DR. SCHNOLL: That is something we are trying to investigate. There are many sources and, hopefully, as the RADARS system matures we will be able to provide that answer but I don't think anyone knows specifically where all the drug is coming from that gets to the street.

DR. SHAFER: Do we even know if it is 1:10 versus 10:1?

DR. SCHNOLL: No.

DR. KATZ: Can you, Dr. Shafer, tell us why you think that is important in terms of developing a rational risk management program?

DR. SHAFER: Sure, because part of the purpose of the risk management program is the concern about drying up the supply of drug to addicts. If that supply is entirely coming from criminal activity and is not coming from doctor/patient activity, or even if 98 percent of it is coming from criminal activity, not doctor/patient activity, that means the ability of these surveillance programs to impact that is going to be almost zero.

DR. KATZ: Maybe it would be helpful to

hear more information on what specific elements of the RADARS program are designed to yield an answer to that question.

DR. SCHNOLL: Certainly the drug diversion part of the program is trying to do that, but also as we do our field investigations the field researchers go into an area and, if possible, try to interview users, abusers in the area to get information about the source of their drug. They also check with other people, local police, people in treatment programs to get that information. As of this time, we don't have sufficient data to put together the types of ratios you would like and, hopefully, we will be able to get that in the future.

DR. SHAFER: How many abusers say I actually got this by scamming my doctor?

DR. SCHNOLL: Not many.

DR. SHAFER: Any?

DR. SCHNOLL: Yes, some do. Some do but it isn't that many. When we ask the question, as I mentioned, what they say is, "I got it on the street." How did the drug get to the street? I don't know.

DR. KATZ: As I indicated yesterday, there

are many issues that we don't have answers on and perhaps one of the things we could accomplish is not so much to give answers in the absence of data but at least to indicate what sorts of data are likely to lead to the right answers. Is that the sort of data that, in your view, would at some point in time, when it becomes available, give you the answers that you need?

DR. SHAFER: Absolutely. Not only do drugs have risk/benefit ratios but programs, like surveillance programs, have, you know, cost/benefit ratios. And, without knowing that information, it is hard to assess whether the program is doing anything, whether it is really worthwhile.

One other quick question, can you give me any examples from your RADARS program of how you have changed the marketing or promotion of OxyContin based upon the feedback that you got from the program?

DR. SHAFER: Well, one of the things we would do, we would gather information, say, about someone in an area who was inappropriately prescribing and needed more education. We would bring more education to that person to try to bring them up to date on proper prescribing. In fact, we

have one instance where a physician was prescribing the drug inappropriately. We had some targeted education with that physician and he realized that there were a number of people in his practice who were trying to scam him and actually reduced the number of people to whom he was prescribing opioids by about 20 percent. So, there was a very effective outcome in that.

DR. KATZ: Dr. Cicero?

DR. CICERO: Yes, I am Ted Cicero, consultant for the company. I run the Key Informant study and I am also the custodian of all the central databases at Washington University. I think what your question was is are we going to be able to--and I think if we can show that map again from Dr. Schnoll--

[Slide]

--are we going to be able to look in an area where we are getting reports of abuse, where is that coming from and also reports of diversion in those areas. You will see a lot of overlapping areas. We have identified right now at a very preliminary level about eight areas where we are seeing both diversion and high rates of abuse occurring. What we need to be doing at this

juncture, and we are in the process of doing it as you see with the map you are seeing here--we have many areas where there is extensive overlap of systems, the poison control; we have also the diversion sites; we have the Key Informant Network.

For instance, I can speak to St. Louis, that is where my residence is, and we are getting reports both of abuse and diversion. Looking into this, it appears that the two are very closely associated. Lots of the abuse is coming off the street and appears to have been diverted in a criminal sort of way.

Now, the question you are asking that we really can't answer is what percent of the street drug is coming from theft or coming from a physician. We don't really have a good enough feel for that now but the important thing I want to leave you with is that we have the power to be able to do it. I think by having these overlapping systems, the natural connection for us at this point is to say, okay, we have diversion in an area. Let's go in there and find out where that was being diverted to. Is it being shipped out of state? Is it at a local level? And the abusers themselves who say they got it off the street, did

they in fact get it from that source? My hunch based on preliminary data is that there is going to be a very strong association between theft of a drug such as this and what actually appears on the street.

DR. KATZ: Laura Nagel, would you care to add to that question?

MS. NAGEL: Thank you. We share your frustration in trying to determine where out of the closed system of distribution the drugs are being diverted. What we tried to do in preparation for this presentation is pull our cases. The majority of them are criminal cases. What Dr. Willis said was that in 60 percent of our criminal cases the source of diversion was a physician or a pharmacist. The other 40 percent were drug thefts, doctor shoppers, people like that. We separated out the doctor shoppers because we perceive that that is a physician who is unwitting, that was duped and, in fact, wasn't necessarily criminally liable.

So, we feel very strongly that although there are thefts, that if we can educate the physicians, if we can reach them whether it is in labeling, whether it is in some sort of restricted

manner, if we can reach the practitioners and educate them on the respect for the drug and the appropriateness for prescribing for the right patients at the right time, the right people will get the drug. But we perceive from our investigations that the physicians are a large, large percentage of our point of diversion whether unwitting or criminal. Therefore, we feel very strongly and support the committee's efforts to reach them because we have to do everything we can and this is a huge part of the problem for us.

DR. KATZ: Can I just ask a little bit about that? Do you have a feel for what proportion of the diversion that comes from the physician as a source is unwitting versus criminal?

MS. NAGEL: No, I would be guessing but we tried to do that when we broke out doctor shoppers. We didn't necessarily identify those physicians in the category we call criminal. If we perceived that a good doctor shopper duped them, well, education is going to help that but we didn't feel it was criminal so we dropped them in the lower 40 percent. But we still had 60 percent. Now, that is our cases; that is not the universe but it is the best data I can offer you, but 60 percent of

our cases were criminal for physicians and/or pharmacists.

DR. KATZ: Thank you. Dr. Baxter you are next.

DR. BAXTER: This is very excellent. I would like to commend you first on the presentation. It is very excellent that my opportunity to speak comes right now because it seems that the key step in risk management is the education of the physicians. In fact, the RADARS system itself is potentially going to be very excellent.

But getting back to the point that Dr. Crawford made and some of my other colleagues, it is very important, once again, as you cited, that the appropriate patient is selected. Patient selection is going to be probably key in terms of managing the risk not only for Palladone but for OxyContin as well.

It also goes back to what we previously discussed about the importance of assessing the risk of abuse because those individuals who are at high risk for abuse are probably not appropriate for selection unless there are certain precautions in place. I would wonder if it would be possible

to add into that boxed warning that patients with high risk for abuse require additional monitoring. Now, what the additional monitoring is, that can be debated but I think that perhaps by adding that into the boxed warning that would cause physicians who are prescribing to at least become aware that there are other considerations when you are prescribing this medication and other opiates to high risk patients.

DR. KATZ: Dr. Haddox, do you care to comment on that?

DR. HADDOX: I am just trying to get back to the boxed warning here. Slide 30, 31 and 32.

[Slide]

I think that this may partially address your concern, the statement there is where we make it a point, with the agency's agreement, that this should be in the boxed warning. Now, if there are other things the agency wants to consider we are certainly going to interact with them in that regard but, to my reading, this addresses your point. Maybe I am not hearing it exactly right but it seems to me that it sets a fairly high cautionary note early on in the package insert, in the ads, and so forth, that this does have abuse

potential and that this should be considered when prescribing or dispensing. I would assume then that those sorts of monitoring would be part of the consideration.

DR. BAXTER: I wouldn't assume that. I think that if it is not said, then it hasn't been considered. So, to go a step further, I think that it would probably be very helpful in helping prescribing physicians, especially those primary care individuals who are not familiar with dealing with patients who have diseases of addiction. It will alert them that they need to first investigate if a person does--at least ask the question because if you don't ask the question, you know, what the heck.

DR. HADDOX: Let me respond in two ways to that, sir. I think now I have a better understanding of what you are talking about. We have a number of educational materials in different formats that strike at exactly that point of how to do an interview looking for risk factors for abuse or addiction. We have it in different ways so that a physician will get the message at different times depending on the materials to which they are exposed. As far as changing the label, we will of

course be happy to discuss it with the agency.

DR. BAXTER: Sure.

DR. KATZ: Dr. Maxwell?

DR. MAXWELL: A couple of things. There was a question about trying to find out where drugs come from on the street and, unless I am mistaken, the instrument that is given to the field interviewers, the last one I got, doesn't ask the question of where they got it. There is no question like that. Secondly--

DR. KATZ: Actually, maybe it would be better just to take one piece at a time.

DR. MAXWELL: Okay, but that is not a question; it is just a clarification.

DR. HADDOX: May I make a clarification as well? That is not the entire contact that the field researcher has. That is sort of getting started, the beginning of the structured interview. The goal was to allow that person to go in. Depending on what we are looking at, those questions are likely going to be asked. Okay? So, the document that you have in your briefing document is sort of the beginning.

DR. MAXWELL: No, no, starting in June a year ago I was asked to be one of the field

researchers--

DR. HADDOX: Oh, I am sorry, when we say field researcher we mean the people that we have hired to go out to investigate signals. You mean you were asked to be a key informant perhaps?

DR. MAXWELL: Yes. Let me also clarify that the only zip code data that is collected from the key informants, from what I can tell, is the zip code where I live. In other words, if I sent in data from Ft. Worth it would not be reflected in the graphs by zip code.

DR. HADDOX: We are aware of that and we are endeavoring to correct that right now by asking the key informants who are at treatment centers what zip codes does 85 percent of your clientele come from so we can try to extrapolate--

DR. MAXWELL: Okay, well, that was not in the June format. I wasn't going to get into that until the question came up. However, one thing I would like to ask is yesterday we saw the DENS treatment data which was unable for most states to break out OxyContin, and it showed that in the past users of OxyContin stayed out on the street for about ten years from your first use until admission to treatment, but in the last couple of years that

has telescoped down to four years. Since you have the DENS data which does specifically ask about OxyContin in terms of our questions about the abuse liability and dependence, the question is are people becoming more addicted quicker with OxyContin as compared to other drugs? I would very much like to see the DENS data run looking at the lag on OxyContin as compared to other.

DR, SCHNOLL: I don't have those specific data right now. We could ask Dr. McLellan to run that information for us but I don't have the precise information.

DR. MAXWELL: Well, I realize that but it might be interesting.

DR. SCHNOLL: Yes. Yes, that might be something we could do.

DR. MAXWELL: Then, lastly, before we go forward with approving another drug I certainly would like to see more in-depth data. We have seen the presentation of what RADARS is going to do but I would really like to see data showing us all the data that has been collected, what is being collected, what is being done, how well the system is working so that we would feel more confident that when we then move into another drug the data

are there and we know the system works.

DR. SCHNOLL: We only had an hour this morning to present. We have extensive data on all of the drugs and just didn't have time, and what we selected were just examples to show you what we can do with the data system. I understand your request but there just wasn't the time to do that.

DR. KATZ: I think one take-home message that I want to make sure is left is that it seems like it is important for the surveillance system to be able, at the end of the day, to distinguish what proportion of street abused drugs come from the prescribing relationship versus coming from diverted sources. So, it sounds like people are recommending that at the end of the day we will be comfortable that the system will be able to accomplish that.

We are half an hour behind schedule and it looks like I have about 12 people still with questions and I have my own questions. So, what I think I will need to do is take one more question and then we will have to go on to our next presentation, and Dr. Saini, you are next.

DR. SAINI: We heard very good things about risk management but I did not hear anything

from the pharmaceutical company regarding the NASPER program. Do you have any comments regarding that, please?

DR. HADDOX: For those who are not familiar, Dr. Saini is referring to a Bill that is in Congress now that would make a federal prescription monitoring program that would be modeled on the CASPER program in Kentucky, which is an electronic program.

Purdue is in favor of well-designed electronic, non-barrier prescription programs. In fact, we have supported those in a number of states. While we share the intent of the sponsors for the NASPER program, I have my own--and I have discussed with other people both in and outside of government--reservations about if it will be too unwieldy to be useful. There are a number of issues. It is very complex, as you are no doubt aware. But I think that prescription monitoring programs right now are being done on a state level. They have been shown to be effective and I think that we will have to see where NASPER goes but I have some questions and other people have raised other questions about is it just too big a data set to manage appropriately.

DR. KATZ: I am going to take the privilege of asking one more question before we stop. We have heard from many people on the committee, and in terms of some of our lectures yesterday about the importance of monitoring the target population that we are prescribing these medications to for the development of negative consequences, other opioid use, including addiction. So, my question is what aspect of the risk management program that we are hearing about monitors our patients for those risks, and how is that data captured, analyzed, what are the outcome measures, etc?

DR. HADDOX: Well, one of the key elements there is the adverse event reporting system where abuse and addiction are by definition serious adverse events. We monitor that on a regular basis. But that is a passive system, as was pointed out earlier. As part of our education, we believe and certainly our numbers would suggest that with the education we put forth with practitioners we are making that perhaps a little less spontaneous reporting system and that we are sort of heightening their sensitivities. So, certainly if you look at the numbers of cases that

we have gotten in, we are getting more of that information and Dr. Schnoll has some comments.

DR. SCHNOLL: Yes, we also have a number of key informants and physicians who specialize in pain management and so we will be collecting information from them regarding what they are seeing in terms of the development of addiction in their own patients.

DR. KATZ: So, is it fair to say then that there is no prospective systematic means in this surveillance system for monitoring patients for the development of any of these complications?

DR. HADDOX: I am sorry, I didn't capture that.

DR. KATZ: I was just making sure I understood that. It sounds like the answer is that there is no part of the system that prospectively and systematically tried to get at the proportion of patients prescribed Palladone or any other opioid who develop any of these negative consequences.

DR. HADDOX: Well, again in the interest of time, we do have a patient registry study with OxyContin that is an open-label extension study of a number of our trials. We are finding that the

rates of aberrant drug taking behaviors or indicators of abuse or addiction are very low in that population, the intended population.

DR. KATZ: Thank you. We need to move on to our next presentation.

DR. APFEL: We forgot to respond to an earlier question about the pharmacokinetics of Palladone. We have checked back in the data and, as we suggested before, the accumulation of Palladone is very small. It appears to be less than 20 percent accumulation.

DR. KATZ: Thank you. Well, let me again thank the sponsor for all the trouble they have gone to in putting together this information for us. We do appreciate all the effort that has gone not only into the program itself but also into the presentation this morning. So, again, I appreciate your time and efforts. Now we need to move on to our next presentation and I would like to introduce Dr. Silvia Calderon, whom I have been keeping on hold for half an hour now, who is an interdisciplinary scientist.

Well, it has been suggested that I call a break and I can never say no to that type of suggestion so, good, let's a 15-minute break and we

will begin then.

[Brief recess.]

DR. KATZ: Hello, again. Just to bring people up to date on what we are doing schedulingwise, we will have Dr. Calderone's presentation now. We will go straight through Dr. Kreek's presentation, then straight through to Dr. Hertz's presentation which will be briefer than we originally thought. Then we will be going straight through to the Open Public Hearing. There are a number of Open Public Hearing speakers, so, to make sure that we don't have any delays, I would request that anybody signed up for the open public speaking make their way up to this--there is a row up in front towards my left reserved for Open Public Hearing speakers.

So, in the near future, make your way up there so we don't need to hunt you down.

Now, we will turn to Dr. Calderone from the FDA Controlled Substance staff who will speak with us about the FDA's perspective on the abuse liability of hydromorphone extended-release tablets.

Abuse Liability of Hydromorphone Extended-Release Tablets

DR. CALDERONE: Thank you very much.

[Slide.]

I will try to cover the abuse liability of hydromorphone extended-release capsules.

[Slide.]

Hydromorphone formulations have been marketed in the United States for many years as immediate-release tablets known as Dilaudid 2, 4, 8 milligrams, injectables, different concentrations 1, 2, 4, 10 milligrams per ml or a solution 5 milligrams per 5 ml and 3-milligram suppositories. Extended-release formulations are currently marketed in the United Kingdom and Canada to be administered once or twice a day.

Palladone represents a new extended-release formulation under the FDA review which is under review by the FDA.

[Slide.]

The proposed strengths of Palladone are 12 milligrams, 16 milligrams, 24 and 32 milligrams per capsules. This new formulation is being proposed for the use only in opioid-tolerant patients and its proposed indication is for the management of chronic moderate-to-severe pain in patients requiring continuous around-the-clock

opioid analgesia for an extended period of time.

Palladone capsules will release the contained hydromorphone over a 24-hour period and, therefore, are to be administered once per day.

[Slide.]

As it was presented to you yesterday, hydromorphone is a Schedule II substance and shares the same schedule with other opioids such as oxycodone, morphine, fentanyl. The meaning of Schedule II; drugs in this schedule have a high abuse potential. They have the highest level of control for an approved drug and, in terms of regulatory requirement, prescriber and dispenser registration, separate record keeping by dispenser, distribution order forms, no refills, manufacturing security and quotas, import and export permits.

Note that the CSA classifies substances by their abuse potential, dependence on by medical utility. We also know, note please, that the abuse potential, the actual abuse of a drug, goes beyond the abuse potential. There are several factors that contribute to the actual abuse of the drug.

[Slide.]

That is why, when we use the term "abuse liability," we refer to the abuse potential of a

drug, meaning pharmacological properties of the drug, and we incorporate, we take under consideration, a social and public-health factor.

Under the social, we incorporate the human sometimes extremely difficult to predict factor. This equation also includes the use of synthesis, the availability of the drug, includes what is known about the drug, the information available of the drug. So it goes beyond the pharmacological properties. It also includes the pharmacokinetics, the chemistry, self-administration, drug-discrimination studies, but goes beyond that.

So, therefore, abuse liability captures other factors and puts abuse potential into a social and public context.

I want to also mention that usually sometimes these terms are used interchangeably.

[Slide.]

It is well known that mu opiate agonists produce diverse effects such as respiratory depression, analgesia, miosis, drowsiness and also they induce changes in mood including euphoria and liking. Hydromorphone, oxycodone, morphine, all are mu opioid agonists. They all share the same type of properties but they exhibit different

relative analgesic and subjective effect potencies.

When analgesia, miosis and respiratory depression are measured, oral hydromorphone is approximately four times more potent than oral oxycodone and morphine whereas intravenous hydromorphone is six to seven times more potent than morphine.

It has been also shown that when euphoria and reinforcing effects of oral and intravenous hydromorphone were evaluated, hydromorphone was ten times as potent as morphine in drug-abusing subjects and in normal volunteers. Therefore, based upon these numbers, 10 milligrams or oral hydromorphone will produce comparable analgesia effects to 40 milligram of oxycodone or morphine.

On the other hand, the same 10 milligrams of hydromorphone will elicit an equivalent euphoria to 100 milligrams of morphine. It is also known another factor we consider in the evaluation of abuse liability is what is known about the history and abuse of the drug.

[Slide.]

Hydromorphone has a documented history of abuse in the United States dating back to the 1970s and it has been subject to the DEA Task Force

attention. Hydromorphone was historically the drug of choice among opioid abusers who often administered the drug intravenously after crushing and dissolving the 4-milligram tablet. Also, DEA reported that the 4-milligram Dilaudid tablet street value averaged $40 and that Dilaudid continued to be diverted and abused.

In the next two slides, I will highlight some of the findings of the Drug Abuse Warning Network Medical Examiners component. Yesterday, you have heard about one of the other databases reporting in DAWN. That is the emergency department. But I will be talking about the medical examiner's component.

Also, I will present to you rates, drug-abuse rates, per prescriptions dispensed and finally I will discuss the limitations that apply when calculating those rates. You will see there are many.

[Slide.]

The DAWN Medical Examiner's database reporting for the '99-2001 period 132 hydromorphone-related deaths and 1,272 oxycodone-related deaths for the same period of time. Adjusting these numbers by the total number

of retail prescriptions, the death rates expressed as number of deaths per 100,000 prescriptions are 7.5 deaths per 100,000 prescription for hydromorphone, 1.8 when considering the whole oxycodone market included single product and combination products.

When recalculating that rate, if we only include in the denominator oxycodone single-entity products, that rate changes to 6.1.

[Slide.]

These rates should be, or these ratios should be, considered crude estimates. We know that the Medical Examiner deaths do not represent national estimates and we know that DAWN only captures 128 jurisdictions out of 3,000 jurisdictions in the whole country.

We also know that the DAWN Medical Examiner Report may include multiple drug mentions and the cost should not be attributed to any of the drugs my itself. We also know that DAWN really includes brand names.

Talking about the limitations regarding the denominator, we know that sales data represents the whole U.S. market. We also know that the denominators include all formulations of the drug.

Although far from perfect, the calculation of these crude rates is relied upon in the field of drug-abuse epidemiology and they have been used to put these numbers into a context.

Having described all the limitations of the calculation, we might say that the difference in the rates might reflect hydromorphone's high potency. Maybe they reflect a different pattern of abuse or maybe the reports have been captured in different reporting areas.

[Slide.]

Based upon the data reviewed, hydromorphone appears to have higher abuse liability than other Schedule II opioids. When compared to immediate-release hydromorphone products currently available, due to high concentration of hydromorphone in the formulation, Palladone has higher potential risks of misuse and overdose than might result in death.

Also, Palladone poses significant risk of overdose in non-opioid-tolerant patients or if Palladone is misused and abused.

[Slide.]

So, in conclusion, risk-management programs should be designed to address the risks

associated with this high-dose opioid analgesia drug product and, as an example, Palladone.

Thank you very much.

DR. KATZ: Why don't you stay up there, Dr. Calderone. Are there any questions from the table?

Dr. Skipper first and then Dr. Shafer.

DR. SKIPPER: Thanks, Dr. Calderone. Do you, then, disagree with what Dr. Haddox said earlier that human and animal-abuse liability for hydromorphone was typically--is morphinelike?

DR. CALDERONE: I think we are confusing two terms. I totally agree that the subjective profiles of the drug are the same. They both are perceived different. We have higher euphoria, higher liking with hydromorphone and, in drug abusers, they would rather go for hydromorphone than for morphine in the same way that hydromorphone is perceived differently than codeine. They will actually see a differentiation.

I think that this profile is the same but there are differences among the mu opioid full agonists.

DR. SKIPPER: So the abuse liability is higher for hydromorphone?

DR. CALDERONE: If we consider the human factor that is sometimes so difficult to predict because we cannot control, the abuse liability is higher.

DR. SKIPPER: Thank you.

DR. KATZ: Dr. Shafer.

DR. SHAFER: A couple of things. I think that you have cherry-picked the data to make your presentation. If you take a look at various estimates of analgesic potency, relative analgesic potency, for hydromorphone and morphine, the Canadian package insert gives 7 to 11, based upon acute-pain studies.

Hill and Zackney cite a figure of seven- to eight-fold difference in analgesia potency. Maher and Forest, 1975, give 8.6. Goodman and Gillman list 7.7. The only study that is approximately 4, which you cite, is the study by Dunbar of 1996.

Similarly, if you look on the other side of the equation which is the subjective effects of the drugs, Jasinski actually gives a figure of 9. But if you look at the standard errors on that, it ranges from 0 to 20, so it is not an exact number. I mean, there is quite a broad variation there.

On the scale of subjects liking, the particular thing about what do subjects taste when they get the drug, he actually gives it a 6.8 which puts it right in the middle of the relative potency for analgesia. If you look at the scales that Jasinski has used and the maximum effect in terms of subjects liking, they are indistinguishable for morphine and for hydromorphone.

Hill and Zackney give a figure of 10, which is the figure you cited. But, again, their standard errors on that range from 6 to 20. So it is not clear from looking at the data that were provided to us that it supports the conclusion that you have drawn.

DR. CALDERONE: Hill and Zackney confirm, or they reported, ratio in terms--when analgesia is measured, they compared 7 to 1. The equal analgesic dose they use is 7 or, I believe that they have gone to 7.7 and their calculations were 7.7.

In terms of Hill and Zackney, they also confirm Jasinski numbers. We have variability in terms of the scale. That is something that we face and it is part of the design and the methodology for these types of clinical-abuse liability. But I

feel very confident we can report it as a ratio but I feel confident that the euphoria and subjective effects induced by hydromorphone, the rate is higher than equal doses.

So an equal analgesia dose is the euphoria and the liking is higher.

DR. SHAFER: All I will say is that the data that we were provided, the numbers don't line up.

DR. CALDERONE: If you read the last conclusion from the Zackney paper--for the Hill and Zackney paper--he confirms a rate of 9 to 10.

DR. SHAFER: I will read the conclusion if you want, but his actual words are, "slightly higher," which is a little bit different than how it is being represented.

DR. KATZ: Dr. Aronson.

DR. ARONSON: I want to pick up on a point of your discussion. I think it is a segue from the question that was just asked prior. I appreciate your conclusions that this is a drug of choice by addicts. I understand the differences of those conclusions being drawn. But one of the comments that was made in this morning's series of discussions that continues to resonate in my mind

was the estimation that there is about 5 percent of patients who have pain that will become addicts.

What is your opinion? Is there data to suggest that the likelihood of that population, that specific population, not the addict population but the patient with pain who could become an addict--is that chance greater with this drug in your opinion and is there data to support that?

DR. CALDERONE: I don't we don't have data to support the actual--to support iatrogenic addiction. What I think, it will be an actual estimate. I think that the percentage is very dependent on the paper you read. I know that those in Fishman reported, like, the incidence of the addiction in patients could go even from 5 and I believe it is up to 15 percent.

So your question is the hydromorphone--I would say that hydromorphone is a very potent and positive reinforcing drug. I think that we don't have a study to support that it will induce--the rates of addiction will be higher with this drug.

DR. KATZ: That is a research area of mine so I can contribute, I think. In terms of the question of what is the incidence of new cases of addiction in patients who were not previously

addicted resulting from the therapeutic exposure to opioids for the treatment of chronic pain, the answer is that there are no studies that address that issue. It is not that there are conflicting studies. It is that there are no studies.

The same is true for patients with risk factors for addiction. There are no studies that address that issue.

Dr. Skipper?

DR. SKIPPER: I just wanted to ask one follow up. Have we done anything to look at street value, I mean comparative, because it seems like I have read that hydromorphone has significantly higher street value than--

DR. CALDERONE: Actually, we don't do those type of studies. The information I presented was provided by the DEA but I really don't know if the sponsor and the RADARS data is collecting any type of information like that. I don't know.

DR. KATZ: Would the sponsor care to respond to--

DR. CALDERONE: The sponsor might have some other information than what we have.

DR. CICERO: I am Ted Cicero, again, from Washington University. Yeah; we do. I think, at

least for OxyContin, the street value is about $1.00 a milligram as it goes up. The hydromorphone, itself, is about $40 a tablet, as best we can tell.

There was also, I think, the question about potency. I think that was raised and I think one of the questions came up and if I can, I would just like to interject at that point. There is no data. There is absolutely no data to support the assumption that compounds with high affinity for the mu opiate receptor are intrinsically any different in their abuse liability.

I think what is getting confused here is that potency is a very different issue in terms of efficacy than it is in terms of producing abuse liability. If you look at the data, all the data in humans and animals, if it has affinity for the mu receptor, it is guaranteed to have reinforcing effects and have a potential for abuse liability. Intrinsically that is a feature of all compounds that have an affinity for the mu agonist.

The fact that one compound requires a microgram where another compound requires a milligram to produce the same effect is irrelevant. This is an important point because you are

suggesting that a given compound, like hydromorphone, has more intrinsic abuse potential than another compound such as fentanyl. That is simply not correct and that is based on many other factors that enter into it.

DR. KATZ: Thanks. Just to return to the program.

DR. CALDERONE: I really want to go back to that question. I really disagree.

DR. KATZ: Go ahead. Dr. Cicero, you can go ahead and sit back down. Thanks for your input.

DR. CALDERONE: I really disagree with that statement. It believe that abuse liability is more than receptor occupancy, more than binding. There is a human component into the abuse liability. It is true, like, Goodman and Gillman even cites the abusers do not distinguish between heroin and hydromorphone and they do distinguish between heroin and any other opioids.

If you have an abuser, will go for the hydromorphone, will not go for the codeine. So, although this is independent of the potency and the receptor occupancy, we know that abusers distinguish between opioids. That is why we try to incorporate the human component into the

abuse-liability calculation.

DR. SKIPPER: Would it not be--I am just following up my question.

DR. KATZ: If you could just, next time, indicate that and I would be happy to recognize you.

DR. SKIPPER: Okay. I thought I was still recognized. But, anyway--

DR. KATZ: You weren't.

DR. SKIPPER: Okay. My light was still on.

DR. KATZ: You forgot to turn it off.

DR. SKIPPER: Would it not be valuable to do some survey to see, at the street level, how addicts value this because wouldn't that be where the rubber meets the road, to take into effect the human component and is there any plan to do that?

DR. CALDERONE: I don't know of any plan to do that, but I think that the study should be designed carefully. We need to think about--the details of the study should be really clear. But it will be extremely valuable to have that information.

DR. KATZ: Just to respond. There was a study published by Daniel Burkhoff a number of

years ago who did go into a prison to patients incarcerated for opioid abuse and asked them to rate which ones they liked most to least. I forget the order, but hydromorphone was near the top of that list.

Dr. Skipper and then Dr. Shafer and then Dr. Cush. Dr. Shafer?

DR. SHAFER: Let me mention that the subject on the table here is a pharmacokinetically modified form of hydromorphone. That is very relevant because the one place where these drugs are distinguished is the rate of onset. Heroin has a very fast onset. There it is really the rate of crossing the blood-brain barrier.

Hydromorphone has an exceedingly fast rate of crossing the blood-brain barrier and I am not surprised to know that subjects find the experiences very similar with I.V. dosing of the two.

With an oral form which is intended to actually--and, as you saw from the graph where the levels in the plasma rise very slowly, that pharmacokinetic difference between the two I.V. pushes of the drugs, or let me say the pharmacokinetic similarity in terms of the brain

concentrations following I.V. push are virtually irrelevant, so it is not clear how extrapolatable those data are.

DR. KATZ: I think, to summarize, it is clear that hydromorphone, by any form, has a high abuse liability.

Dr. Cush?

DR. CUSH: I don't have questions.

DR. KATZ: Are there any other questions for Dr. Calderone based on her presentation?

Thank you very much for speaking with us. Our next speaker will be Dr. Mary Jeanne Kreek, whom I am delighted to introduce. She is a professor and Head of the Laboratory of the Biology of the Addictive Diseases at Rockefeller University. Anyone who has got even the most tangential interest in this area will know that Dr. Kreek has been really a pilar of this whole field for an extended period of time and it is a privilege for us to have her here.

Long Acting Opioids: Challenges in Pharmacology

DR. KREEK: Thank you very much, Dr. Katz.

[Slide.]

Thank you all for inviting me to be here today. I have been asked to speak today on the

general topic of challenges with long-acting opioids. What I am going to cover today will really be a mixture of topics but really focusing on my perspective which is addiction and the treatment of addiction.

I really have to put up for something that is not on any slide, but I will be addressing different kinds of problems related to long-acting versus short-acting opiate use, some of the nuances, some of what I perceive, at least, are the societal needs at this time.

But, at the same time, I would like to point out one question that I think has not been asked today and I am going to put it up front because I think it is very central to when you are considering abuse liability, and that is who is the abuser and who is participating in abuse. It is an additional question to the very cogent superior questions I heard about where is it coming from, how is it coming, how is it getting to the abuser. Those are all very, very important questions. But who is the abuser is also a critical question.

I will tell you from years of trying to answer that question, being forced to answer that question, I have found that most of the abusers in

our urban centers are persons who actually have heroin addiction and are looking for either sustaining their heroin addiction and/or unable to get into treatment.

I think one thing I would like to say a priori; we must, as a society, I think, accept addictions as diseases separate from each other in their later forms and we must aggressively treat those addictions so we decrease the numbers of persons at risk while--and I am primarily a scientist--we try to learn more about the basis of addictions, who is vulnerable, what are they vulnerable for and how can we do better primary prevention as well as early intervention.

Those are kind of philosophical comments, but I think they need to be said and we do need to ask who are the people misusing drugs of abuse.

[Slide.]

In terms of major issues, I am going to start with my summary first and then I will go into some of the specifics. Your handout, handed out today, if you got a colored copy, is actually easier to read. If you didn't, I'm sorry, but it will go into things I certainly won't have time to cover.

Major issues; I think education is critical. How we are going to do education, how the FDA, DEA, all our wonderful regulatory organizations and our scientists and our schools and our private sector can all provide education. We all have to work together to do it.

There are some major problems very specifically related to physician use or prescribing of long-acting opioids. They are major problems that I think we need to think about addressing generically as well as specifically.

One, there has been a lack of education in recent years of classical pharmacology, pharmacokinetics and pharmacodynamics. That is a general statement that I think we all will concur. Look at medical students now as opposed to five, twenty and thirty years ago.

However, having said that, that is no excuse. It needs to be updated and it needs to be made adequate. One of the real gaps I have found, as I have lectured to scientists but also physician-scientists and physician groups, is the lack of knowledge about long-acting versus short-acting opiates, mu opioid receptor agonists.

That is astonishing. I also find that

lack of knowledge with DEA and FDA and others in regulation as well as many other lay people. So I think we need to worry about the medical education. We also have had both discovery, synthesis and development of both intrinsically long-acting, methadone, LAAM, buprenorphin as well as formulation of short-acting compounds into long-acting preparations.

[Slide.]

There is also a lack of medical-school and other healthcare professional and neuroscience education about addiction. The specific addictions, approach to treatment, identification, diagnosis and management. There is a real lack of awareness of prevalence. 10 to 20 percent of all Americans have an addiction. Look around the room. There are a lot of you.

There is lack of knowledge about genetic vulnerabilities, predictable chronic-drug-use induced changes in the brain and environmental factors ranging from early prenatal and perinatal problems to set and setting, peer pressure, availability and host factors.

So we have physicians as well as other healthcare professionals who don't know enough

about the long-acting versus short-acting mu agonists pertinent to today's discussions and we also have physicians and healthcare professionals that have been taught very little about addictions.

There are medical schools that do a very good job in one or both and there are some that do a poor job in both. The same is true for nursing schools, for science educators at the post-graduate level. We, therefore, have problems. Inadequate knowledge; that can lead to increased morbidity and mortality which I am also concerned about. Today is focused on abuse liability, but I can concerned about the deaths that occur when physicians misprescribe because of lack of knowledge.

[Slide.]

There are also physicians with inadequate time. The pressures of HMOs force many physicians to be close to script writers even though they didn't plan to do and they don't want to be. The majority of problems lay in these two realms; inadequate time, inadequate knowledge. Some do wish for profit or are willing to, for diverse reasons, become prescription writers; that is, the illicit practice of medicine.

I do think this is also important.

Similar constraints of specific education and time lead to inappropriate enforcement. I have had the great privilege to teach many DEA field officers about long-acting versus short-acting opioids and when it is appropriate to use which. I have to say, they have been incredible responsive. Denise Curry and I have discussed over the years how wonderful it would be to have even broader teaching manuals for our enforcement people. This, of course, is in our context of pharmacotherapy for opiate addiction.

[Slide.]

What are the prevalences of addictions in the U.S.? Approximately 15 million alcoholics, 2 million cocaine addicts and about 1 million heroin addicts. You see absolutely lacking on this slide persons who are addicted to licit drugs and broken out by type like mu agonists. We actually don't have those data. We have talked about it today, the need to general better data, more data.

Many groups have tried. It has been very difficult to do so. It needs to be done much more thoroughly. There will be inherent problems even if one does a better screening. For instance, we have just heard by the DAWN network, you get a

denominator that is simply compound. It cannot be finer than compound. You do not know the formulation, the route of administration, the mode of administration, when you do such kind of detection.

This is something that I may or may not get to today but I want to point out that approximately 1 in 10 to 1 in 20 who self-expose to alcohol become alcoholics. About 1 in 10 to 1 in 20 that self-expose to cocaine become cocaine addicted. About 1 in 3 to 1 in 5 that self-expose, nonprescription, non-medically indicated, to heroin, become heroin addicted.

Again, this becomes terribly important when one considers the question of who is misusing or abusing a drug such as an opiate formulation. Is it someone is already addicted? Is it somebody who is a drug abuser trying a lot of things? I think we could expect to see very different kinds of outcomes depending on how we define the terms. Critical.

[Slide.]

What are the factors to develop an addiction. This is actually a very early formulation from my lab but I don't think there is

much controversy about the three major types of components. We now know that, of course, environment plays a very important role and I have run over some of these, set and setting, cuing, comorbidity, both psychiatric and medical, as well as peer pressure, stress and stressors which is on some of your handouts, not on others, I am not going to get into today.

I would be glad to come talk another time about that, but we know that stress and, indeed, pain is a stress, stress alters responsivity. But there is evidence to suggest in the setting of pain, there is less of a pleasant euphoric drug effect and more of a pleasant relief-of-pain effect.

Genetic factors. This is sobering but many studies have shown that 25 to 50 percent of the relative risk of developing addiction is on a genetic basis. The studies for alcoholism are three decades old. The studies for other drugs of abuse are much more recent. However, there is a controversy about whether or not there are specific genes dictating for specific addictions.

Our own formulation is closer to that of Ming Swann at Harvard which is there will be many

polymorphisms of many genes contributing to any addiction. If one happens to have depression or anxiety syndrome, the genes contributing to those disorders may also contribute.

But there will also be some variants that are very specific for specific types of drugs of abuse. I think the data, not only epidemiology but of specific polymorphisms, is beginning now to bubble up to support that Swann hypothesis which we also agree with.

Drug-induced effects. This is extremely important. The people to my left may get nervous about it but we know that chronic exposure to drugs of abuse alter the brain. We also know, however, that the on/off effects of drugs of abuse alter the brain in ways that sometimes steady state doesn't. Now the people to my left will feel very happy because what my lab has shown is that the more one approaches steady state, the less problems you get in altering the brain and those very brain changes may contribute to the behaviors that we know as self-administration and addiction. It is a powerful statement.

[Slide.]

We know the endogenous opioids are

involved in each of the addictions. I have heard no discussion of those today. Probably it is in more arcane sessions but, in fact, we are always talking about the competition between the need for more, the lack of enough endogenous opioids and, therefore, the administration of exogenous opiates, whether it is for the relief of pain or modulation of other systems.

[Slide.]

The mu opioid receptor was cloned about a year after the delta receptor was cloned by Kiefer and Evans, and Leah Yu and George Uhl. Two groups simultaneous came up with a mu receptor which is this longest one and which has more unique amino acids, primarily because of its length, with the other uniqueness of each of the three receptors residing in this extracellular and intracellular space where binding occurs and where signal transduction occurs.

This is going to be important. I am sure this committee has seen come and go kappa ligands and will see coming and going delta ligands as well as mu ligands. They have some actions in common, some differential actions and they, in part, mimic the endogenous opioid system.

[Slide.]

It was alluded to by Dr. Katz that I have been in the field for some years and sometimes my former mentor, Dr. Dole, likes to refer to the fact that I started when I was five or six, which is very complimentary. But in 1964, I had the opportunity, as a first-year resident in internal medicine to cross 68th Street from what is now Cornell Medical School New York Hospital to the Rockefeller University to join a team that was then coalescing headed by Dole who recruited two women, Dr. Neiswander, a seasoned psychiatrist working in addiction, and myself.

As we would, like with this people that Marie sent us to see on the streets of New York and the prisons and the detox centers, Vince and I became convinced, and now I think there is incredible data to support it, that heroin addiction is a disease. It is a metabolic disease of the brain with resultant behaviors of drug hunger, drug self-administration, despite knowledge of negative consequence to self and others.

It is not simply a criminal behavior or due alone to any sort of personality or other personality disorder. The elegant studies of

Weisman and Ronceville and others have shown that a wide spectrum of psychiatric disorders may be comorbid conditions. Indeed, if you look at the flip, about 40 to 50 percent of heroin addicts have no comorbid condition.

[Slide.]

Heroin is very short-acting in self-administration, therefore, self-administration occurs three to six times by the heroin addict. When they can't get heroin, they will look for another reinforcing drug. And, yes; intravenous hydromorphone, intravenous morphine, are high on that list.

When they can't get a reinforcing agent, they like to get illicit methadone. It has been out there. It was called "dollies" when we began our work, dolapinhydrochoride, and, in fact, they would all say, "If you can get nothing else, take a dolly. It will help you get through your withdrawal symptoms."

Now we hear illicit use of methadone by many who are saying, "Take methadone and self-medicate while you are waiting to get into a treatment program." We have inadequate treatment programs primarily, I believe, because medical

education has not taught this is the disease that must be addressed by physicians and all the manpower that goes with physicians, healthcare personnel, in general. I think that is extraordinarily unfortunate.

If you look at this arrow which follows our narcotics blockade tolerance paper of '66, you will see the what we ask after the first studies where we had found that one could induce people into treatment with this compound, and I will come back to that in a minute, we had to study its safety.

[Slide.]

What were our goals in '64 for a medication to treat an addiction? I present these because I think they are critical for treating an addiction but what we have learned, and what we had learned by the first ten years of our work, made us begin to education pain specialists. I think some of you may cringe on the committee but, in fact, it was crossing the street to Memorial that allowed us to help share what we were learning with Dr. Hood, Dr. Foley, Dr. Portenoy, names known to many of you, about the potential efficacy of long-acting opioids and, contrary to my medical-school

education, that tolerance develops much more slowly when you have sustained opioid level than when you have intermittent opioid level, something now readdressed and affirmed in animal models by many groups.

So we wanted a long-acting opiate to prevent withdrawal symptoms, to reduce craving and also to normalize any physiologic function disrupted by drug use. We wanted to target treatment agent to a specific site of action such as the receptor.

Dole, along with Collier and Martin, and our group, the three of us at Rockefeller, we talking about opiate receptors in '63, '64, as the work was conceptualized and then initiated in '64. But the receptors were not fully defined satisfactorily until '73 when Schneider, Teranius and Simon, all three, did so within a month.

[Slide.]

We also wanted a medication that was orally effective. Why? To get away from the lore and the dangers, then hepatitis B, later HIV, now C, of use of needles, sharing of needles. We wanted a--and I think this is critical and not necessarily satisfied in some formulations into

long-acting, perhaps of long-acting, drugs a slow onset of action, a long duration of action and a slow offset of action.

Now, there are two kinds of long-acting compounds, but, at that time, we were looking for one with intrinsic long-acting properties.

[Slide.]

Ray Hood had been, as part of the U.S. government, in postwar Germany and had brought this compound back thinking it might be good for pain management. It had never been brought to the clinic in any of its studies in Europe. This compound was studied by Hood at Memorial and Beecher at Harvard. I am sure some of you have read the classic papers where they found a single dose of methadone was similar to morphine and efficacy of about three to six hours.

But when multiple doses of morphine were given to an opiate-naive person, both Hood and Beecher saw respiratory depression ensue. They knew, therefore, that methadone would not be good to give to opiate-naive or weakly-naive persons. They, therefore, dropped it from much more studies for pain and, in fact, it had been used only very modestly by the Lexington group for short-term

detoxification of opiate addiction.

But when I read that study, or the studies, from Beecher and from Hood, it became apparent to me that, even though we had no gas chromatography, no radioimmunoassay, we had to look and talk to patients to make our observations, that this compound might be intrinsically long-acting and, clearly, morphine and heroin, in its diacetyl man-made variant, are not. They are very short-acting.

[Slide.]

So we started with low-dose methadone 10 to 20. This is an induction which is still recommended for methadone and buprenorphine. Start with low doses and taper them up even when you have evaluated that a patient is tolerant, then, going up still slowly, so that the degree of tolerance was never exceeded. We found that a person could be totally functional behavioral with no drug craving.

[Slide.]

In our cross-tolerance studies, we superimposed intravenous heroin, intravenous hydromorphone, intravenous methadone and intravenous saline against the background in two

series, each four weeks long, of Latin square, double-blinded designs. We found that 80 to 100 milligrams a day of methadone would blockage against the intravenous effects of up to 200 milligrams of heroin.

Now, these were important studies that have been replicated four times for methadone, two times for buprenorphine and two times for LAAM. Cross tolerance develops. Cross tolerance is critical.

When we introduced the concept that methadone, indeed, is superb for management in chronic-pain patients, and parenthetically has become the major analgesia of choice in several countries, we taught induction, stabilization, but here to stay just over the degree of tolerance developed by an individual to be able to achieve pain relief.

And the groups doing that find that much lower doses sometimes in the realm of 30 to 50 mgs a day are adequate.

[Slide.]

One can see this tiny bump clinically observed. We found that, indeed, methadone was profoundly different; oral onset after 30 minutes,

duration of action 24 to 36 hours and withdrawal symptoms after 24 hours. But it was not until a few years later, about nine years later, that Chuck Interisi and I independently developed gas chromatographic methods for measuring plasma levels of methadone.

What one sees after an oral dose is this modest rise, barely a doubling of the nadir and then a steady state over the 24 hours. The 22 to 24-hour data were not published until 2000 when Jay Pett let us publish it as part of a PET study. It is flat as a pancake.

When methadone is used in divided low doses for management of pain, most of my colleagues in pain management prefer to give it two times a day or sometimes three to get this modest little bump. It is not necessary to do so and we hold their hands, but patients sometimes feel more comfortable having that bump.

Heroin has a half-life of three minutes, its 6-acetyl metabolite, 30 minutes and about four hours for the active monitor metabolite. Methadone, both Interesi and I learned, in its racemic for use in therapeutics for pain or addiction has a half-life intrinsically of 24

hours. Using stable isotope techniques with selected ion monitoring GAMS, we learned that the active enantiomer has a half-life of 48 hours. This is what we find at the 22 to 24th hour after methadone dose, flat as a pancake.

[Slide.]

We went on to ask how much occupancy of the brain is required working with Eckelman here at the NIH and Kenner Rice, we first were able to map thirteen major regions of the brain for mu receptors not done before this study. We have a steady-state ligand for radionuclide as long acting as is the compound and we found that, indeed, the pain regulation center of the thalamus has the highest amount of mu receptors in healthy humans followed by the limbic system which we know is involved in reward, emotion and addiction, the amygdala, the anterior cingulate as well as the nigra-striatal system also involve in long-term memory and consolidation, the caudate and putamen, part of the nigra striatal system.

[Slide.]

Shown in the orange bars, as we predicted, there is less than 20 to 30 percent occupancy by methadone during steady state when doses of 80 to

100 milligrams a day, adequate treatment doses for many patients, are used.

[Slide.]

We know that this was a predicted result since our laboratory and others had shown that each of these functions, disrupted by the on/off effects of short-acting opiates such as heroin including stress responsivity, gonadal function, immune function as well as other functions such as GI function, not mentioned here, all normalized during steady-dose methadone treatment.

So, 20 to 30 percent occupancy allows 70 percent or more of mu receptors coupled and ready to go with the endorphins acting there for their normal modulation.

[Slide.]

There are now 200,000 people in the U.S. in treatment with methadone. That is about one-fifth of the estimated persons eligible for treatment and methadone is still hampered by regulations that insists there be one year of heroin addiction, multiple regular self-administration. The one alteration when buprenorphine was approved last year by the FDA for treatment of addiction was DSM-IV diagnosis of

addiction was allowed as entry. That would be about two to three months of daily multiple self-administration in most cases.

We know that there is a voluntary retention in good programs which use 80 to 150 milligrams a day of methadone combined with adequate doses of behavior and counseling as documented by the McLellan-O'Brien group to be essential and that heroin use steps down so that, by one year, less than 20 percent of programs using adequate medication and behavior had any illicit heroin.

[Slide.]

When you see higher uses than that, you have to be concerned. We also have learned several things about this compound. All mu opiates are not alike. They are full agonists. They are partial agonists. A beautiful example of a new treatment medication that is a partial agonist is buprenorphine.

Mu agonism is a characteristic of methadone with probably the fullest agonism of any compound according to Steve Childers latest cell-biological work. Also, after the cloning, one could ask the question of what happens when

endorphins bind to opiate receptors. You probably all know that they internalize and we now know that only two of the exogenous compounds robustly internalize after binding and the only one used in pharmacotherapy is methadone. It behaves exactly like beta-endorphin and metencephalon.

It binds to the receptor and goes inside. So what? We don't know yet, but we think it may, in fact, have a great deal to do with the rate of development of tolerance--tolerance. Remember tolerance and physical dependence are dissociable different molecular phenomenology.

I was pleased to hear Dr. Kleber deny DSM-IV and say dependence is not addiction. I hope we can get the term changed. 100 percent of long-term opiate-treated persons for pain are opiate tolerant and they are opiate dependent. They are not addicted. Addiction means compulsive drug seeking and compulsive drug taking despite negative consequences to yourself.

A methadone-treated patient who was no longer using illicit heroin is no longer a heroin addict. If they are not illicitly abusing cocaine or another drug, they are no longer an addict. They are a former addict in management with opioid

pharmacotherapy. Our semantics are critical if we are going to communicate.

Now, I heard today two or three different people say not more than 5 percent of pain patients become addicted. Those are the guesstimates that are usually out there. There have been no rigorous prospective studies. They are very tough to do. We appreciate that.

5 percent is not nobody and 5 percent is a number that I think may, in fact, be correct because we do know there are certain persons that come off their need for opiates. Their pain source is gone and they cannot be tapered off. I will say I think the very best pain doctors continue to manage them and manage them correctly.

Some pain doctors are nervous about that. The patients, therefore, do doctor shop. When they doctor shop, they get the label of addict. We all, in our treatment resources, have some persons referred to us who have been shoppers. Others simply difficult-to-manage pain patients and other persons that no longer need it.

The final "twofer," if you will, with methadone, or maybe it should be a "threefer," now, full agonism, internalizes like endorphins and both

enantiomers have NMDA-antagonism modest activity. Therefore, like the MK801 which started in the clinic and failed, but we know that NMDA antagonists do attenuate tolerance.

So it is hard to dissociate with methadone whether the very, very slow development of tolerance is because of full agonism, internalization or NMDA antagonism or some combination of above.

[Slide.]

Now, we know that desirability, craving, hunger lead to self-administration. We know the dopaminergic system is involved in this and we know that certain regions of the brain play a real role, and we know that mu agonists can alter dopaminergic function. But there is ample evidence, including the work from Koobenbloom and from our own lab suggesting you can get rid of dopamine and there is still self-administration.

You get rid of the mu receptor and there is no self-administration. However, I think key to all the considerations of any compound is in the reinforcing properties of opiates and, to date, most but not all other drugs of abuse, the exception being the hallucinogens. But the rapid

rate of rise, be it of heroin or of cocaine, in blood and presumably brain are positively related to their reinforcing effects.

So if you recall that first curve of heroin, rapidly up, rapidly down, the rapid fall from blood and brain of drugs of abuse are positively related to the onset of the negative reinforcing or withdrawal effects. So, ideally, one wants to achieve a steady state.

[Slide.]

Now, unfortunately, many formulations try to achieve that, but the flatter the curve, the better, the slower the onset the better, and the less possibility there is for crunching, mooshing or whatever terms are currently used in the package insert, the better.

I would argue that intrinsic properties are even better because intrinsic properties you don't have to worry about formulation. You take the compound as it comes. We have been able to show--and those of you who are rat and mouse doctors, like I am part of time, methadone is the fastest half-life of the mu agonists in the rat and mouse. 48 hours in humans for the active enantiomer, 24 hours for the racemic.

Half-life in a mouse is 60 minutes. Half-life in rat is 90 minutes. So if you read a study on methadone in the animal, you have to rethink that.

[Slide.]

LAAM is also very long-acting. LAAM is enjoying some use but not a lot because of the QT interval. I would love to speak to the FDA about the QT interval issue another time. We have very good computer-driven EKG machines now which is overreading in every medication. So we have got to get the cardiologist to weigh in what is clinically relevant. That is across the board for AIDS drugs, phychotrophic drugs, opiate drugs, et cetera.

LAAM has metabolites that are active, unlike methadone, and the metabolites make it even longer acting.

[Slide.]

Buprenorphine approved a year ago is a compound which is a partial agonist, no oral prep. The sublingual prep, however, has enormous abuse liability in many countries of Europe and India.

This has led to its being recommended to be formulated with naloxone. The first naloxone preparation with an opiate was done in 1972 when we

published a paper in 1973 that I bet not more than three in the room have read where we combined naloxone with methadone. The problem was we didn't need it because methadone is an extremely boring drug.

I showed you its profile when given orally. It has a very slow onset of action and, even if you give it intravenously, it binds to every plasma protein which we later were able to elucidate. Its first pass through the liver is not rapid biotransformation. We showed in a perfused live prep, it is bound there and is slowly released like a gigantic spantab. So it sticks to all proteins, specifically and non-specifically. It is released from the liver. Unchanged methadone comes out in bile, undergoes enterohepatic and comes into the blood stream as unchanged methadone.

For most compounds, that is not true. Buprenorphine intravenously does have a very rapid onset of action. Therefore, many abusers would take the sublingual prep elixir and inject it to get a high. By adding naloxone, naloxone has a half-life of only thirty minutes so you don't protect all the opioid-agonism effect, but you blunt the high.

The same was true with the old T's and blues problem where naloxone was added to pentazazine which was being used intravenously. You prevent the high by adding the naloxone, therefore decrease the bioavailability. Whereas buprenorphine has a long dynamic action of 24 to 48 hours, its half-life is extremely fast, three to five hours. Its sustained action is due to its very long mu-opioid-receptor occupancy.

That occupancy is so tight, however, that, in the anesthesia literature, some of you will be aware of a few anesthesia-overdose deaths where naloxone and naltrexone and namefine could not reverse the effects of buprenorphine, not many when taken by the sublingual route. The maximum effective dose in humans is 24 to 32 milligrams. Unlike the rat, there is not an inverse-agonist effect.

[Slide.]

The treatments for addiction now. The effective ones are the top three, methadone maintenance, LAAM maintenance and buprenorphine-naloxone maintenance which are comparable except for the fact for those with high degree of tolerance and physical dependence, the

highest dose, effective dose, of buprenorphine, 24 to 32 mgs, approved 16 mgs, is the equivalent only to 60 to 70 mgs of methadone.

The Hopkins group of Stitzer and Bigelow have recently reproven our early data that the majority of patients need 80 to 150 a day of methadone and, in fact, with the purity of heroin now so high in the Northeast, it may be even higher.

So, to conclude, to provide the most effective treatment for major addictive disease we need to have a combination of behavior and pharmacotherapy and mu agonists are our answer for those long-term heroin addicts and other opiate addicts. To provide the most effective treatment of pain, we need long-acting mu opioid agonists.

[Slide.]

We need them both. So I would propose that any healthcare provider should ask the following questions of themselves when thinking about using a medication. Is the medication formulation short-acting or long-acting. That is not a judgmental question. That is an academic question. I put up front, I think, for chronic pain, long-acting is better.

On the other hand, you have to know what long-acting means, what its ramifications are, what its dosing intervals are, once a day, twice a day. You have to know precisely what its onset and offset are.

You secondly have to ask is this patient opioid naive, modestly exposed, long-term exposed, and thus tolerant. Long-term formulations are really not appropriate for anyone who is not long-term exposed and tolerant.

Finally, you have to ask the question, does this patient have a problem with some kind of drug abuse or addiction. Most of our patients come to us with family histories of alcoholism, not other drug abuse, because the other drugs were not so available two generations ago, one generation ago.

Or are there other indicators suggesting increased vulnerability. Do you need to treat persons with vulnerability to develop a addiction for pain? You bet you do. You need to treat persons with an addiction who have bona fide pain as well.

People ask me about managing methadone maintenance. I will tell you what you have to do

is use a short-acting opiate superimposed on the steady state of long-acting. Don't increase the long-acting. It won't work for acute pain. Superimpose it and then back off quickly.

But we need to ask these questions--I would argue we need to make every physician do a check list to ask these questions and say, "Have you answered each one of these?" before you make your prescription.

[Slide.]

This is simply the compounds we could be talking about.

DR. KATZ: Dr. Kreek, I am going to have to ask you to wrap up because of the schedule.

DR. KREEK: That's it.

DR. KATZ: Thanks very much for your insights. I appreciate it. I think we should take the time for a question or two. Dr. Bril, you were first.

MR. BRIL: Thank you for the fascinating talk. I guess my fundamental question then would be what is it about this class of receptors that results in an irreversible change, I guess, because your addicts really need to be on a sustained methadone program or some exogenous opiate instead

of endogenous production looking after the receptors. What happens that causes that?

DR. KREEK: Actually, you have hit on something that is the origin of a lot of research, is there some way that we can make the endogenous opioids do the job. And the answer is acupuncture doesn't get it up there high enough and all the blockers of biotransformation of encephalins have not worked to date.

It is a laudable goal. I will ask, are there other examples where brain changes occur and, indeed, with many diseases, there are examples of the brain changes occurring. Some of the changes occur in Parkinsonism and Alzheimer's and other neurodegenerative diseases have some parallels in certain aspects of each of the addictions.

We know that, in endocrinopathies, in general, and I would say as a class of diseases, the addictions come very close to some of the endocrinopathies where one has an excess, either sustained excess or pulsatile excess, of hormones. One can see changes downstream from receptors in signal transduction systems and, on further downstream, in integrated, if you will, in this case, neurobiology.

So the fact that short-acting drugs of abuse, and I could have shown you three zillion, mRNA, peptides, proteomics, what have you, that change, very notably, for the opiates, constant interactive receptor bombardment with a short-acting opiate like heroin, like morphine, alters the gene expression of genes that regulate our stress responsivity, for instance CRF and CRF receptor. Those are downstream events.

But these, then, in turn alter behaviors. What we find when we give a steady dose which is actually moderate or high, depending on your perception, you undoubtedly increase the thermostat to a certain point that a new homeostasis develops.

You can call it homeostasis, as you will recall from med school, until it becomes disproportionate. Then it becomes disruptive and the word allostatis is used by McCuen and Koob and others for that state. But we know that a steady dose of, for instance, methadone, LAAM or buprenorphine actually allows objectively studied disrupted physiology to normalize.

We have many published studies as do many other people. So I can show those to you. But notably is stress responsivity which our own group

thinks is quite central to the acquisition and development of addiction. What I didn't get to show you but we now have some polymorphisms that, in fact, alter binding to beta-endorphin.

[Slide.]

Look at the two right-hand panels, signal transduction after beta-endorphin binds. Beta-endorphin requires, obviously, the full integrity. This polymorphism, one in five of you in this room have a copy of, the allelic frequency is that high. Friends of ours at Hopkins proved what we predicted. They got there first. My people were furious.

[Slide.]

You give naloxone challenge, a paradigm we developed. If you have one copy of this very common polymorphism, you have different stress responsivity than you do if you have the heterozygote shown in blue.

[Slide.]

My friend Chuck O'Brien did another study I asked him to do, please. He had studied naltrexone for treatment of alcoholism which you guys approved a couple of years ago down here--many years ago, actually.

He and Krantzler got together. They went back and consulted their patients who had been in a naltrexone trial because they were consented for genetics at the time. This paper is just now coming out in Neuropsychopharmacology. What Chuck and Hank were able to show is that persons with one copy of this variant are the ones that respond to naltrexone treatment for alcoholism, nobody else.

So there is a lot of exciting stuff coming along with polymorphism. No doubt, the genetics are playing a role. I can't tell you a thing about addiction yet. That is not true, but I can't tell you because the paper hasn't come out yet. I can tell you that the polymorphisms are going to begin to be essential, gentlemen--I'm sorry--for studies of pain management in the future, in the very near future.

Thank you.

DR. KATZ: Thanks very much for your insights, Dr. Kreek. We appreciate it.

We are going to move on now to the FDA presentation. We are going to hear from Dr. Sharon Hertz who is the Team Leader in the Division of Anesthetic, Critical Care and Addiction Drug Products.

FDA Presentation

DR. HERTZ: I can start off with a little good news, I have no intention of speaking for an hour so it will be just a few minutes.

[Slide]

I am going to talk a little bit about some of the challenges. We have heard a lot about challenges throughout the last day and a half. I am going to talk about some of the challenges for the risk management of modified-release opioids, specifically some of the issues and challenges that we have seen when looking at the proposed plan for Palladone.

[Slide]

You have heard described between yesterday and today a lot of information. You have heard the roles of the FDA and DEA in risk management, benefits of clinical use of opioids, risks of misuse and abuse of opioids and data reflecting those areas, and you have heard about concerns around prescription opioid diversion.

[Slide]

We have heard general principles of risk management, examples from both non-opioids and opioid programs that already exist. Today we have

heard about the abuse liability of hydromorphone, specific features of the risk management program that has already been started for Palladone, as well as some of the challenges associated with long-acting opioids and addiction.

[Slide]

I think the biggest concept that we have heard though is that there are all these challenges so the task at hand for today, one of the tasks at hand, will be, based on the discussion that we have had--is the Palladone risk management program, as it has been defined, likely to result in safe use, limit the potential for abuse and misuse without limiting the access for appropriate patients. So, will it achieve the basic goals that have been set for it?

[Slide]

The challenges to risk management which are common to Palladone are common to all the modified-release opioids. I am going to go over a lot of these areas quickly because they have really been covered a number of times.

While I am going to be reviewing what we think might be some of the limitations for this plan, I just also want to state that we should keep

in mind that this represents one of the most detailed plans that has been established so far and it really represents I think one of the best efforts so far. So, we are going to discuss limitations but keep in mind that this is what we have to work with so far.

[Slide]

The approaches to meeting these challenges have also been discussed between yesterday and today in terms of the tools available and span these areas of education, surveillance and intervention.

[Slide]

These elements of risk communication and education have been incorporated into the Palladone plan. One of the questions though that this area raises is do we want to rely solely on the sponsors of these products to educate physicians? And, we need to think creatively about additional programs to help ensure that the physicians prescribing these products are fully informed about the risks as well as the benefits, and the proper approaches for treating patients with chronic pain with opioids.

One of the examples for approaches for

this has already been discussed somewhat, perhaps linking licensure for prescribing scheduled products with some type of demonstration of adequate knowledge.

[Slide]

The surveillance encompasses several areas we need to know about, exposure data, clinical use, drug abuse, adverse event data. A number of existing data sources have been incorporated into this risk management plan.

[Slide]

The National Prescription Audit from IMS Health and the National Disease and Therapeutic Index from IMS Health provide information on the prescriptions written and the patterns of treatment of disease encountered in office-based practice but these databases cannot tell us whether the prescribed drugs are used by the intended patients or if prescriptions were written appropriately. The patient tracking and analysis report tracks patients for the prescriptions filled by participating pharmacies so while we can get some longitudinal information, again, it is not designed to track non-medical use. DENS is another existing database incorporated into this program that I will

discuss a little bit later.

[Slide]

The abuse data has also been described, sources of different information. I am going to discuss DAWN again in a moment. The National Household Survey, which has been retitled but it escapes me right now, is somewhat limited because it is self-reported. The Toxic Exposure Surveillance System is also somewhat limited because reports to poison control centers are more likely or somewhat likely to represent unintentional cases of exposure, accidental exposure, as well as some intentional exposure but it is not really set up to define abuse or set rates for abuse.

[Slide]

DAWN has been frequently considered for use as a numerator. We have a database that reflects events resulting in emergency room visits, or we also have the medical examiners' cases. But DAWN does not distinguish between products for any given opioid. At least historically, this hasn't been true. There may be some changes to the system that will be helpful for this in the future. There are also some other anticipated changes in the

reporting of the DAWN data and for the near future perhaps that is going to limit the availability of establishing trends using this information.

[Slide]

As described today, we have heard about the RADARS program and the data sources involved with that surveillance.

[Slide]

Some of the concerns with the Key Informant Network which, just to remind you, collects cases of abuse and addiction by survey from key informants knowledgeable about the emergence of drug abuse in their catchment area, includes addiction treatment specialists, pain management specialists, impaired health professional programs and other informants, but there is an uneven geographical distribution for the informants. About half are responding for each survey and it is not necessarily the same participants for each survey. Sites with high rates may be reflecting activity outside the three-digit zip code. This sounds like it is going to be addressed. Again, we have questions about the denominator, what to use with this information. Also important to note is that this is a non-random

selection of informants.

[Slide]

The Drug Diversion study, based on law enforcement personnel working on prescription drug diversion, suffers somewhat from a small number of participants and a high turnover rate among those participants. The data collection is inconsistent. For instance, data on dosage usage is not collected consistently by each program or by some programs at all.

[Slide]

DENS, which is incorporated into RADARS but preexisted RADARS, also has some shortcomings. This is a program that is funded by the Office of National Drug Control Policy and the Center for Substance Abuse Treatment. Data is currently collected on five opioids. There are some limitations to the sampling, with a preponderance of urban areas. It is only covering adult treatment programs and we are concerned about non-adult abuse as well. These kinds of programs also suffer from high rates of staff turnover. These are all things that can impact on the usefulness of the information available.

[Slide]

The Poison Control Center study, similar to TESS, is going to be limited by the kind of information reported into the system. So, there may be an under-representation of the kinds of events we are looking for related to intentional abuse. It is useful information in terms of the concerns we have about unintended and accidental exposure.

[Slide]

We struggle--what is the proper numerator? What is the right case definition? Should it be abuse, addiction, some combination with misuse, diversion, dealers, problem prescribers? We worry that the actual case definition might ultimately underestimate the incidence of some of these problems. As noted, we don't really know what is the best approach for creating a denominator. Patient exposure and prescription data don't report what is going on in terms of availability or what is happening to these products when people access them by means other than acceptable prescription writing. So, they may be underestimating exposure.

Population in kilograms sold represents such a large number of individuals or product that it may not provide the sensitivity to changes in

abuse or prescribing patterns that we may want for detecting signals early.

[Slide]

The sponsor has defined a signal detection level of at least five cases per 100,000 population in a three-digit zip code. Again, we just don't know what is the appropriate sensitivity that we should have for these programs.

[Slide]

Then, once we have information do we even know what are the appropriate comparators? How do we establish baseline when the systems become developed and available after problems develop, for instance, with OxyContin information or prospectively even with a product like Palladone? How do we establish a baseline against which to look at change? Then, how will discrepancies that are detected in the data be resolved? What I mean by ambiguous reporting responsibility is what will be the appropriate course of action associated with detection of signals from other sponsors' products?

[Slide]

The arena of possible interventions is very interesting but, again, we don't know when to intervene, what interventions are necessary or most

appropriate, and who should be doing this intervention. Should the company be responsible for correcting problems that are detected with this system?

[Slide]

So, again I raise for you the task at hand, and this is a little bit more formally presented based on the questions that have been developed for today's session. Based on the information that has been presented at this meeting, and taking into account your earlier discussion and deliberation about risk management plans for modified-release opioids, does the Palladone risk management plan, including its proposed labeling and indications, define a program that will likely result in safe use of the product and limit the potential for abuse and misuse of the product while assuring that appropriate patients are able to receive the medication? Thank you.

Open Public Hearing

DR. KATZ: Well, I guess our work is cut out for us but, luckily, we are going to the open public hearing now and we will be able to eat lunch before we tackle those thorny questions. So, are all open public hearing speakers available?

I have to read that statement again that I read twice yesterday. Again, this statement or version of it is read prior to each of the open public hearings: Both the FDA 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, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, 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 and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial 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 first speaker is Khari LaMarca. Is Khari LaMarca here?

[No response]

Our next speaker is Dr. Tom Stinson. Because of the change in our schedule for today we have more time for public speakers. Public speakers will actually have ten minutes today and we will give you a two-minute yellow light prior to the end of your time, at which time the red light will come on.

DR. STINSON: Thank you. My name is Tom Stinson. I am an anesthesiologist in Medford, Massachusetts. As far as I know, I have no conflicts of interest.

Mr. Chairman, members of the committee, I have a few comments about an aspect of risk management that has only been alluded to in earlier testimony briefly, namely, the management of the legal risk to physicians who prescribe opioids to chronic non-cancer pain patients. As previous speakers have noted, there is an apparent increase in number of physicians who are being subjected to regulatory or criminal prosecution in connection with opioid prescribing. These actions are frequently based on legal standards which are vague

and uncertain, incorporating such poorly defined terms as legitimate, adequate and professional.

A well-formulated risk management plan for Palladone has the potential of providing a remedy for this problem by addressing physicians' justified reluctance to use opioids of this sort based on fear of violating ill-defined legal rules and medical standards. To avoid perpetuation of this problem, any risk management plan for Palladone should be sufficiently detailed and well-defined, including definitive standards for documentation, so that compliance can be regarded by physicians as a reliable, safe haven for the prescribing of Palladone. Thank you.

DR. KATZ: Thank you, Dr. Stinson. Would anyone from FDA care to address Dr. Stinson's question about whether it is even possible to include documentation standards or other aspects of the risk management program that would deal with this concern that physicians have about prescribing Palladone? Is that even a possibility and in what form could it be implemented?

DR. MEYER: That is really much more along the lines of practice of medicine; it is not something that ordinarily FDA considers itself to

have purview over.

DR. KATZ: Dr. Van Zee, you are next.

DR. VAN ZEE: My name is Dr. Art Van Zee. I am a general internist and practice primary care medicine in St. Charles, Virginia, which is a small coal mining town in southwest Virginia, where I have been for about the last 27, 28 years. I have no financial disclosures.

I appreciate the opportunity to make comments today regarding risk management issues surrounding Palladone.

[Slide]

As an overview of where I am going with this talk, I would suggest to you that the information in the literature suggests that sustained-release opioids have no significant benefit over immediate-release opioids, save the convenience of b.i.d. or q.i.d. dosing.

[Slide]

I would suggest that the risks of sustained-release opioids are distinct and greater than immediate-release opioids. I would also suggest that one of the most important factors to consider in Palladone risk management is the way that this drug is marketed, and I will briefly

spotlight the marketing of OxyContin.

[Slide]

These studies compared OxyContin with immediate-release oxycodone and essentially showed comparable efficacy and safety.

[Slide]

It is also of interest to look at the new drug approach for OxyContin, submitted by Purdue in 1995, and this was the medical review officer's conclusion at that time, who was Dr. Curtis Wright. He had suggested that the summary for safety was that OxyContin was equivalent to immediate-release oxycodone, with an adverse event profile that is as good as immediate release and would not allow a better claim.

[Slide]

He went on to conclude with a summary of efficacy, that OxyContin appeared to be a b.i.d. alternative to conventional q.i.d. oxycodone. Approval is recommended. Care should be taken to limit competitive promotion. This product has been shown to be as good as current therapy but has not been shown to have a significant advantage beyond reduction in frequency of dosing.

I think Purdue Pharma, as a corporation,

had confidence in Dr. Curtis Wright's professional capabilities and sometime subsequent to his work at the FDA, he was hired by Purdue and remains in their employee up to this year.

[Slide]

Other slides looking at sustained-release opioids have compared sustained-release morphine versus OxyContin and these have been comparable in efficacy and safety.

[Slide]

Immediate-release hydromorphone was compared to 12-hour sustained-release hydromorphone and is comparable in efficacy and safety.

[Slide]

And these are two studies in cancer patients, OxyContin versus sustained-release 12-hour hydromorphone, comparable in efficacy and safety in this study.

[Slide]

So, in summary, I would suggest that that information would show that immediate-release opioids and sustained-release opioids are clinically comparable in efficacy and safety if dosed appropriately. Sustained-release preparations appear comparable in efficacy and

safety with the few studies that you have available to you comparing one to the other.

[Slide]

So, my summary of the benefits of sustained-release opioids would be that they certainly can carry some convenience of b.i.d. or daily dosing; certainly the convenience of less pills; and there is certainly a sub-segment of patients that are intolerant to other opioid preparations. All of us have these people in our practice and this may be a real benefit to them.

[Slide]

Let's talk a little bit about what the risk of sustained-release hydromorphone could be. Certainly the risk of addiction when taken exactly as prescribed is unknown. There have been some speculations on this but the risk is really unknown. We don't have any definite data on that. Five percent was a figure discussed today. If, indeed, it is five percent and you have a million people prescribed opioids for chronic, non-malignant pain and your iatrogenic addiction is 50,000 people, that seems to me an enormous harm and you would have to weigh that against whatever benefits you could say were produced from your

treatment.

There is certainly an increased rate of addiction when used non-medically or recreationally. There are literally tens of thousands of new opioid addicts in central Appalachia that are there over the use and abuse of OxyContin. There is an unprecedented epidemic of IV drug use and hepatitis C that we have never seen before.

Basically, the predominant story that I hear, and I have probably seen hundreds of young people that are OxyContin dependent, not the uniform story but the predominant story is that they had recreationally used Proxid and Lortab. This is how many young people party these days with beer and pills, and they certainly used those, snorted pills, for example Lortab at parties, were able to walk away from that and once they were exposed to OxyContin they were not able to do that and became rapidly addicted. People do not snort molecules or milligrams, they snort pills. If you do a 40 mg OxyContin at a party, it is going to be equivalent to doing eight Percocets and your risk of addiction is enormously increased. There is the risk of overdose and death with high potency dosing

in one pill for these opioid-naive patients.

[Slide]

So, to continue on with looking at what the risks are of Palladone, I would say it would be relevant to get a brief overview with the promotion and marketing of OxyContin. As we have seen from information presented here today, the block-buster commercial success of OxyContin cannot be attributed to its superiority over other available opioid products, and I would suggest it had much more to do with the promotion and marketing.

There were at least four cornerstones that were influential in the commercial success of OxyContin. One was the aggressive marketing for chronic non-malignant pain. There was aggressive marketing to primary care physicians. The risk of addiction for chronic non-cancer pain is certainly one of the major stumbling blocks that primary care physicians have in prescribing opioids for non-cancer pain, and Purdue Pharma has systematically trivialized the risk of addiction for chronic non-cancer pain.

They use sophisticated marketing data to target and influence high opioid prescribing docs. Purdue obtained IMS Health marketing data which

identified the opioid prescribing patterns of all physicians in the country. They then divided this from top to bottom in ten segments or deciles, if you will, with the highest opioid prescribing physicians down to the lowest. They then targeted their marketing energy on the top few deciles. This type of marketing data will reveal, I think, what physicians might have a larger proportion of chronic pain patients in their practice, but it also reveals which physicians are the most liberal prescribers of opioids and, in some cases, the least discriminate, if you will.

This targeting consisted of much more frequent and intensive visits by the sales representatives. It also included targeted mailings with information and sometimes Internet detailing meant to influence prescribing.

Purdue coupled this approach with a lucrative incentive plan for the sales representatives. One sales rep in Florida, a few years ago, made $100,000 in bonus incentive pay over and above her $50,000 salary because of the high OxyContin sales in her territory.

[Slide]

How does this marketing approach go from

the paper to ground level? What does it look like on the ground? We looked at five state graphics yesterday. They were obtained through the ARCO system that detailed opioid prescribing down to the retail level.

DR. KATZ: Dr. Van Zee, I have to ask you to wrap up your comments.

[Slide]

DR. VAN ZEE: Basically, this targeting of highest prescribing opioid physicians meant practically that physicians that had been high prescribers--these are just selected counties--of narcotics previously became high prescribers of OxyContin.

[Slide]

We talked yesterday about the regional differences in OxyContin prescribing and that it correlated with high availability, and these were the demographic areas of abuse. DR. KATZ: Concluding statement?

DR. VAN ZEE: I would suggest that if the FDA's allowed indications for Palladone are the same and the marketing is the same as OxyContin, then we will almost certainly replicate the OxyContin abuse tragedy in proportion to its

general availability.

I would certainly support unrestricted use in cancer. I think it is most prudent to have restricted access to Palladone for chronic non-cancer pain. This could be made available through a compassionate use program.

The concept mentioned yesterday of specialized DEA certification for prescribing Class II drugs is intriguing and needs to be explored. Thank you.

DR. KATZ: Thank you, Dr. Van Zee. There was another public speaker, Khari LaMarca. Is that person here?

[No response]

Thank you. Let me just remind people on the advisory committee that it is not appropriate to discuss advisory committee issues during lunch, and we will resume the meeting at 1:30. Thanks.

[Whereupon, at 12:40 p.m., the proceedings were recessed for lunch, to resume at 1:40 p.m.]

A F T E R N O O N S E S S I O N

Committee Discussion

DR. KATZ: This is the discussion portion of our meeting, the main discussion portion. If everyone around the table could pull out their questions, we are going to go more or less according to that list of questions.

Let's start by finishing up with Roman numeral I and trying to address Dr. Dworkin's hanging question about the benefits of moderate-release opioids. That is a question that is still hanging in the air. Is there obvious relevance to understanding the risk/benefit potential for Palladone and other modified-release opioids?

So, the last question to try to get at in Roman numeral I will be what is the evidence of benefit of modified-release opioids over immediate-release opioids? I will open it up for general discussion, but Dr. Strom's exhortation is still ringing in my ears about evidence. So, personal opinion is fine and I would love to hear the opinions of the experts around the table, but I just think people should flag their comments by what level of evidence they are referring to, and

refer to particular clinical trials and such experiences if they can. Dr. Gillett, you are first.

DR. GILLETT: On page ten of the slides this morning, how secure is the formulation from abuse if it is promoted as being possible to sprinkle it on food?

DR. KATZ: That sounds like a very important question but I am going to table that for the moment because we will get to it in the risk management portion of the discussion. So, don't let me forget. Let's just return to that issue. What are the benefits that we can attest to about modified-release opioids over immediate-release opioids? Dr. Leiderman?

DR. LEIDERMAN: Actually, could I just ask a question, perhaps a related question in a slightly different way? One of the things that I think we are trying to get at is who are appropriate patients for not just the modified release but for the high dose, high potency. We are talking about this very narrow group of drugs. We are not talking about all opioids. Who are appropriate patients? I think it has been suggested, because it has been raised in other risk

management plans, who are appropriate prescribers?

Then, a related question to who are the appropriate patients is how do we define chronic and persistent pain? For example, the JAMA paper that is included in your background information with Dr. Portner, as a co-author on persistent pain and chronic pain in a methadone patient population defined it operationally as chronic severe pain that persisted for more than six months or impaired function. So, I just want to put that out there.

DR. KATZ: Fair enough. I want to get to this issue of evidence for modified-release opioids. Unless there has been a change over on the FDA side where that question is no longer perceived as being of interest, I am going to focus on that. The issue of patient selection and whether certain patient populations should not be permitted access to this drug we are going to get to in question number three. The issue of whether certain prescribers are more appropriate will also come up in question number three. The question of definition of persistent pain will come up in question two. So, don't let me forget those. I am going to try to stick to my agenda and at least get some questions answered.

Finally, are there any opinions about whether modified-release opioids do have benefits or not over immediate-release opioids? Dr. Van Zee actually just gave us a lecture on that very subject. Would anybody care to add to the discussion? Dr. Cush?

DR. CUSH: I think we have heard, I think convincingly, that there is no advantage.

DR. KATZ: Are you including that there is no advantage of convenience or compliance?

DR. CUSH: No, that is an advantage but as far as efficacy or safety, I don't think that that has been demonstrated. So, to me, compliance, as was stated, is one thing that is attractive about them.

DR. KATZ: So, there is a compliance and convenience advantage. Again, in terms of level of evidence, are you reporting that from your own impression, experience, or is there data that you have in mind in making that assertion?

DR. CUSH: Impression based on what I have been presented here, at this meeting.

DR. KATZ: Because we have not actually seen data on convenience or compliance.

DR. CUSH: No.

DR. KATZ: Dr. Ciraulo, you are next.

DR. CIRAULO: Thanks. I think at least one advantage would be the level serum concentrations that one achieves. I happen to believe that as the level rises there is a euphoric effect and then during the decline you do get withdrawal symptoms. Even if you have the same actual serum level you have more chance of withdrawal. So, the closer you get to a flat serum level of the drug, the better.

Then, I would refer also to Dr. Kreek's lecture about the issue of tolerance. I know better for the benzodiazepines and she can talk about the products, but intermittent use is associated with higher tolerance so you are less likely to develop tolerance. I believe that is how I understood her lecture and I know that is the case for benzodiazepines.

DR. KATZ: Right, so it sounds like you are saying that the flatter serum level profile may be an advantage because it is less likely to produce euphoria which, in turn, is less likely to produce addiction.

DR. CIRAULO: Yes.

DR. KATZ: So, that really would be more

of a theoretical advantage, right? We didn't see any data that compared the two classes of agents with regard to euphoria or addiction.

DR. CIRAULO: No, we didn't see that data but there are data in the literature that would suggest that that is true.

DR. KATZ: Thank you. Other advantages of modified-release opioids? Dr. Shafer?

DR. SHAFER: I am searching right now to see if I can actually give you the references off my laptop, but when transdermal fentanyl was initially developed, it was developed for postoperative pain control and it was only very late in the program that that was thought to be dangerous and it was switched to chronic pain control. There were a number of studies done on the transdermal fentanyl preparations examining the quality of the analgesia and the influence of that on patient recovery, and they were quite positive. Compared to the salutary pattern that you get with repeated IM or IV dosing, the continuous analgesia from fentanyl in the postoperative population was found to be highly preferable to patients. Now, I am not advocating that this be used in a postoperative setting but you want data and there

is data in that entire study group, and there was a whole series of studies there showing that patients did better when they were provided continuous analgesia.

DR. KATZ: Are you suggesting then that at this point in time one can consider improved analgesia in the postoperative setting an advantage of modified-release opioids?

DR. SHAFER: Yes, but I don't extend that to say that I am advocating use of these in the postoperative setting but I am advocating that, yes, continuous analgesia is beneficial to patients I think in any setting.

DR. KATZ: Other potential advantages of modified-release opioids? I think it is appropriate to hear from the sponsor if they can refer us to any clinical trials or other data that suggest advantages of a modified-release opioid preparation over an immediate release. I realize I am springing this on you. You can do it in five minutes if you like. Dr. Saini?

DR. SAINI: The aging population of America and the people who are older, sometimes they get demented and they can't remember, and they are on a number of drugs. So, having a long-acting

drug, this way they don't have to remember if they took the drug or not. If they have to just take one pill a day or take a fentanyl patch every three days, it makes sense. I don't have any data, but for aging people who have memory problems it is ease of convenience so it makes sense that a long-acting agent should be beneficial.

DR. KATZ: I think the point that you make is worth emphasizing, that we shouldn't trivialize the importance of convenience or enhanced compliance since those are essential for achieving the benefits from any form of therapy. Dr. Aronson and Dr. Strom.

DR. ARONSON: I think your question is quite profound. I wish to reframe it in the context of our intent rather than the risk. I have heard evidence that perhaps the risk of an addict going toward a sustained release for the benefit that that addict would have might be mitigated compared to a shorter-acting drug.

Having said that, I wish to reemphasize that I am curious, as you, to know if there is any data that would suggest that this modified-release version of the drug is beneficial for the treatment of pain in non-malignant chronic moderate to severe

conditions. I would defer to some of my colleagues with expertise in psychiatry to help me understand if there is any reason to think the opposite, that the trigger of pain itself might be a motive that we wish to have to take a drug and in that instance I am wondering if that is a good thing that we would be losing by using a longer-acting agent.

DR. KATZ: So, you are suggesting the possibility that there might be an advantage to feeling your pain and responding to it with medication. Dr. Strom?

DR. STROM: I know we don't have data on this but I want to emphasize the importance of it and my disappointment at the answers I am hearing because I don't buy convenience as a viable argument for a symptomatic drug. If you are dealing with an antihypertensive drug, it is a different situation but if somebody is in pain they will want to take the medication; if somebody is not in pain they won't want to take it.

Now, I have heard from my pain colleagues for a few years that pain is better controlled at a lower dose if you maintain people pain free as opposed to having them go in and out of pain. To me, that is a very viable argument if there is data

underlying it.

It is clear that these formulations have greater risk associated with their use. I have heard two at least theoretical benefits, one being the one I just described and the other being, in fact, if they are less addicting for whatever reason. But if there is no data supporting either of those benefits and if there is substantial increased risk, and there is good reason to think there is increased risk from the sustained formulations, why in the world do we need them?

DR. KATZ: Dr. Bril and Dr. Ciraulo.

DR. BRIL: I guess it follows on to this a little bit, I am not sure, if I am the patient with chronic pain that I have had for months or years, that I want to feel my pain four times a day to make my physician feel better about giving me something that makes me feel better and pain free. Feeling my pain once a day is probably going to be enough.

So, I don't really know data on responses in pain four times a day versus once a day dosing, I just do know that my patients prefer to be without their pain as much of the time as they can be, and that is just general, practical experience.

I don't have numbers and percentages. So, I think that is a real advantage. Beyond the Alzheimer's theory, it is relieving pain in the patient who has come to you to have their pain relieved and not letting them have it as frequently that is necessary. So, I think those are real advantages that are inherent. Now, yes, I do know you would like epidemiologic data there.

DR. STROM: If I can respond, you can take the second dose a little bit earlier and still not have the pain in between. Again, the convenience is not a reason to take the risk of the fact that you have high dose products that, when people abuse, they will die.

DR. BRIL: This is an obsessive patient who remembers to take their pills spread out every single time. But if a person has pain relief and gets busy, then they are in the middle of whatever it is, then their pain comes back and they have to go and take their pain [sic] and wait again as opposed to just taking it once in the morning. So, I can see the rationale for once a day dosing, and it is more convenient to take the pill once a day than three, four times a day.

DR. STROM: Again, this is symptomatic

therapy. I am hoping I am wrong, and certainly what I have been taught by my pain people would say that I am wrong, but is there not the data, as I have been told before, that the total amount of narcotic necessary and the total level of control is better if you maintain someone pain free as opposed to wait until they are in pain first?

DR. KATZ: I think what you are saying is very clear. You are saying that there is one potential advantage that people claim anecdotally, at least some people, that with a modified-release opioid you may be able to get away with lower doses and at least as good pain control, or some people say maybe better pain control at the same dose but you will believe that after you see data.

The second point is that it would be attractive if these low-release formulations were less likely to produce addiction based on this less euphoria model, or whatever model it was, and you will believe that when you see data that demonstrates that. Dr. Ciraulo?

DR. CIRAULO: I wanted to respond. I didn't want to be in the position of being the advocate; I was trying to do what the Chairman wanted us to do and find the positive aspects and

not shift to the risk. I think I agree with you that there is substantial risk so I didn't want to leave the impression that I was saying that this was enough to make this worthwhile.

DR. KATZ: That is the task at hand, which is to try enumerate the potential advantages and then try to determine to what extent they are supported by evidence. Dr. Baxter?

DR. BAXTER: Yes, actually there is data available. The PCA pump data supports that continuous analgesia will result in less total amount use. So, there is data available. I am sorry, I can't tell you who and where.

DR. KATZ: Actually, if I could just clarify that, there are a number of studies now comparing PCA where the patient controls the dose, small intermittent doses administered by the patient to fixed doses and to IM, etc. which showed advantages, but that is not continuous analgesia; that is actually small intermittent doses titrated by the patient, the opposite. Now, if you compare PCA with the constant continuous infusion provided by the machine to PCA by itself, generally the continuous infusion is disadvantageous and it tends to be associated with similar analgesia but more

side effects. So, I want us to be very careful in making those extrapolations but I appreciate your point. What was the second thing?

DR. BAXTER: The second point is when we are talking about situations where there are people who have histories of addiction who then have chronic pain syndromes, it has been my experience, and I don't know if there are any studies available, that when you use long-acting narcotics to address their pain needs, you have a better outcome basically because you don't develop that pain, take a drug, pain, take a drug--that cycle, because the essence of addiction is to take a pill or take a drink and then take another and take another.

DR. KATZ: Fair enough. Thanks. Dr. Haddox?

DR. HADDOX: Yes, sir. I have four comments in response to the question that you sprang on us. The modified-release drugs that we are speaking about today are single-entity opioids. As a result, there is no co-analgesic which might have toxicity in patients who require larger doses. For instance, you are giving someone 40 mg of OxyContin twice a day as opposed to the equivalent

amount of Percocet or Percodan you are avoiding the acetaminophen or the aspirin issue.

Secondly, it is very hard to do these head-to-head studies because if you are looking to try and show convenience, for instance, you are sort of unblinded by the fact that you diminish that because even the person who is getting the dummy immediate release has to take it every four hours.

There are two studies, however, that we think address the issue. One is Betty Farrell's comparing MS Contin versus MS IR in an open-label cancer study, the City of Hope, and what she was able to demonstrate was that there was an improved quality of life in the sustained-release group as measured by things such as impact of the pain on sleep disruption, on mood and relationship, the ability to interact with other significant people.

Secondly, there is a randomized, controlled study by Scheville, in the literature, dealing with total knee replacement, looking at time in rehab following total knee replacement, comparing controlled-release oxycodone to immediate-release oxycodone in roughly equivalent doses, with the immediate release being p.r.n.

versus the controlled release being on a fixed schedule. They were able to show that there was a faster return of range of motion in the controlled-release group and that they were discharged from rehab statistically significantly earlier.

DR. KATZ: That is very helpful. Thank you very much. Dr. Storm?

DR. STROM: Yes, just to follow-up because this is such a central issue, is there anybody else who has reviewed either of those papers? The fact that it is hard to do the study doesn't convince me and, because I don't think the issue of convenience is a central issue here, I think it could be done blinded. But even the unblinded study, if you are talking about Andrea Scheville, I know Andrea. She is about to enter our program to learn how to do research--

[Laughter]

So, I don't know that study but it leaves me worried about it and I just want to be sure that somebody else, who is a pain expert, has seen these two studies, or FDA, and has some sense that those are reliable because this is obviously very central.

DR. KATZ: Where is Dave Haddox? Oh, do you think you could get us those studies?

DR. HADDOX: Sure.

DR. KATZ: That would be great. Is anyone around the table able to answer Dr. Strom's question, having seen those studies? I, myself, haven't seen them, I am embarrassed to say so we will look forward to reviewing them. In any case, those two particular studies, one deals with a small population of cancer patients where I think the role of modified-release opioids--I don't know anybody who questions their value. And the second--

DR. HERTZ: May I? I did actually review one study, I don't know if it was exactly the same one, looking at return of function in a rehab population following knee replacement and looking at modified-release oxycodone versus immediate release, and we actually found that the study didn't have merit. I don't know if it was exactly the same one. I can't recall the author but the one we reviewed was methodologically flawed and we didn't think that conclusions could be based on it.

DR. KATZ: Well, I think the flavor of the discussion, and somebody chime--Bob, did you have

something to say?

DR. DWORKIN: I think it needs to be said, not to muddy the waters, and to follow-up on what Dr. Strom was saying, I think certainly in our pain clinic, and I think this is sort of widespread experience, about a third of the patients getting OxyContin are taking it t.i.d. and not b.i.d., attenuating this convenience issue plus, of course, many of the patients on modified-release opioids are getting breakthrough. When you add in the patients getting t.i.d. rather than b.i.d. and the patients getting breakthrough, I don't know what to think about as I listen to this convenience argument. I have no data but I think it is a widespread sense that these aren't patients, at least in pain clinics and I don't know about general practice, who are taking only b.i.d. drugs.

DR. KATZ: I will put you on the spot again and maybe the sponsor can help educate us there as well. Is there any data from marketing sources or any sources that looks at the median dose frequency or the proportion of patients taking different numbers of tablets, comparing those on controlled-release opioids versus those on immediate-release opioids?

Well, I got them scurrying again. Let me say what I was going to say a minute ago, which is that it seems like the sense of what I am hearing is that there are a number of potential advantages to modified-release opioids, one, that potentially and some people feel anecdotally, one could possibly control the pain better at lower doses.

Another advantage is that perhaps they are less addictive either by virtue of not producing as much euphoria or by not being associated with withdrawals or having reinforcing effects from a behavioral perspective, or any other variety of potential pathways.

A third potential advantage that may be supported by a small study that we need to review is that perhaps patients can engage better in rehabilitation, at least after total knee replacement.

Another potential advantage is a few of the quality of life parameters that Dr. Haddox mentioned for the cancer patients, reduced sleeping and improved social interaction I think was the other, again, in a small cancer population.

It sounds like, at best, we have small randomized trials, and for some of these issues we

have anecdotal evidence and that is it. That is my sense of what everyone has said so far. Dr. Haddox?

DR. HADDOX: Can I make sure that I understand your question. You want to know if market research data indicated the frequency at which OxyContin was prescribed?

DR. KATZ: No, my question was do people on controlled-release opioids take fewer doses per day than people on immediate-release opioids, fewer total number of pills, pill taking episodes per day?

DR. HADDOX: I don't know the answer to that from a data standpoint, but since everyone else was talking anecdotes, I have some of those myself having treated a number of patients with this type of therapy using various long-acting drugs, and I think it varies quite a bit with the person. It varies with the population. The population that I saw at a tertiary referral center was probably not representative of the average pain population.

We know from the 1999 survey that the American Pain Society and the American Academy of Pain Medicine did that 51 percent of the patients

with chronic moderate to severe pain are being seen at the primary care level, not at the specialist level. I can tell you that even within my practice there was a great deal of variability. Some patients found that even though they had to take p.r.n. medicines because their pain was not constant throughout the day, taking a long-acting medicine at night got them through the night without any interruption but when they were up and active during the day they needed the p.r.n. but they didn't mind that because during the day they were awake anyway, for what that is worth.

DR. KATZ: I appreciate it. Dr. Strom, a final comment on this issue?

DR. STROM: Yes, I really have a question to the pain experts. Isn't it standard teaching that you should be on a basal long-acting analgesic plus rescue therapy as a standard and if, in fact, you are not requiring some rescue your basal dose may be too high?

DR. KATZ: Who does pain education and would like to answer Dr. Strom's question about the standard?

DR. SAINI: That is the standard teaching for acute pain management, not for chronic pain.

DR. KATZ: I am surprised that you are asking about what people are educated since we have heard so many times today that education, if not based on data, can do more harm than good. That was very out of character for you I think, though we only met yesterday! Dr. Jenkins?

[Laughter]

DR. JENKINS: I would like to ask for you or the committee to characterize a little bit more about the level of evidence to support the purported benefit of reduced potential for addiction for the sustained-release products because that has obviously been a very hot topic, and I am concerned about the transcript of this meeting showing the advisory committee as saying that there is a reduced potential for addiction for modified-release or sustained-release opioids without some characterization of what is the level of evidence to support that. So, I would like to hear more quantification, if you can, of that level of evidence.

DR. KATZ: Would anybody like to answer Dr. Jenkins' question describing the level of evidence behind the relative predictive potential of long- versus short-acting opioids? Dr. Skipper?

DR. SKIPPER: I would refer to the methadone data, that methadone is not a primary drug of choice and doesn't seem to cause addiction as commonly or as readily. The problem with the CR compounds is that they can be segregated and then they are not CR compounds. You know, as Dr. Kreek said, if there was intrinsically slow onset, and what-not, then I think it would be easier to make that case. But I am not confident in that at this point because we haven't had enough information to feel secure.

DR. KATZ: Dr. Ciraulo?

DR. CIRAULO: It is my feeling that the evidence is suggestive but certainly not anywhere close to being definitive. I think there are two issues. If you look at the rate of brain penetration and if, for instance, you have two different formulations, one that enters the brain more quickly and produces euphoria, and then you have an infusion that is slower, say, diazepam, the rate of euphoria is definitely lower with the same chemical compound.

Now, I think we are mistaken if we believe that all opioids that are mu agonists act in the same manner. So, you know, when we talk about the

level of absorption or the rise in the serum level or the drop in the serum level, that is only half the story. The other half is what is going on at the receptor level, which I think is quite complicated, as we heard from Dr. Kreek's presentation. But since I am the one who brought it up, I would say addiction is not the proper way to phrase that. I would say the rate of increase in the plasma level or the kind of plasma level has an influence on subjective effects such as euphoria or dysphoria related to withdrawal. To the extent that that is related to addictive behavior, then there is a relationship. I would not say that the evidence is very strong for the link to addictive behavior.

DR. KATZ: Do any of our epidemiologists, Dr. Maxwell, FDA, anybody, feel that after reviewing the hundreds of slides of epidemiologic data that we have seen over the last day and a half, one can use that data to address the hypothesis that short-acting and long-acting opioids have a different potential to be associated with addiction? Dr. Leiderman?

DR. LEIDERMAN: That is a bit of a big question. If I can answer sort of a narrower one

since I don't think our SAMHSA epidemiologist colleagues are still here, I think, as we learned from the OxyContin experience it is very important to say this is a lesson for a lot of the parties involved, that the controlled-release formulation that had been thought to potentially significantly reduce risk of overdose, misuse, abuse and addiction turned out to be very readily violated. Thus, you have just higher dose of an immediate-release opioid. Basically, all of the ones we are talking about are shorter-acting opioids. Methadone is really I think the only long-acting drug and that is really not sort of on the table here; it is not being reformulated to my knowledge.

DR. KATZ: I think it is fair to remind ourselves that we are really dealing with two separate problems. One is the diversion of modified-release opioids where the modified-release mechanism can be defeated at which point it becomes a high dose of an immediate-release opioid, and nobody is suggesting that that has a lower abuse potential, I don't think.

Then the question Dr. Jenkins asked I think is in the setting of therapeutic use of

opioids where one is prescribing to patients, is the prescription of a long-acting versus a short-acting opioid associated with a lesser likelihood of producing addiction?

To summarize the committee's answer to your question, I think it is that the evidence that we have is very indirect. There is a study by Dan Prokoff, suggesting that if you talk to people in jail they will prefer short-acting opioids versus long-acting. There is the methadone maintenance experience which is an experience with a population of patients whose primary diagnosis is substance abuse where they seem to have resolution of their addictive behaviors on methadone. Are those pain patients? Probably between 30-60 percent of them are but, again, that is a very indirect source of evidence.

We have evidence from other sorts of therapeutic agents and from opioids to suggest that a more rapid rise in serum level is associated with more euphoria. The relationship between that and addition is speculative. And, that is the summary of the evidence. Have I missed anything? Dr. Maxwell?

DR. MAXWELL: Just very quickly, we can't

separate out the other opioids but clearly something is going on with the treatment data and the emergency room data. I just want this in the record, that there has been a significant increase in both the emergency room and the treatment data, and we don't have even the '91 and 92 data presented to us but something is happening.

DR. KATZ: I think I heard Dr. Strom say, and other people seemed to nod their heads, wouldn't it be great if that were the case and wouldn't we love to see data showing that?

I am prepared to leave question one. Does anyone on the FDA side have any more questions that I am not planning on covering down the line? If not, we will move on to question two and I will read the question: In response to reports of abuse/misuse of modified-release opioids, the FDA changed the indication for OxyContin and other modified-release opioids to, "for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time." Please comment on the appropriateness of this indication and provide any specific recommended changes that may further enhance the safe and effective use of these

products.

So, we can open it up for discussion on this issue, what people think about this label and could it be improved to make the use of these medications more safe or more effective. Dr. Crawford?

DR. CRAWFORD: Thank you, Mr. Chairman. Earlier this morning Dr. Baxter raised the potential for consideration of inclusion in the labeling to say that there is a high risk for abuse that requires additional monitoring. I would like to put that back on the table, as well as expand on it.

We have heard several times the fact that CIIs cannot be refilled and a new prescription per se is required by DEA for each new therapy course. However, we also heard that there are few limits on the dispensing on the amount of drugs, other than perhaps insurance coverage. So, while some give a 30-day supply or so, others might give a 90-day supply and, as we all know, there are other ways for clinicians to assist patients, or for whatever reason, to circumvent that by post-dating and other processes. So, I am wondering if also there should be consideration in the labeling of the need for

routine periodic reassessment of therapy by the prescriber.

DR. KATZ: So, as I am hearing it, the team of both of you has come up with the suggestion for the label that would include screening patients for their risk for negative outcomes of opioid therapy and having an enhanced monitoring system for such patients. The second half of your suggestion would be to recommend periodic reassessments of those patients as part of therapy.

DR. CRAWFORD: Yes, except it wasn't a team because we followed instructions and we didn't talk about it at lunch.

[Laughter]

DR. KATZ: No, but by interaction here during the meeting. Does anyone have any comments about that suggestion? Dr. Baxter, any comments?

DR. BAXTER: Yes, I think that it is important because the producer actually has a lot of material that is available to help prescribers, but my experience with residents and other providers is that if they don't have to do anything extra, they will not do it. So, I think that in the spirit of trying, I guess, to manage the risk even further, we should periodically review those

individuals who are found to be at increased risk in the first place.

DR. KATZ: Thank you. Dr. Bril?

DR. BRIL: I think what I might like to see in something like this would be a better definition of extended period of time. What do you mean by that? We are talking about educating the prescribers and that is fairly open-ended. Perhaps that could be a little better defined.

DR. KATZ: I think that sounds like an important question and I do want to make sure that we visit this point brought up by Dr. Crawford. What do people feel about whether it would improve the safety or improve the effectiveness of these treatments to expand this labeling statement to include recognition of patients who may be at higher risk, recommending enhanced monitoring for those patients and recommending frequent reassessments? Frequent reassessments, by the way, is present in every guideline for these opioids that has ever been put forth so I don't think that would be new but, certainly, the notion of screening patients at higher risk and having enhanced monitoring would be a step forward. What do people feel about that? Dr. Cush?

DR. CUSH: I am all in favor of that. I was also thinking the same thing, as I said earlier. I think that to have it in the indications section is a bit awkward. It is currently in a black box and I agree with you, the way it is worded in the black box I think is a little too soft and doesn't slap you as it should that this is something that needs to be taken seriously as far as risk assessment and monitoring as an important part of the warning and use of these drugs, but to have it in the indications is a little bit awkward. If it could be succinctly put in there that marked severe chronic pain should have provided an appropriate risk assessment or risk benefit assessment at the outset, but if it is a little awkward if it isn't included in the front.

Usually what goes into the indication, as was said earlier, is marked or severe, with or without functional impairment. Just to comment on that, we did review that issue at our analgesic and nonsteroidal meetings in the past, and setting that up as an outcome measure was a big problem for all the people because you have back pain you might be able to show improvement in function but if you have, say, cancer pain and someone is debilitated,

and what-not, how are you going to show improvement in function? Everybody has functional impairment but whether you can improve it is another issue. So, I don't know if function should be in there but I do like this idea of putting a higher standard as far as the need for risk assessment and monitoring.

DR. KATZ: Dr. Shafer, you were next and then Dr. Strom.

DR. SHAFER: First, I also do agree with the suggestion of my two colleagues here on either side. Something that is missing from the OxyContin package insert that is present in the Palladone package insert is the statement that the long-acting drugs should not be the first-line therapy. In order to be consistent with that and also I think with things we have said around here, that we wonder if there is really evidence of efficacy--well, if they aren't efficacious let the patient push you towards needing the drug--I would suggest that also be applied to the OxyContin package insert, that it not be the first-line therapy but, rather, be used when immediate-release preparations have either proven that that opioid is the correct opioid available and that the pain itself is even responsive to opioids.

DR. KATZ: Thank you. Dr. Strom?

DR. STROM: Firstly, I would like to agree with Dr. Shafer's suggestion. Especially given the iffy data we heard earlier about benefit, I think that makes a lot of sense.

In terms of the other suggestions, certainly including periodic reassessment makes sense. It is sort of motherhood and apple pie and no surprise that it is in every guideline.

In terms of screening for risk assessment and monitoring, I am not agreeing or disagreeing but I am going to do my usual thing and ask for data. I think it is important to realize that any intervention has toxicities. You know, how valid is our ability to do risk assessment, and is monitoring useful? Because if we say to people they should do it and they falsely believe they are able to do it, it can lead them down the line of giving it to people who maybe shouldn't be given it, or be reassured about people who they shouldn't be reassured by.

So, we haven't heard any data that I recall that shows that risk assessment is, in fact, well validated, well proven and if you do risk assessment and monitor people you will have better

outcomes than if you don't. Given that we don't know if that is true--I mean, if there are data on that, that is fine. If not, I would argue we shouldn't be including it, especially in the indication.

DR. KATZ: So, you are asking two questions. One is do we have validated screening criteria and, number two, do we have evidence that enhanced monitoring in that subgroup is effective. Dr. Hertz?

DR. HERTZ: Thanks. I just actually wanted to ask Dr. Shafer to clarify. I just didn't quite catch exactly what he said. Was the comment that OxyContin should not be used as first-line therapy? Do you feel that should be in the indication or actually somewhere in the label?

DR. SHAFER: It shows up for Palladone in the black box warning, as I recall, and I think it probably should be in the same place for OxyContin. This would be consistent across the class of extended-release opioids and I think that actually makes good medical sense as well.

DR. KATZ: So, let's return to Dr. Strom's question. We have heard a suggestion that has actually resonated through many of our sessions,

that there are certain people who are at higher risk for negative outcomes of opioid therapy but that that enhanced risk can be mitigated through some appropriate monitoring system. Dr. Strom asked the question what is the evidence that we can identify which patients are at high risk and low risk and we can appropriately classify those patients, and then further evidence that any different way of approaching those patients reduces their risk. Would anyone like to take on Dr. Strom's question? Dr. Baxter, did I see your hand up?

DR. BAXTER: No, you didn't and I will let my esteemed colleague handle this one.

DR. KATZ: Dr. Skipper, go ahead.

DR. SKIPPER: There is plenty of data on the CAGE questions, just four questions. You know those questions, right?

DR. STROM: CAGE is just a way of measuring that somebody is an abuser. That doesn't predict they are going to abuse a drug you are about to put them on.

DR. SKIPPER: But it is a screening tool that has been shown to be sensitive and fairly specific, and it is easy to administer. It takes

one to two minutes. There are also other tests--

DR. KATZ: So, those are tests for the diagnosis of addiction--

DR. SKIPPER: Right, for substance abuse.

DR. KATZ: Are you aware of any data that assesses the predictive value of responses to those questionnaires for the subsequent development of opioid addiction in patients being treated with opioids for chronic pain?

DR. SKIPPER: No, but we do know that people that have the substance abuse problem would be at higher risk to be given these meds.

DR. KATZ: How do we know that? What data are you referring to that can give us a sense of evidence-based comfort in that assertion, which I think we all feel is true, but Dr. Strom's question is what is the evidence.

DR. SKIPPER: I will have to think about it and look into it but I am sure I can find something.

I wanted to say one other thing about screening, and that is other high risk groups would be people with psychiatric problems, such as bipolar disorder--

DR. KATZ: Again, based on what data?

DR. SKIPPER: There is plenty of data that shows that. The report to Congress on co-occurring disorders--

DR. STROM: Co-occurring is different.

DR. SKIPPER: Well, I am saying that people with psychiatric disorders, a number of them, have a high risk of substance abuse.

DR. KATZ: Let's move forward with that clarification. I think it is fair to say, and somebody can challenge me if I am wrong, that there is no data whatsoever on trying to classify patients with chronic pain being given opioids for their chronic pain in terms of whether they are at higher or lower risk for using them. The only study is one small retrospective study of 20 patients where we compared patients with and without histories of substance abuse for their subsequent development of destructive behavior on opioids and identified some risk factors. But that was one very small study and is still, to date, the only one on chronic pain.

Unless anyone is aware of any other studies in patients with chronic pain predicting addiction when they are prescribed opioids, the next issue is, well, can we find indirect evidence

from the world of addiction where we can look for risk factors for the development of opioid abuse in general, forgetting about chronic pain? I think that, Dr. Skipper, is what you were trying to get at, that is, can we analogize from the world of addiction.

So, let me reframe the question then and say to our addictionology colleagues what are the risk factors for opioid abuse in the land of addiction? And, what evidence is there behind our assertion that those are risk factors? Dr. Ciraulo, would you care to take that on?

DR. CIRAULO: Well, I just wanted to refer to Dr. Passik's talk yesterday. There are some references included in that, and I don't know if our pain colleagues are familiar with these articles about aberrant drug-taking behaviors and how our pain colleagues consider the quality of these articles. I haven't reviewed the original articles but, clearly, they point to probably more predictable and less predictable characteristics. It does cite studies of cancer in AIDS and I can speak to the standardized measures used in psychiatric diagnosis which are appropriate. I don't know if that data is hard enough but there

was some presented here yesterday.

DR. KATZ: Dr. Dworkin, did you have a comment?

DR. DWORKIN: Well, my sense is that there really is no systematic prospective research addressing this question of risk factors for aberrant behaviors in chronic pain patients. So, then the question is can we extrapolate from risk factors in the general population for opioid abuse to this medically ill population? I am a little bit skeptical about that, especially if what we are talking about is adding it into the label. I mean, it seems to me if you are going to put in assessment of risk factors being necessary in a label, it should be based on the patients that the drug is indicated for, not an extrapolation from the general population. I could be wrong, but my sense is there are no reasonable prospective, systematic studies of risk factors in pain patients.

DR. KATZ: Dr. Baxter?

DR. BAXTER: Yes, I agree with that in the sense that I am hard-pressed to cite for you some studies that have been done. But, on the other hand, when I was referring to making an assessment

I was talking about asking the question if a person has previously had problems with opiates in the sense of having abuse; if they have, in fact, had any problems in the past with other substances; and, as my colleague mentioned, having a history of psychiatric illness. All of these things are known to put people at a higher risk. So, if you have this type of information, well, then I think that would behoove the prescriber to have a heightened sense of awareness that the possibility is there and that it is more likely in those individuals than in people who answer no to those questions.

DR. KATZ: So, we have a proposal that from personal experience, clinical judgment and from extrapolation from the general population from the world of addictionology we can put forth some probable risk factors that still would need ultimately verification in a chronic pain population, those being history of psychiatric illness, history of substance abuse and history of prescription opioid abuse being the three that you put forth. Any comments on the reasonableness of those criteria for flagging patients at high risk, even given the fact that our level of evidence is no longer at the clinical trial level? Dr. Bril?

DR. BRIL: I would agree fully. I mean, clinical trials are great if we have them and prospective, randomized studies are wonderful but we still have to deal with the world as it is, and there are a lot of areas where we don't have grade A evidence. We still have to deal with the person. As long as you know what the level of evidence is you are dealing with, then you still have to approach the problem. I mean, yes, maybe there is a lot of research to be done but I think it is an eminently reasonable approach to trying to identify patients who are at higher risk.

The issue yesterday and today--and this is what I found exciting about Dr. Kreek's talk--is that we really can't identify in a fail-safe manner those patients who will be tolerant, or dependent, or have changes in their mu receptor. Perhaps when we get the genetics of it worked out we will be able to do a profile and say this patient should not receive an opiate ever, or you may always have to give this patient this drug, and these patients are safe. But we are nowhere near that yet--perhaps we are very near to it, I don't know but we are not there yet. So, in the meantime we still have to do something to try and be safe in

our prescribing practices.

DR. KATZ: Dr. Strom?

DR. STROM: I am someone who lives in non-randomized data for a career. I agree with you completely from a clinical point of view. We are not making clinical recommendations now; we are making regulatory recommendations. Regulatory recommendations need to be made on the basis of science and shouldn't be made if there isn't adequate underlying science underlying it. That is not to say that clinically you shouldn't do what makes the most clinical sense but we shouldn't be making rules that people are going to get sued for if they don't follow them if there is no scientific basis underlying it. On top of that, any intervention, again, has bad side effects of its own. Unless we know what will improve things we shouldn't be requiring it.

DR. KATZ: What we are trying to do is advise this division of the FDA as to what is a reasonable way for physicians to practice medicine, although it does verge into discussion on labeling, and then they go on and decide what is appropriate from a regulatory point of view.

DR. STROM: I thought question number two

is here is the labeling, how should we change it? And, our discussion was what should we put into the labeling.

DR. KATZ: It is, and I can be corrected but I think our role is to provide clinical wisdom and insight and evidence of data that addressees the issue of the label, and they will decide how to write the label in the end. Would anyone from FDA care to comment on that?

DR. MEYER: It is certainly true that the discussion today, whether science or opinion, is advisory to us and we greatly value both. It is very helpful for us to know when it is opinion and when it is data based, however.

DR. KATZ: Dr. Skipper?

DR. SKIPPER: It is already in the package insert, you know, that it shouldn't basically be used in people that have a risk of misuse, abuse or diversion.

DR. KATZ: Could you read that language?

DR. SKIPPER: This is proposed on page 32. It says, Palladone can be abused in a manner similar to other product agonists, legal or illicit. This should be considered when prescribing or dispensing Palladone in situations

where the physician or pharmacist is concerned about increased risk of misuse, abuse or diversion.

So, it makes only sense that since they are saying there is a risk that we should advise people to screen for those risks.

DR. KATZ: Not to put words into Dr. Baxter's or Dr. Crawford's mouth but it sounds like that wording suggests that if, for whatever reason, you happen to develop a concern, then you might want to go in some direction and I think what you are saying is that your are recommending a more proactive screening process whereby each patient for whom the physician is considering that medication ought to be screened. Then, if they make it into the high risk category, whatever screening criteria the physician uses, they perhaps should be monitored differently.

DR. SKIPPER: Yes, absolutely correct. You are great!

[Laughter]

DR. KATZ: Now, I haven't heard anyone say that that is unreasonable in terms of the clinical practice side, forgetting about writing a label for a second. I haven't heard anyone say that that does not represent good medical practice and that

one ought to screen one's patients for whether they might be more high risk or low risk and consider a more proactive monitoring system for those that may be at higher risk, even given the uncertainties in both the categorization as well as the efficacy of the monitoring. Does anybody feel that that is not a good way of using these medications? Dr. Cush?

DR. CUSH: Well, I would make the suggestion that makes you want to argue with me, that is, if we were to have a proviso asking for some risk assessment in there, I would suggest that when these prescriptions are being written a one-page form goes out with the prescription which is a risk assessment. Some of this is taken from Dr. Passik's presentation from yesterday which I thought very good, but a risk assessment, some goal setting and some outcome measures. It is a one-page thing. It sort of indicates that some discussions went on between the physician and the patient about risks and concerns and achievable goals, and that can be part of a restricted access system which could be part of a database that is collected over time.

Going back to Dr. Strom's point which I agree with, indications should have some rigid

evidence-based principles behind them, and I would ask him to comment if he thinks this is wrong but I think what we heard yesterday and today is that there is a real need here, a real concern about abuse potential. Based on what we see, we don't know a lot about what is happening and the mechanisms behind it and, hence, there is a large area of study that is needed. Without doing something proactively in the form of labeling we are reliant upon who to do this.

DR. KATZ: Actually, it may interest the group that there is a validation study that is ongoing right now to develop a self-report questionnaire that will screen patients for high risk and low risk for prescription opioid use. So, hopefully, that questionnaire will be available in nine months, or something like that. Dr. Rose and Dr. Strom and then I am changing the subject.

DR. ROSE: What I would like to suggest is that we shouldn't say that the physician should do their own mental screening and then treat those patients that they suspect might be at high risk for abuse in one way and not treat the others in that same way. I believe that all patients should be treated the same, much the same as we are doing

in emergency rooms and screening everyone for domestic violence rather than just saying, well, this person doesn't look like a victim of domestic violence. I think you have to treat all patients the same and you have to have a level of concern for everyone in the same manner. Then, once you have assessed everyone, then you can make your decision.

DR. KATZ: Dr. Strom?

DR. STROM: Yes, I agree. Again going back, I think any intervention has negative side effects and if you reassure people that these are people you don't need to worry about and you are reassuring them incorrectly, then you potentially increase risk.

In terms of the other question that I was asked about the specifics of the risk management plan and having a form for use with everybody, that would be used with everybody, and I am much more comfortable with something like that that is used for everybody and we will presumably talk later on about the specifics. I still think in that kind of recommendation in anything we think about as we talk about the risk management plan, remember that these plans have side effects of their own. They

will shift people to other drugs. People will not get access--the more we put into the plan, the less access patients will have to the drugs. Maybe if they don't work well that is appropriate but if they have unique benefit it may be appropriate. But that is a different question and we need to keep that kind of thing in mind.

I think it is very important to differentiate between clinical thinking, which you apply to an individual patient at hand and what you would do from a system point of view, which is being applied to a population because you have the balloon phenomenon, you squeeze here and it expands somewhere else. When you apply any kind of intervention it has side effects and we need to think clearly about what those interventions, therefore, should be.

DR. KATZ: Did I hear you say that rather than classifying patients into high/low risk based on criteria that are not validated and just have an enhanced monitoring system for the putatively high risk ones, you would propose an enhanced monitoring system for everybody?

DR. STROM: I would propose an enhanced monitoring system for everybody in studies to find

out what real risk factors are. Again, a key difference in clinical decisions and regulatory and population decisions is that in the clinical situation you are forced to act in the absence of data; from a regulatory point of view, we shouldn't be recommending actions unless there are data that we know that the actions will make things better rather than worse.

DR. KATZ: I am going to change the subject slightly, still keeping within question number two. One of the aspects of this statement that is put down here in question number two is for the management of moderate to severe pain. Nobody commented specifically on whether they felt that moderate to severe pain was an appropriate entrance criterion for appropriate use or whether that should be just severe, or whether it should be mild, moderate and severe, or whether we shouldn't mention pain intensity at all. Does anybody have any comments on that aspect of the label? Dr. Gillett?

DR. GILLETT: In particular, I wanted to underline the functionality definition that was supplied yesterday, and I can't remember by whom, but the scale becomes an objective scale in terms

of functionality whereas a subjective scale in terms of pain relief and so forth. I think that anything we can do to get into a two-way measure would be a benefit to the patient and to the provider.

DR. KATZ: Dr. Strom?

DR. STROM: I want to echo that. I certainly wouldn't restrict this to just severe pain. I think that pain practitioners are very used to thinking about a visual analog scale and measures of moderate to severe pain. But, as you all well know, the same person will rate some people's pain sometimes mild; sometimes moderate; sometimes severe. So, the actual use of the scale is totally arbitrary.

I think what matters more is that the pain is severe enough to cause functional impairment and that you have tried other alternatives and the other alternatives haven't worked. I guess what I am talking myself into is that I would remove the issue of severity of pain completely and talk in terms of pain severity enough to impair functionality after having tried other alternatives and it didn't work.

DR. KATZ: So, if I have a severe pain

that is seven out of ten on a zero to ten scale, severe in intensity, but I am still able to get through and function, which is actually not such a bad description of my present condition right now--

[Laughter]

--you wouldn't let me take opioids?

DR. STROM: If it is not impairing your function one could argue is it severe? Again, it leaves a lot of vagueness in the definition of function.

DR. KATZ: Just to be absolutely clear, pain intensity is a well-validated construct and there are, you know, fifty years of data on the validity of pain intensity as a construct, and one way of measuring pain intensity is with a verbal categorical scale that includes descriptors such as mild, moderate and severe. Are you suggesting throwing out that paradigm?

DR. STROM: I am suggesting, (a) it is a lot less well validated--and John Farrow who some of you know worked with me is showing that--than people think and, (b) that primary care docs, who are the ones who are prescribing most or a large proportion of this medicine, are not giving visual analog scales and they don't know what moderate to

severe pain is in the same context. They do know that if patients have enough pain it is interfering with their function.

DR. KATZ: So, your suggestion remains replacing pain intensity as the entrance criterion with the functional impairment?

DR. STROM: From an indication point of view, not research-wise. Again, you know, I am not saying that research-wise but from an indication point of view.

DR. KATZ: I think it would be appropriate to give Laura Nagel from DEA, since her group put forth removing moderate as a suggestion, a chance to comment on their reasoning behind that proposal.

MS. NAGEL: Candidly, we follow very closely what was just put forward. It was the question of what is moderate and what is severe, and does everybody understand that to be the same, and when is it appropriate as a first-line or second-line? I am personally thoroughly enjoying the conversation and would very much follow the functionality statement. If I understood properly, you would still be using severe and moderate but what you would be doing is tying those same concepts to functionality, which might make it

easier for non-specialists to follow. That is what we were trying to get to when we brought these up, that is, a term that would be understood by the generalist and understood better by citizens also as to what it means, and still using the scales and having it not necessarily be the first-line of defense as well.

DR. KATZ: So, you are endorsing the idea of eliminating the subjective pain intensity rating from the entrance criterion but replacing it with a patient self-report of impairment of function, to be endorsed by a physician?

MS. NAGEL: Yes.

DR. KATZ: Dr. Meyer?

DR. MEYER: Maybe this is turning the tables on Dr. Strom, what data do we have to suggest that--

[Laughter]

--I am serious, that a physician understands the subjective self-report of impairment of function better than they understand a report of mild, moderate or severe pain?

DR. STROM: I think your question is very legitimate. I don't think the physician understands either of them very well. I think the

difference is that we are dealing with symptomatic treatment and what matters is what the patient reports. I think an arbitrary definition of moderate or severe is arbitrary and what really matters is--you know, the goal here is to relieve symptoms and does the patient have pain severe enough that they need this therapy and other therapy hasn't relieved it. That is a question of functionality. That is just a question of English in a way that a patient would understand. So, I am not looking here to target the physician. I think the moderate to severe targets the pain physician; it doesn't target either the primary care physician or the patient. I am looking to target the patient because ultimately the only way to find out if somebody has pain is to ask the patient.

DR. KATZ: Dr. Dworkin?

DR. DWORKIN: I couldn't disagree with Dr. Strom more because it is the simple fact that function is the slipperiest concept in the whole chronic pain world. How do you compare function in a 35-year old, single mother who is employed, with fibromyalgia, and a 75-year old retired quadriplegic who has spinal cord injury pain? If I knew the answer to that, I would know a lot more

than I think any of us know in the chronic pain world right now. I completely agree with Nat that, you know, a zero to ten scale or none, mild, moderate or severe pain scale has a lot more weight of reliability, validity, responsiveness evidence base behind it than anything any of us could come up with in the next five years regarding function. I rest my case.

DR. KATZ: Dr. Bril and then Dr. Strom.

DR. BRIL: I guess my question also is what is the real purpose of the functionality? Pain is a patient symptom from none to the most severe and the patient really is the one who has to report and you assess your efficacy on what they are doing. Is the functionality reassuring the physician more because you feel better? If the patient doesn't have pain, they are not at all impaired with their function so that really validates the fact that they don't have pain? Whereas, if they say they have severe pain but they are still working, then they really don't have such severe pain so you are putting your judgment on their pain again?

So, again, who is making the decision about the patient's pain and the patient's pain

relief? Is it the patient or the physician? I think if it is the patient, then VAS which has been used in a lot of scales is quite good, and most people really know what mild, moderate and severe is through use if they are using that. Whereas, impaired function, for the reasons stated, can be very, very difficult and I think isn't any more validated. I mean, I don't really see that it is validated in this field at all.

DR. KATZ: Dr. Jenkins?

DR. JENKINS: I think this is a very good discussion and this is exactly what we need to hear because, as you know, we have been hearing advice from various parties that the moderate to severe--the moderate part of that indication is a significant problem and there are those who have suggested that eliminating the moderate from the indication and limiting this to severe pain might actually lead to less prescribing. There has been the hypothesis that less prescribing means less drug that is out there with potential to be diverted, misused or abused. So, it is very important for us to hear this discussion so that we can understand the committee's views on what we should be doing in this regard.

A little bit challenging some of what Dr. Strom has said, we are a science-based regulatory agency but that doesn't mean that we always rely just on randomized, controlled clinical trials to make our regulatory decisions. An example I would give here for putting the indication for opioids into our risk management concept is that I don't think there is any doubt that if you studied patients with mild chronic pain and treated them with a modified-release opioid I don't think there is any doubt that you would not find the drug to be effective. But we would not feel comfortable in the risk/benefit analysis recommending modified-release, high dose opioids for patients with mild chronic pain.

So, putting this into a risk management perspective, I think it is very interesting and important for us to hear from the members of the committee about that moderate pain. I don't think there has been any suggestion from anyone that we should change the indication with regard to severe pain. The congressman who testified yesterday--I think everyone I have ever encountered with this has said we view this as a legitimate and valuable drug for people with severe pain, but there are

some who have questioned whether this really is needed or necessary or has a favorable risk/benefit balance for patients with moderate chronic pain. And, I am not advocating the position one way or the other; I am just trying to make sure that the committee understands the issues and gives us your answer in a risk management concept.

Clearly, these drugs are effective in relieving patients with moderate chronic pain. The question we are trying to get from you is, is it appropriate that we indicate these drugs for moderate chronic pain, given their risk. So, you really need to look at this indication question as not simply what have the clinical trials proven to be the case because we have to go beyond that when we do our risk/benefit analysis. So, we really are interested in hearing what your risk/benefit equation analysis for moderate chronic pain is.

DR. KATZ: Let's focus on that specific question then, and the specific question on the table right now is what is the risk/benefit analysis for the use of modified-release opioids for the treatment of chronic pain that is moderate in intensity? Dr. Shafer? I am starting my list all over again so if you want to talk, raise your

hand again.

DR. SHAFER: I would absolutely leave moderate on there, just to answer your question bluntly. I am concerned that taking the word moderate off would be an invitation to prosecution by the DEA, and my DEA colleagues have assured me that it would not be used that way but, nonetheless, as a clinician I may well interpret it that way and it might, I think, significantly restrict access.

I am uncomfortable with people with moderate pain having to beg for adequate analgesia, and the diverters I think are not going to say, "well gee, it's only moderate pain so my pain's just not enough. I suspect the diverters, although, again, I don't have data on this nor will there ever be data on this, but I think we can know things from reasonable extrapolation and diverters are very likely to be dissuaded by limiting it to moderate [sic] use because somebody's pain will just be a whole lot worse because it was fabricated at the outset. So, I would very much be against removing moderate. I think that it would actually be a significant restriction for use by clinicians. I would interpret it that way.

DR. KATZ: And from a therapeutic perspective, it sounds like you are also saying that the risk/benefit analysis of using opioids in this population is favorable.

DR. STROM: Well, you know, we have a lot of data presented even by Dr. Van Zee who got up there and said it certainly is no worse. And the safety studies, and there was a safety aspect to that, said it is no worse. So, I don't see a problem.

DR. KATZ: Other comments on this issue? Dr. Wlody, you are next.

DR. WLODY: I would like to make two points, again not necessarily based on evidence but opinion. First of all, when you are talking about moderate pain I think almost by definition you are talking about people who may have failed on NSAIDs at this point and then what is left other than opioids, either controlled release or immediate release, which is a separate issue? Certainly, in this group of patients, you know, I am not sure what the alternative is at that point.

Second and sort of philosophical, you know, if we are talking about what a big problem untreated pain is in this country, we are not

talking about untreated severe pain. I think that is recognized. We are not talking about untreated mild pain; we are talking about this large group of patients with untreated moderate pain and I think, you know, we have to provide the mechanism for treating these people effectively.

DR. KATZ: Dr. Bril, you were next and Dr. Rose.

DR. BRIL: I wouldn't remove the word moderate either. You know, patients with mild pain don't really want anything; they are happy to live with it quite often. When you talk about side effects of a drug they say, "oh, no, it's not that bad." So mild is no problem at all. It is moderate where patients really need relief, and in the chronic pain conditions I deal with the agents that I have available to me are not universally effective or universally tolerated, no matter what they are, whether they are antidepressants or anticonvulsants which I tend to use first; I tend to go to the adjuvant analgesics. So, I would not wish another therapeutic avenue to be closed to me because there are a lot of patients there who still don't have relief and who need this option and you would be depriving them of this potential relief.

That is not to say I think every patient responds to either short- or long-acting opiates either. I mean, there is still an unmet need.

Moderate though is the level where a lot of my patients are willing to accept the risk of side effects in order to obtain relief. Moderate is really quite a marked level of pain for them, as well as severe, so I would not remove moderate.

DR. KATZ: So, it sounds like what we are hearing is that restricting the use of these medications to just individuals with moderate [sic] pain would worsen the under-treatment of the pain problem and may or may not have an effect on reducing the diversion or abuse of this.

[Comment from the audience]

DR. KATZ: Oh, did I say the wrong thing? Thank you.

I would like to move on unless there are any comments. Unless there has been some gross misapprehension of what the committee thinks, I would like to move on to the next issue.

DR. JENKINS: Dr. Katz--

DR. KATZ: Go ahead.

DR. JENKINS: Does anyone on the committee not agree with the proviso that the indication

moderate to severe chronic pain with all the other conditions that are in the labeling or that you have suggested--does anyone not agree that that is the appropriate indication for this drug? Is anyone in favor of severe only?

DR. KATZ: Should we go around and see what people think?

DR. JENKINS: Sure.

DR. KATZ: Let's do that then just to be sure everyone has had their chance to respond. Let's go round the table and everyone can take half a minute and let us know what they think about the issue of moderate to severe and, if it should be modified, in what way should it be modified and why. Where should we start? I guess, Dr. Crawford, you are the first regular member.

DR. CRAWFORD: I support moderate to severe for the reasons already articulated.

DR. KATZ: Dr. Shafer?

DR. SHAFER: I support moderate to severe.

DR. KATZ: Dr. Baxter?

DR. BAXTER: I support moderate to severe.

DR. KATZ: Dr. Gardner?

DR. GARDNER: I support moderate to severe.

DR. KATZ: Dr. Aronson?

DR. ARONSON: I support moderate to severe but I wish to speak to that a little bit further. I also recognize that the concern is accessibility and availability and that if we do support, as a committee, moderate to severe the likelihood is that there will be more available and more accessible drug.

Having said that, I would like to turn back to the recommendation, I thought a very elegant recommendation that spoke to the labeling having a requirement to ask physicians to behave in a way that we all would perceive--evidence not withstanding, we all would perceive to be the best way for physicians to behave, which is to take a history and elicit those risk factors in those patients that we believe would potentially be diverters. It serves all good. I think it is very hard to find the risk in that, again evidence not withstanding. I think the benefits of that far outweigh the risks, and I think if we are to say moderate to severe we ought to do that with the caveat that we are working with a heightened sensitivity that we have to police ourselves perhaps more than we would otherwise.

DR. KATZ: You favor leaving moderate to severe and adding language to the label that encourages enhanced management of high risk patients.

DR. ARONSON: Yes.

DR. KATZ: Thank you. Dr. Saini?

DR. SAINI: Moderate to severe, leave it the way it is written here.

DR. KATZ: Dr. Kahana?

DR KAHANA: I also would leave it as moderate to severe but I would want to reemphasize the point brought up earlier by Dr. Shafer that these patients should have failed immediate-release treatment first because that at least would reduce the number perhaps--there are no data but perhaps it would reduce the number of prescriptions available for the sustained-release products and I think they really are a significant risk. I am not sure that anything we do to reduce availability by restricting physicians, however, is going to change what happens on the streets. I think we all have to recognize that. We just don't have any information.

DR. KATZ: Dr. Bril?

DR. BRIL: Moderate to severe.

DR. KATZ: Dr. Rose?

DR. ROSE: Yes, I am in favor of the moderate to severe and I was planning to make that comment also that previously--I think it was Dr. Wlody who said something about patients failing nonsteoridals and going on to this drug, this is not appropriate, and all of the other material that we have about Palladone indicates that the patient needs to have already been on opioids on high doses and that this would be a conversion to the longer-acting drugs. So, I am in favor of the moderate to severe with the understanding that Dr. Kahana just verbalized about having failed other therapy.

DR. WLODY: I favor retaining moderate to severe.

DR. DWORKIN: I am comfortable with moderate to severe, uncomfortable with recommending assessment of any risk factors unless they are replicated and potent, and I don't think we have any, and I am also uncomfortable with limiting it to people who failed IR. Moderate to severe is fine.

DR. CUSH: I am only in favor of severe but with the proviso that it could be worded as

medication for chronic severe pain, or marked pain or severe pain, or moderately severe pain that impairs function, the reason being that in a primary care doctor's office and in my rheumatology office and in a pain doctor's office we all see a lot of moderate to severe pain. I would not like to see as many Class II drugs being written in a primary care doctor's office and I should be writing a whole lot less than is being done in a pain specialty office. So, I worry about the moderate being abused by a large segment of the prescribing population and for that reason I think severe should be on there. Again, pain with functional implications could be useful but that assumes that function is modifiable and it may not always be so. So, that is why severe pain or marked pain with functional impairment.

DR. KATZ: Thank you. Dr. Bobek?

DR. BOBEK: I support moderate to severe as well, and the package insert change that was recommended as well about it not being the first-line opioid choice.

DR. KATZ: Thank you. Dr. Skipper?

DR. SKIPPER: Because these drugs, or at least OxyContin, appear to recruit new addicts and

cause deaths, and because there is no good evidence that the CR drugs are better than the IR drugs for controlling moderate pain and there are other options for people with moderate pain, I would say severe pain and add the limitation in function.

DR. KATZ: Thank you. Dr. Ciraulo?

DR. CIRAULO: I would favor severe as well for the reasons that have been mentioned. I think that one of the risks that we haven't talked about the past hour or so is a public health risk, and I think clinical experience with other agents really makes this a high risk for diversion and the consequences of diversion are going to be disastrous, and I think this should be reserved for severe.

DR. KATZ: Thank you. Dr. Maxwell?

DR. MAXWELL: Severe and, again, I am very concerned, and maybe it is my lack of knowledge, but I haven't heard evidence of why we need another drug like this right now. I am very worried about the damage that we could see if it is out and gets mishandled as OxyContin was. If it comes on market and it is well controlled and we don't have this kind of diversion, then I think it is appropriate to go back, after there is more data coming in, and

perhaps consider adding on moderate but right now I am really opposed to this going on the market.

DR. KATZ: Thank you. Dr. Strom?

DR. STROM: I would not restrict it to severe, and the main reason is I think there are people who have moderate pain and significant impairment of function, not functional status as measured by a scale but there are things they want to do that they can't do because of pain and I think they should have access to these drugs. I think it should be specified as second-line drugs, that people should be tried on the milder drugs first.

DR. KATZ: Dr. Gillett?

DR. GILLETT: I agree with Dr. Strom. My point is that you can't calibrate yourself and develop a quantitative basis for any risk assessment on this. The nurse walks up to you and says how are you feeling today? You pause and you don't know what you are talking about because you don't have a pH meter for your pain scale. I just think that we need to have something like severe impairment in order to use a chemical like this.

DR. KATZ: Dr. McLeskey?

DR. MCLESKEY: Thank you, Nat. I think

from an industry perspective we would obviously support the broader use of moderate and severe pain. If I could also respond though to the issue that Dr. Aronson raised just a moment ago about heightened sensitivity and the other issues of maybe enhanced screening and monitoring that have been raised previously as well, I just wanted to comment, and this will probably resonate with other topics that you will be discussing later in this session, that that would represent a hurdle and it might be a hurdle for clinicians that ought to be placed. If it is, as we consider all these ideas, I would just like for the clinicians especially on this committee to comment on is it too onerous a hurdle or is it something that would be acceptable.

I would also like to plant the seed that as we apply those kinds of strategies it might actually be something, if it were specific and relatively easy for a clinician to accomplish them, that in fact it might be reassuring to the clinician that once it is satisfied, then there might be easier ways to document compliance and potentially reduce the risk of reprisal.

DR. KATZ: Thank you. Dr. Jenkins?

DR. JENKINS: Just one final point on this

side I wanted to ask the committee to clarify because, as we went around the table I think it was very useful to hear your individual thoughts on the question, but I think I did hear some people responding to the question as it is written, which applies to the currently marketed modified-release opioids including OxyContin and some of the modified-release morphines. I heard some of the committee members seemingly talking towards Palladone. So, I guess I am interested in understanding whether the comments that we just heard apply to Palladone or to the currently approved modified-release opiates or all.

DR. KATZ: Well, let's do that by show of hands. Whose comments were related? This is what I am going to ask so hold on for a second. Whose comments were related to just OxyContin, whose were related to just Palladone, and whose were related to both?

OxyContin--who was talking about OxyContin in their comments that they just made? OxyContin alone?

[Show of hands]

So, one person actually read the question. Who was talking about Palladone alone?

[Show of hands]

That is great. Who was talking about both medications without making a distinction?

[Show of hands]

Does that answer your question, Dr. Jenkins?

DR. JENKINS: That is helpful. Thank you.

DR. KATZ: Great! Dr. Rappaport?

DR. RAPPAPORT: Could I just ask Dr. Dworkin to clarify why you felt that previous use of IR should not be a requirement?

DR. DWORKIN: I guess I don't have any data on this. My impression is that there are some patients, and here I am not referring to Palladone; here I was referring to OxyContin for that specific qualification--I think that 10 mg is a low enough available dose formulation that there are certain circumstances--of course I am not a physician--where that would be a dose that one could initiate a patient on and there wouldn't be a need for having that patient to have either been on an IR form of oxycodone or to have failed an IR form of oxycodone for some reason. Of course, as the label suggests, it is a different story entirely with Palladone.

DR. KATZ: Any comments from our friends from Purdue prior to leaving this subject?

DR. HADDOX: I appreciate Dr. Jenkins clarifying what my reading of question two is, and that is that recommended changes may further enhance the safe and effective use of the products, and I presume that means modified-release opioids which includes more than OxyContin and Palladone. There are a number of modified-release morphines, as has been mentioned, and there are also modified-release fentanyl products on the market.

So, given that, I think that any restrictions you are talking about, if you are going to answer the question as I understand it, apply to all, to this class, if you will, or the subclass. I think that the screening recommendations that have been put forth, if I were in practice now doing this, would apply to that subclass, the modified-release opioids.

I also think that we are leading ourselves a bit astray by breaking the indication that the FDA placed here for you as a sample into its tripartite units. This, unlike Palladone, is a three-tailed test. That is, it is not just moderate or severe pain. That is not the

indication for OxyContin. If that is all you have, that is not the indication for OxyContin. If you have moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time--three conditions--then you are a candidate for OxyContin. I think it is very, very different.

I mean, I used to be a dentist, recall, and I had lots of people with moderate pain after dental extraction who did not meet the OxyContin indication because it wasn't going to last for an extended period of time; it was going to last for a couple of days. They would be on a nonsteroidal and they would be on Tylenol and it would be done. So, I think we need to keep that in mind.

We have addressed this actually with DDMAC in an addendum which we are putting in our adds for OxyContin that says when used in this context, moderate or moderate to severe, it does not include commonplace and ordinary aches and pains, pulled muscles, cramps, sprains or similar discomforts. If the committee would think that would be useful to add to the PIs of all these things, we certainly would be willing to discuss that with the agency.

I think it is also important to remember

the slide that Dr. Lipman, I believe, showed yesterday of Dr. Cleland's work, showing that moderate pain has substantial impairment when it is persistent, not moderate pain from a sprained ankle that lasts for a day but moderate pain that is persistent.

The issue about science, I think we need to get back to that. I have a concern about the discussion of placing "not as a first-line drug" in the package insert for OxyContin and I presume other non-Palladone modified-release drugs. The reason is there is a 20 mg dosage form for OxyContin. Remember the fourth test of Palladone is that you must require and be able to tolerate 12 mg a day of hydromorphone. That is why it can't be the first-line drug. It is not for use in people who are not opioid-tolerant. That is why it can't be the first-line drug.

We have science the agency has seen where we have studied OxyContin in opioid-naive subjects and OxyContin was deemed safe and effective based on those data. Remember what Dr. Portenoy said yesterday, that there will be situations when in this continuum of care along a course of progressively more intense analgesics there might

be a reason to start someone on an opioid as a first-line drug.

From the issue of abuse, if someone was going to abuse a 10 mg OxyContin why would they pay $10 for that on the street instead of buying two Percocets and getting the same amount of medicine? So, I think we have to be careful that we are not mixing apples and oranges here. Palladone is a different product for a different indication than OxyContin. There are overlaps. There are some similarities but they are not a one-on-one thing. I have data actually from two other studies on other things that we have discussed previously, if you so desire.

DR. KATZ: I think that the critique is fair that it may not have been entirely clear as people were giving their answers whether they were talking to the entire class of modified-release opioids or just Palladone, OxyContin, etc. We certainly could revisit that in detail now but, given the time and given that we still have a long agenda, I would pose the question to the folks from the FDA as to whether you would like us to take the time to go through that clarification or whether you have heard what you need to hear from us.

DR. JENKINS: I would suggest that we move on because there are a lot of additional issues that are beyond just the indication, and I think the points we have heard are very valid. No one, I think, around the table was thinking of this just as a moderate to severe pain indication. That was just to get to some of the suggestions that have been made. No one was taking this out of context and I don't think the committee members, as we went around the table, were taking it out of context because most of the committee members actually advised adding additional type of qualifications to the indication. So, I don't really think, from the agency perspective, it is necessary to revisit the issue. I would like to get on to the questions about risk management plans, access, etc.

One thing to clarify, the way these questions were set up, the first three Roman numeral questions, and number III has a lot of sub-parts, were really focused on the currently approved modified-release opiates, with the final question being specifically applied to Palladone and whether you think that the Palladone risk management plan is adequate for safe and effective use. So, you may want to keep that in mind as you

go through the questions under Roman numeral III. They are primarily directed towards the currently available products but, obviously, there is overlap with the Palladone and the Palladone plan is the one that you have heard most about today, and I won't be surprised if you have trouble distinguish and keeping those as true separate categories.

DR. KATZ: Thank you. One last observation I will make before we take our break is that it seems clear that people who treat pain for a living and who worry about the problem of under-treatment of pain tend to favor the more open label, whereas people who treat the complications of opioid abuse, obviously, favor the more restrictive labeling. So, what is needed is for somebody sitting on top of both of our groups to kind of weigh and balance all of it and put it together in the interest of public health. I am not sure any one individual of us has the capability of doing that sitting around the table. A 15-minute break.

[Brief recess]

DR. KATZ: Let's move on. I know this is the time when people's stamina starts to drag and people start to think about how they are getting

home, but let's try to redouble our mental energies towards the last hour and a half of our meeting. I am going to read the next question, which will take me half a minute or so, and then we can start discussion.

The FDA is currently reviewing a number of proposed risk management plans for modified-release opiate analgesics. Again to reiterate what Dr. Jenkins said earlier, this question will be referring to currently available modified-release opiate analgesics. Is that right, Dr. Jenkins?

DR. JENKINS: Obviously, we are also reviewing the Palladone plan but we are asking you a specific question later about Palladone.

DR. KATZ: So, we should consider that this question is with relation to all modified-release opioid analgesics?

DR. JENKINS: Yes, this is kind of more of a generic question.

DR. KATZ: Fair enough. Thank you for the clarification.

In order to make informed and appropriate determinations in regard to these risk management plans, we need to carefully consider which elements of risk management would most likely increase the

safe use of these products for legitimate patients and result in a reduction in abuse, overdose, addiction, and misuse in the medical setting. In addition, we must also take into consideration the potential adverse impact of these various risk management elements on patients, prescribers, and pharmacists, as we do not wish to impede proper pain management. In light of these concerns, please discuss the following elements of risk management.

Now we are going to discuss number one. That will be the topic of discussion for the next little while: Restricted access--some risk management programs have attempted to manage risk of drugs through various interventions that attempt to limit product use to appropriate patients. Examples of such interventions have included efforts to limit prescribing to a subgroup of physicians based on established expertise or completion of specific training in safe use of the drug or to limit prescribing to a subgroup of patients such as patients who have failed other available therapies or patients who have the most severe manifestations of the disease.

Discuss the role of restrictions in access

in addressing concerns about the abuse and misuse of modified-release opioid products and how any such measures may impact on the use of these products in appropriate patients.

So, let me just focus everybody's attention on the key elements of this very long question. Restricting to certain types of physicians, would that help solve the problems we are concerned about? Would that impede appropriate pain management? Restricting to certain kinds of patients, would that help solve the problems we are concerned about? Would that have any negative impact on appropriate pain management? Open for discussion. Dr. Shafer?

DR. SHAFER: First of all, I need some clarification. When we are talking about restriction here, are we talking about restriction through the process of, for example, the package insert where it says only these physicians should write prescriptions, or are we talking about some sort of administrative mechanism that actually assures that either the patients have met certain qualifications, for example, the pharmacists have to verify the presence of certain lab data for them to even get physical access to the drug?

DR. KATZ: My understanding is that this could refer to any sort of administrative mechanism for restricting access to physicians or patients. Dr. Jenkins?

DR. JENKINS: Yes, this is primarily intended towards things that go beyond just the package insert. As Dr. Trontell described in her presentation yesterday, there are examples of risk management programs that have gone beyond the package insert and actually put in place mechanisms such as those that are described here. So, we are talking here about restrictions to access that go beyond simply the indication statement or any statements in the labeling about who should or should not receive the drug or who should or should not be prescribing the drug. We are talking here more about any specific programs to try to make sure those limitations actually occur.

DR. KATZ: So, that is another level of the question I guess, if you believe that this is an appropriate goal of restricting to certain patients or physicians, what sorts of programs could one envision to implement such restrictions? Go ahead.

DR. SHAFER: Then just to ask for more

clarification, in terms of these programs, are we talking about all Class II, or are we talking about Class II modified and extended release, or are we talking about Palladone?

DR. KATZ: Go ahead.

DR. JENKINS: We are talking about the Class II modified-release products.

DR. KATZ: Dr. Aronson, you were next.

DR. ARONSON: Yes, I will speak to the question. My opinion is that access to a certain specific physician group ought to be liberal as we need to recognize that the majority of physicians in our country are not specialists and there are an awful lot of patients out there with pain that would likely be seeing those physicians who are not specialists on a first-line basis.

Having said that, I think that it is reasonable that we expect a certain hurdle--I think that was the word that was coined earlier--but a certain set of criteria that anybody meets to demonstrate their understanding of the implications of writing these particular drugs. I think we ought to be careful to establish those criteria so that they are openly accessible to all physicians but significantly high enough that there is some

degree of assurance that they do understand the implications of writing these drugs.

DR. KATZ: Just to be clear, you would not suggest restricting by specialty but you would suggest restricting to physicians who have in some way, shape or form demonstrated competence to prescribe these particular products.

DR. ARONSON: Correct.

DR. KATZ: Dr. Strom, you were next.

DR. STROM: By nature I am an activist and believe more in restriction than education because we know education doesn't work, at least beyond medical school. But in this case I think restriction would be a mistake. The reason is that I think any intervention has side effects, as was talked about a few times, and it is very clear that if you restricted access here it would reduce access to the drug to patients who need it for pain. It is not at all clear that it would in any way affect the problem of drug abuse or overuse. If in fact there was less of the modified-release opioids so people would use less of that, they would use more of something else. So, absent evidence or even reason to think that it would really affect the nation's problem, reduce the

nation's problem of opiate abuse, I would think that restricting access would cause problems and would not have any benefit.

DR. KATZ: So, you are saying that you also would not restrict, but you also don't even like the idea of restricting by competence because you are not persuaded that one could actually create competence through the typical educational programs that we implement. Dr. Maxwell, you are next.

DR. MAXWELL: I want to talk just about Palladone for a minute because something was in the presentation yesterday that was not discussed that I think we need to think about. When Xyrem was brought to market--now, Xyrem is gamma hydroxobuterate and to avoid the abuse problems it is available only through a central pharmacy. So, it would seem to me that as this drug rolls out--and I think those of us in addictionology almost think it is not going to be a problem of people turning into addicts, it is going to be a problem of an awful lot of drug deaths on the streets. It is going to be in bodies; it is not going to be an addiction because of the strength of this drug and the potential for abuse and the side

effects.

Could it not come through a central pharmacy? That way you can assure the doctor that for him even to write it there would be controls on the distribution so we could get out of this business of the back door sort of thing. If the drug turns out to be less abused and not the problem we thought, it could spread out. But I am very worried about dead people. We may ease the pain of some but we are going to kill an awful lot of others with this drug.

DR. KATZ: So, you would favor restricted distribution through certain pharmacies, as well as restricting to certain types of physicians.

DR. MAXWELL: No, I didn't say that about restricting physicians. Is there some sort of course I can take, an educational course?

DR. STROM: Can I just clarify, are we talking about Palladone now?

DR. MAXWELL: Yes, Palladone.

DR. STROM: I wasn't talking about Palladone, I was talking about other non-Palladone drugs.

DR. KATZ: That is a fair clarification. We should actually stick with non-Palladone--

DR. MAXWELL: But that is an option that needed to come out that was not discussed yesterday that should have been.

DR. KATZ: Fair enough. Dr. Bril?

DR. BRIL: I guess my experience is a little bit different. I have a couple of thoughts about how you might find this out, your effectiveness and get some evidence here. I don't know how long you have had to have a DEA license to prescribe Class II drugs in the U.S. That contrasts I think to our situation where we don't need a license from, say, our CMP to prescribe Class II drugs or the equivalent. So, if you knew the interval before and you looked at the level of addiction in the country before the licenses became mandatory and then compared to an interval afterwards you might see if you have actually influenced the percentage of addicts that you have through restricting or granting special licenses through the DEA to physicians. That may be one way to look at this question.

The other way, you could actually perhaps compare a population base here with one north of the border to look at the percentage of opiate addiction, if you can get comparable numbers from a

place, you know, where you have restrictions to a place where you don't have the same kind of restrictions to see whether restrictions work.

Those are just two approaches. I don't have that information myself. I don't know of any of this information in Canada; maybe Health Canada does.

MS. NAGEL: We register any physician that applies that has a legitimate license for the state. There is no delay. When they come in and pay our license, then they are able to show that by the state. We provide them with a registration. There is no lag. There are no qualifications other than a state license.

DR. KATZ: Just to reiterate that, you don't need to have any qualifications, other than an M.D. degree in this country. You don't need to demonstrate competence in prescribing controlled substances in the United States of America in order to obtain a DEA registration to do just that. Is that correct?

MS. NAGEL: Yes.

DR. KATZ: Dr. Shafer, you were up next.

DR. SHAFER: First of all, let me say I would strongly support, by way of restriction, that

the DEA require people to have a certain amount of CME credits before getting CII approval across the category. I don't believe about education not working. Actually education is quite effective, having recently taken a driver training course to that effect.

If people have to take a certain number of CMEs and, you know, it can be Internet based and there are all sorts of interesting ways of doing this for the whole Class II opioids, I think that is a smart thing to do. I am uncomfortable differentiating the intermediate release and the slow release from the immediate-release products because I think that in doing so you may kind of trivialize the risk of the other ones. These are all dangerous drugs, and I am not convinced from the data that I have seen that any particular opioid in the Class II category is intrinsically more dangerous than any other one, or that any release pattern is intrinsically more dangerous. I think they are all dangerous.

Now, there are some unique properties. If somebody were to distill the hydromorphone out of the Palladone tablets, they would have something that would look like heroin. So, that is an

interesting risk that is a little bit unique to this drug because of the characteristics of the IV formulation that might be distilled out. That is the kind of thing physicians need to be educated about through a program. Otherwise, I would not favor a program that targeted either slow release or that targeted a particular molecule in the Class II drugs.

DR. KATZ: Laura Nagel, s response to the education of physicians issue?

MS. NAGEL: For everybody's information, we have been working with FDA and this is one of the things we have been cooperatively working on with FDA. Dr. Katz actually brought it up six months ago about trying to work with the state medical boards to require some sort of continuing education before you would be able to renew your DEA registration.

What we will have to do, just for your information because nothing in the government moves quickly, we will have to actually have legislation. The way the law is written it says we "shall" issue a registration. So, if we are going to put a requirement on your registration that you would, in fact, have gotten some up to date education, we

take a very positive view about it. We do believe there are the outdated and the duped, and we think this is probably the best way for us to try and reach them. So, that is something that we are working with the FDA on.

I am hopeful that actually Massachusetts could be somewhere--we could kind of go first. But we are going to have to work with the state medical boards because I don't think you want DEA defining practice of medicine. So, we are going to have to go back through your state boards and work with them but that is something that we absolutely do agree with you on, and I can speak for the FDA Commissioner, he does also.

DR. KATZ: Thank you very much. The second piece of your comment was related to whether we are making a false distinction between modified release and immediate release.

DR. SHAFER: The number one drug on all of these lists has been Vicodin. So, if you want to talk about the biggest single problem that we face as a health problem here, in the United States, in the way of diversion of prescription drugs, it is Vicodin, which is an immediate-release drug.

DR. KATZ: This may be an artifact of the

purpose of this meeting and I don't know if, Dr. Rappaport and Dr. Jenkins, you want to address that issue.

DR. JENKINS: We clearly recognize that all the opiates are abused and the comment about the hydrocodone--I guess Vicodin--being the one that always shows up at the top of the list. We were focusing here on the sustained-release products or the modified-release products because of their unique characteristic of having such a high dose in a given tablet and the risk of serious adverse events and death, as well as potentially the risk of greater liability for addiction because of that characteristic of the product, very high dose, sustained-release characteristics that can be overcome by someone who has that desire. So, that is why we were really focusing here--we recognize that all of these products are abused and will be working with DEA on all these products, but for now we were focusing on the modified-release products.

DR. KATZ: Dr. Rose, you were next.

DR. ROSE: In talking about whether or not we should be restricting the prescription of these drugs, I would be in favor of restricting the modified-release drugs in some way, keeping in mind

that we already have the OxyContin out on the market which does have a history now of abuse, both being diverted by the patient who receives the prescription from a duped physician to physicians who are running drug mills.

So, there is definitely a need for education like Dr. Aronson said. There has also been the comment made about education doesn't work. So, I would like to combine those and say we should restrict them to the educated physician, restrict the prescription of that to the educated physician but we would have to do a little bit of stepping back because I am talking about all of the modified-release drugs and that would include OxyContin. And, now we have physicians who can all prescribe the drug. So, it would be kind of hard to get that into the practice of medicine.

In a way then, I am just talking about Palladone. I think it is appropriate to have some restrictions on the prescription or these drugs, at least at the beginning. We are here basically to talk about Palladone, and if we have made mistakes in the past as it relates to OxyContin, it doesn't mean that we have to make more mistakes in the future about Palladone. I am not saying keep

Palladone off the market; what I am saying is that if it is going to be marketed, market it in an educating fashion. So, I would be in favor of a strong education aspect in this.

Then, the aspect of how long some physician has been in practice before they could prescribe any one of these drugs, my impression from just hearing stories in Pennsylvania is that some of the doctors, who are running drug mills and prescribing these in a criminal fashion, is that some of them have been in practice for years, and years, and years, and they are tired of practicing medicine and they are running these mills, and they are making a lot of money on their way to retirement. So, I don't think that the number of years you have been in practice is really the answer to that.

DR. KATZ: Dr. Cush?

DR. CUSH: I am generally opposed to restriction but I do think that somewhere, not only in the package insert which is usually not read by physicians--I know that the agency would like to think that they actually do read package inserts but I think studies have shown well that doctors don't. They go to them as references for

particular issues rather than to read the whole thing to be instructed on the proper use of a medicine. I think we have to indicate somewhere along the way the gravity of writing a Schedule II drug, including this new drug Palladone.

So, either you do some sort of extra course work and then you become part of the club that can write this prescription, or I will make a case for a one-page registration that can be done on a periodic basis where patients can receive that. In that one-page form that is filled out they could have documentation of need, of goals, of outcomes that would include risk assessments and outcomes that could also include serious adverse events and that would be, again, instructive as far as the overall outcomes of this program, and what it means, and I think we could learn a lot from that and that would be very important as far as whether this should be applied to other drugs in the same class.

I do think that such a measure does not restrict people from getting this particular new drug because there are plenty of other drugs available and this new drug does not provide any tremendous unmet need so that we need to make it

open to as many people as possible. I think it is a good opportunity that we should study this drug as it enters the market.

DR. KATZ: It is probably my fault that you are talking about both Palladone and the other modified-release opioids together. So, let me ask you to clarify your suggestion about a patient registry then. It sounded like you were suggesting that patients should be entered into a patient registry. Are you talking about patients who are prescribed any modified-release opioid, or just patients who are prescribed Palladone when it comes on the market, or something else?

DR. CUSH: I think you have to start somewhere and I think you should start with a new drug on the market. If that proves successful as a deterrent, as a means of fixing the problem of diversion, of fixing abuse or lowering abuse potential, then it should be adopted to the class. But I think that you have to start somewhere and, again, I think that one page is not an impediment in my practice of medicine. I do this all the time. The patient is leaving the room--oh, I need to fill out a prescription for you to go to physical therapy, which is a one page thing. I

have to write out a form. I do this all the time and it usually reflects the context of what happened in the course of the visit, which in this case would go to the issues of risk assessment and reasonable goals and why I am using this particular drug.

DR. KATZ: I haven't heard anybody say that they favor restricting the use of modified-release opioids a priori to a certain type of patient, one with this disease, that disease, you know, this history, that history. Am I missing something? Is anybody actually in favor of restricting to a certain kind of patient and I missed that? So, that is a take-home message then.

The suggestion is on the table about patient registry, but I just want to also follow-up on the suggestion that came up earlier about restricting to physicians that meet some competency criteria. The reason I want to talk about that for a second is that it seems like that would be very unlikely to impede the appropriate practice of medicine in terms of the negative potential of various interventions that we could come up with. Whether it would have a positive effect on reducing diversion, addiction etc. is another question, but

is there anybody who feels that there would be big downsides to establishing physician competency in order to prescribe these drugs? Bob Dworkin, did you have anything you wanted to say at this point of time? You are actually next on the list.

DR. DWORKIN: I was going to make the same suggestion that Steve was going to make about DEA requiring some minimal level of CME. My concern, to follow-up on your question, is that it sounded like this could be a five- to ten-year process, and then what are we going to do while the DEA sets into place a CME requirement for re-registration? If it really is going to take five- to ten-years, it is nice to know that that is on the long horizon but what about the near horizon?

MS. NAGEL: And that is actually correct, sir. It would not be a quick fix; it would be a long-term project. Thank you for bringing that up because I don't want to leave anybody with the impression that we are going to do this quickly. It is something that we hope to do but it will be long-term, not a short-term.

DR. DWORKIN: So, it seems like we are all in favor of that but that doesn't really address any of the need for the next ten years.

DR. KATZ: Although it may be possible, in collaboration with the state medical boards, to fast track this pre-legislation. Is that correct?

MS. NAGEL: That is what we hope to do. We hope to get a couple of states together and they may have data to present in the future on the utility of the program. I mean, we hope to do what we can quickly but the reality is--I don't want to say ten but I would say to you it is probably a three- to a five-year process because legislation will have to get changed; medical boards will have to get on. So, the short-term is the products that are out now and more products that are coming out soon.

DR. KATZ: Dr. Trontell, do you have something to add?

DR. TRONTELL: Not on the topic of physician competency but I will have a question of clarification about patient registration based on Dr. Cush's remarks. I can wait if you like.

DR. KATZ: Go ahead and do it now.

DR. TRONTELL: If you could clarify, since we have tended in the agency to refer to registries as, in fact, some central repository of information on patients, are you referring to something that

might be maintained, say, in the patient's chart with the physician in the nature of a physician-patient agreement, or something, in fact, where there is some collection of these data and oversight?

DR. CUSH: I would envision this being not part of the chart because it is something that goes along with the prescription, and it should actually reflect what should be in the note or the context of what happened in the course of the visit. So, if it were to be copied and put in there, that would be fine but it should also reflect what is in there anyway. But I would envision this thing either being given with the prescription to the patient and the patient takes both to the pharmacy and then it gets submitted and sent to a central depository. Then you can use that to collect information on a patient on a drug over time. Again, it has to show up with every prescription. I mean, I have heard that sometimes you can only give two weeks at a time, so maybe quarterly patients are registered or a patient is registered if a doctor goes on line and fills this stuff out on line by doing some check boxes and it is checked that way.

DR. KATZ: Thank you. Based on time, we only have time to spend another minute or two to talk about restricted distribution by either patients or physicians. So I want to try to restrict the next few comments to comments specifically to the area of restricted distribution, and, Dr. Gillett, you are next.

DR. GILLETT: As a big supporter of extension work, we use that for pesticides because restricted use pesticides have to be sold by a person with a license that gets four units each year of continuing education. This means that the hardware store salesman or the pesticide applicator has to have that license. You at least ought to have that same level of teaching education for a drug of this class.

DR. KATZ: So, you are in favor or requiring demonstration of physician competency--

DR. GILLETT: yes.

DR. KATZ: --for prescribing all modified-release opioids.

DR. GILLETT: Yes.

DR. KATZ: Dr. Skipper, you are next.

DR. SKIPPER: I wanted to mention that it appeared from the data, from the DAWN data and

other data that the interpretation of OxyContin did recruit new non-medical substance abusers, and it is my impression that there was a significant death rate, you know, 500 to 1,000 people a year, from overdoses of OxyContin. That has been my impression. I don't know, we didn't hear any discussion of the death rate.

Anyway, I have been wanting to mention something during this entire meeting, and that is that I think there is a significant stigma against substance abusers. If we were talking about a new antibiotic coming on the market that was taken by kids and they died, then it probably wouldn't get introduced. So, somehow we are feeling okay about introducing more drugs that are probably going to be abused and kill people, and it is probably going to be kids that are experimenting and I just think we need to keep that in mind.

DR. KATZ: Dr. Crawford, last comment on this issue.

DR. CRAWFORD: Thank you. It is a quick one. I am just a bit sensitive that all of our discussion has focused on the diagnosis prescribing side to physicians. There are others with prescriptive authority. Whatever occurs with

physicians should also be extended to such as advanced practice nurse practitioners and perhaps dentists with certain indications, and others. So, that is my only comment.

DR. KATZ: That is a very good point. We should all be probably using healthcare providers or some more general term like that for the purpose of this discussion. Is that what you are saying?

DR. CRAWFORD: Actually, I would like to see in any of the language physicians and other prescribers.

DR. KATZ: Thank you. Referring to my colleagues from the FDA for a second, would it be useful to go around the table and see what people's sort of final stances are on restricted distribution through either pharmacy, competency demonstration, patient types, whatever the individual would like to put forth, or are you satisfied with what you have heard?

DR. JENKINS: I think we have heard a pretty strong sense from the members of the committee that they favor educational competency, some sort of maybe working with state medical boards and/or the DEA to have a requirement to renew your authority to prescribe. I haven't heard

anyone suggesting that we should limit in any way the ability to prescribe these drugs to, say, pain specialists, anesthesiologists, in other words, not general internists or family practitioners. So, if anyone feels that we should be restricting the specialty of the physician to prescribe, it would be interesting to hear their thought process there.

I did hear some suggestion that maybe some of that might apply to Palladone because of some of its unique characteristics, and I did hear one suggestion about maybe a central pharmacy as a way to introduce a drug like Palladone.

DR. KATZ: So, holding off on Palladone for a moment, is there anything else you feel you need to hear about question three as we have discussed restricted access to existing or forthcoming opioids?

DR. RAPPAPORT: Well, by training is still an issue that should apply to all of the products. So, as Dr. Jenkins just asked, maybe we should make sure that there is nobody who feels that we should put any restrictions by training for the general class physician, prescriber training.

DR. KATZ: I am sorry, could you just articulate that question one more time, Bob?

DR. RAPPAPORT: Restricting by specialty or physician training is still something that could apply to all of the extended-release opioids, and if there is anybody who maybe feels we should do that, we haven't really addressed that specifically.

DR. KATZ: My sense is that everyone who was endorsing education as a requirement for dispensing modified-release opioids was referring to the whole class and I think maybe as a requirement of DEA registration, referring to all opioids.

DR. RAPPAPORT: Yes, I understand that, but I am also asking beyond that, is there anybody who feels there should be limitations by specialty training.

DR. KATZ: Does anybody feel that there should be limitations by specialty training? Again, we will talk about Palladone in a moment.

DR. JENKINS: I think a corollary to that question, as Dr. Trontell described yesterday, is that some of the risk management programs have actually had, for example, physician attestations that they are aware of the appropriate use of the drug and they maybe have taken a course offered by

the sponsor. Is anyone suggesting that we should be considering such a program, beyond what we talked about, where you would have to have some educational requirement to get your DEA license? Is anyone suggesting that we should have something where, in order to prescribe OxyContin, in order to prescribe modified-release opioids, or Palladone that you should have to, you know, say I have taken this course? I am aware of the indication. I am aware of the safe use--basically a physician attestation of adequate training?

DR. KATZ: Dr. Ciraulo?

DR. CIRAULO: I would recommend you follow the buprenorphine model and be certified in a similar way.

DR. KATZ: Dr. Rose?

DR. ROSE: It has been suggested that there be some kind of a registry. I believe Dr. Cush made that recommendation. I would be opposed to the registry because there are privacy issues here. A lot of patients would not want their information to be going to the pharmacist, to be seen by the pharmacist. But I am very much in favor of requiring the physician to make certain documentation on their own medical chart so that if

it were necessary to see that chart by any regulators or any DEA agents coming into the office, they could see that there was documentation on that patient's chart for prescribing.

DR. KATZ: It sounds like we are ready to move on to the next issue. I am going to skip over to the final page of our list of questions where it says "question for day 2." Since there are only 15 minutes left in our meeting and since we are supposed to talk about the Palladone risk management program, it seems like we ought to get to that. Then if we have time we can cycle back to some of the other details of the other program suggestions.

So, I will go ahead and read this question: Based on the information that has been presented at this meeting, and taking into account your earlier discussion and deliberation about risk management plans for modified-release opioids, does the Palladone risk management plan, including its proposed labeling and indications, define a program that will likely result in safe use of the product and limit the potential for abuse and misuse of the product while assuring that appropriate patients are able to receive the medication?

Open discussion. I am starting my list all over again so if you would like to be recognized, raise your hand. Dr. Aronson then Dr. Cush.

DR. ARONSON: One of the things that I heard this morning in the multifaceted plan by industry to roll out this product was a proposal to do it in a staggered, if you will, staged launch. It was mentioned that there was a proposed four-month lag to separate their first initial selective launch before they implement their second. I question the legitimacy, for lack of a better word, of that time line. We did not, for example, see data yet analyzed from 2002 with respect to the DAWN and other, if you will, outcomes from their RADARS program and if it is already ten months into year before we have had a chance to analyze 2002, why would they think four months of a staged launch should serve any positive purpose in their wishing to have feedback? So, I would propose that that be extended considerably before they go on to their next phase.

DR. KATZ: Let me dwell on what you are saying for a second. It sounds like your first point is that you are endorsing a staged launch.

Right? It seems like you are implicitly endorsing it.

DR. ARONSON: I accept the concept of rolling this drug out in a staged, selective manner, yes.

DR. KATZ: Your second point is that while you endorse and like the idea of a staged launch, you feel like four months is too short for the data collection and reporting and all the other reasons that you alluded to.

DR. ARONSON: I don't think we would be able to gain anything one way or the other by that time line.

DR. KATZ: Right. Do you have a sense for what time period you would recommend?

DR. ARONSON: Based on history, I would say a year. We are now at least ten months into this year and we have not yet analyzed the data that they wished to have presented to us today from 2002.

DR. KATZ: Fine. The third piece of your comment that I would like to focus on is that it sounds like you have some idea of what data one would need to see in order to determine whether that first stage in the staged launch should be

followed by a second stage.

DR. ARONSON: Well, I spoke to that earlier as well. I wanted to know what metric, what tools they were actually going to analyze in a processed outcome manner to decide whether or not they would go on to their next level, and I did not hear that answer very clearly. I think we do need to have that answer. I think any strategy has to have a goal, an endpoint, and I would like to know at least prospectively what that is before we accept their plan.

DR. KATZ: Well, i would feel back to put the sponsor on the spot again; I have done that to them a couple of times; so I will put you on the spot instead. What information would you like to see? Forgetting about this database or that database, as a clinician or someone interested in these medications, what information do you think would be necessary in order to decide whether the results of that first stage suggested you should go to stage two?

DR. ARONSON: It is my presumption that the whole initiation of the RADARS type program, etc. was to understand better for the purposes of minimizing the risk of diversion and abusive

behaviors with what is potentially a very dangerous drug. So, I would like to know, in fact, that we do have data that help us understand that, and whatever behavior modification we would propose to implement does have an effect to mitigate that and prevent it.

DR. KATZ: Thanks. Dr. Cush is next.

DR. CUSH: I think that the manufacture of the RADARS program was multifaceted and impressive and I applaud them for that. I think it is an important arm of a risk management program, but I think as far as the question is stated, will it actually result in the safe use of the product and limit the potential for abuse, I think the program they laid out is one that collects data and points out problems and tells us where diversion may be occurring or problems are occurring, but we have kind of already heard that with the drugs that have already been out, like OxyContin and what-not. I think it is going to give us new information on a new product and maybe how that is being abused. Maybe that will generate answers, but I don't think that this necessarily, as it is laid out, is a program that will actually encourage safe use and discourage the abuse. I think that we need other

measures to do that.

DR. KATZ: So, the program consisted of data collection and then also analysis, and there were never interventions that the sponsor proposed in response to signals that they might receive from their data. Are you suggesting that you don't feel that the interventions that they proposed would be effective in reducing problems that might arise?

DR. CUSH: I don't recall any specific interventions, other than calling the DEA where appropriate, that were going to be identifiably impressive, at least I don't recall any from their presentation. I think, again, EAB will be helpful in analyzing that data. It is an impressive group of people and I am sure they will do a good job and come up with things but, as set forth, the program itself does not meet the stated goals of the question for day two.

DR. KATZ: It sounds like we are wrestling with the issue of whether the data that is going to be collected will be sufficiently informative to address the issues at hand and, secondly, whether the interventions that are proposed will address the problems revealed by that data.

I am actually going to turn to Dave Haddox

for a minute. Specifically, Dave, if you could remind us what the interventions are?

DR. HADDOX: The risk management program for Palladone is not just the RADARS system. The RADARS is one component of the surveillance aspect of the risk management program. The interventions include everything from the educational sorts of things we talked about, the outreach, making sure that practitioners have proper patient selection, the patient package insert, those sorts of things; and targeted interventions based on findings from RADARS or from other sources, other signals; and the nature of the intervention will depend upon the nature of the signal.

I would also like to clarify the phased launch. I think maybe I wasn't clear this morning. The phased launch, the four months, what we are going to be testing during the four months--we will, of course, be collecting RADARS data simultaneously but the goal of that is specifically to address the concern that Mr. Woodworth from the DEA mentioned yesterday, and that was message integrity. Does the practitioner understand the message--proper patient selection, proper dosing, how to minimize risk and abuse, those sorts of

things? That is what we are going to be testing. We will certainly be looking at this concurrently, but at four months we think is probably a reasonable break point to see what we have found, if 95 percent of the physicians got the message or have 5 percent gotten the message right.

DR. KATZ: Thank you. Dr. Aronson, would robust data on the integrity of the messages that are heard by the various individuals in the cycle--would message integrity be sufficient for you to go on to the second stage of launch?

DR. ARONSON: Not necessarily. How are you going to determine whether or not they got the message?

DR. HADDOX: The plan is to do research to find out whether they got it. You can do telephones; you can do surveys; you can do face-to-face interviews and basically you sit down, very much like the IMS product to which Mr. Woodworth made reference yesterday, and say what do you know about Palladone? What did you get? Find out what the practitioner understands, the person who is dispensing, the person who is prescribing. If they say, well, gee, it is for moderate to severe pain where a round-the-clock opioid is

necessary for a certain period of time in an opioid-tolerant patient, good, you got that, you got the proper patient selection. What do you know about the dosing? Is it the first opioid or not? Those sorts of messages.

DR. KATZ: Let me interrupt for just a minute. We are not going to get into the details now about exactly how those data are going to be collected so for the purpose of discussion, assuming that those data could be collected and reported in four months and you can feel confident about message integrity, that everybody is hearing the right message about this product, is that sufficient for you to proceed to the next stage of the launch?

DR. ARONSON: The concern I have, and I think it has been echoed by many during the sessions over the last few days, is not that this is a good drug when used properly and intended for the right subset of patients, but the consequence of it being misuse is real and alarming to all of us. So, what I would hope to get out of this staged, if you will, launch is an understanding of the potential harm. However not intended, it is nevertheless real. There is that potential and so

how can we learn about modifying its further, if you will, launch to minimize that?

DR. KATZ: You are saying that no is the answer to my question? That hearing about the message integrity would not be sufficient for you to go to the next stage?

DR. ARONSON: Not with that time line.

DR. KATZ: Dr. Trontell, did you have a comment to add?

DR. TRONTELL: Yes, a question for Dr. Haddox, to this point have you done, in fact, any pretesting of message integrity, and might you explain why you would test the message after the product was on the market as opposed to before?

DR. HADDOX: I am not aware that we have done any. That that is called preapproval promotion, isn't it? I think that is proscribed.

DR. TRONTELL: Certainly, in the case of patient information, label comprehension and other forms of assessment of whether or not the informational content has been understood.

DR. HADDOX: Actually, the phased launch is going to be talking about the message integrity of prescribers and dispensers. That is the focus right now, not talking about consumers or

caregivers, not that we wouldn't consider that as well but that wasn't the focus.

DR. TRONTELL: And my suggestion was if education and comprehension of the information were felt to be critical, I might suggest, or ask in this instance whether or not you thought to extend that to physicians as well since they are tested and certified in other settings.

DR. KATZ: Dr. Jenkins?

DR. JENKINS: I think the question maybe you are trying to get at about the message integrity is, is it enough to know that they got the message? How are we going to test for actual behavior? I think it is very common to note that people know what the message is. We all know what the speed limit is on I-270 but we also know how many people adhere to that speed limit and how they rationalize why it doesn't apply to them. So, I guess I am interested in knowing how is Purdue Pharma planning, during this phased launch, to not only assess message integrity but actual behavior of implementing that message.

DR. HADDOX: Well, as I mentioned in my presentation, this is an evolution right now. We have been thinking about this for a while. One of

the things we will be doing, of course, is looking in the databases where one can track a unique patient, which are not very common. We could assess that this was a person who had been exposed to another opioid and, if they had never been on an opioid before and were all of a sudden exposed to Palladone, that would be a clue that the behavior was not correct because it would then be a first-line opioid. But we are open to suggestions on that.

DR. JENKINS: Do you have anything built into your proposal that would say, okay, we get to that four, six, whatever month time point and find that the results aren't what you hoped to see, what do you do then? Do you continue on the same level of your launch scale or do you intervene but then proceed to the broader launch that you are proposing?

DR. HADDOX: Retrain the sales reps if there is an issue that we are concerned with or the agency is concerned with, and not expand until we have satisfied that issue.

DR. KATZ: Dr. Strom, you were next.

DR. STROM: I am very impressed by the effort that has been put forth. As a tangential

thing but important, I think it is very important that it be public, that the data that emerge and your advisory committee sees be available, be published, not be kept secret.

But I still am left with two major concerns about the plan as it is proposed. One is concern about the lack of data that there is a unique benefit to these longer-acting drugs. Combine that with the fact that there clearly is a unique risk, particularly in the very high dosage forms here, makes me worried. So, what I would suggest is that, (a) there certainly shouldn't be a 32 mg formulation yet, which would be the highest risk and I don't see any reason for that; people can always take two 16 mg.

I like the idea of phased marketing. Perhaps the initial phase of the marketing should be at the lowest dose only and it should go on long enough to generate both data that there is some advantage, as a separate set of studies, to patients of using these formulations as opposed to the immediate-release formulations and that there isn't substantial abuse of the lower dose formulation. Because if there is already substantial use of the lower dose formulation using

the mechanism of data collection that are being proposed, then going on to the higher dose formulations is going to be even worse.

DR. KATZ: Dr. Rose, you are next.

DR. ROSE: I guess I am going to be very much agreeing with Dr. Strom. I agree that a one-year initial phase is far, far superior to the four months. I don't think four months is enough at all to collect any bit of information.

I believe that what we should expect after a year is two sets of just statistics. The first set would be a knowledge and documentation of adverse events of diversion and abuse, which is going to happen; it is just a matter of how much, how severe, etc. Then, the other set is the benefit information on appropriate patients treated appropriately. Then take those two bits of information and decide what the risk/benefit ratio is. Because we could have a very great benefit but if the risks are far superior to that, then I just don't think it is a wise drug to have on the market. So, I would like to see these two phases come together at the end of a period of time that is significant.

DR. KATZ: So, you are suggesting more

than just extending the duration of the first phase to a year, but you are suggesting that continuing into the second phase should be based upon data that relate to the outcomes of interest rather than surrogates like message integrity. Is that what you are saying? Is that what you were saying, Dr. Strom?

DR. STROM: That is exactly what I was saying.

DR. KATZ: But it sounds like you are both also saying something more than that, which is that measuring safety is not sufficient to make a decision about the risk/benefit analysis of this drug but that there has been an unsatisfactory amount of data on the benefits of this medication over immediate-release formulations, and that you could only interpret the safety data, whatever it is that comes out, in light of clinical trials that relate to relative efficacy, which is a whole separate kettle of fish and we understand that; you are not going to get that from a patient registry or an observational database.

DR. STROM: Exactly correct. The other thing I would add is that in that first phase it should only be available in lower dose.

DR. KATZ: Thank you. Dr. Shafer, you are next.

DR. SHAFER: Several points, first off, I commend Purdue for putting the program together. I think actually it is a very meritorious program. If asked right now just to vote up or down on the program presented, I would vote to support it.

Number two, I absolutely support one year being a better program, and I think that that is an important message that you are hearing uniformly from the committee. If you want to look at, you know, bodies hitting the pavement, I have concerns, both in our conversations here and in the conversations we have not had during breaks--

[Laughter]

--that in four months you are not going to see the really serious morbidity and mortality that we are concerned about, which you might see at one year. I have heard nothing about how the program interfaces with prescription drug monitoring programs run by the states. It is kind of mysterious because there was a lot in our packet about that and I am surprised that that has not shown up in our discussions and I would like that to be addressed.

I would like to see an educational component to it, talking about the risks of opioids in general and some of the unique issues with both sustained release and then with sustained-release Palladone. I don't know how to put teeth in that to be sure that the vast majority of practitioners get the educational program in order to practice without being formal. I don't know how you put teeth in to make sure that that happens and that people actually sign up and get training, but I think that would be an important addition to the program, particularly since we have heard that the DEA will not be able to make that happen as part of registration for your license any time soon.

Lastly, we are not really coming at this tabula rasa. There are data from Canada and the U.K., where the drug is available, and I would just like to know what is the experience there.

DR. KATZ: That seems to be a good question. Laura, do you have any information about the experience in other countries?

MS. NAGEL: No, I don't.

DR. KATZ: Anyone from FDA, anybody know that?

DR. HADDOX: The adverse event experience

in the two countries mentioned has been very, very little abuse.

DR. KATZ: Numbers?

DR. HADDOX: I don't have the numbers. I am not in charge of drug safety, but we can probably get them for you.

DR. KATZ: Maybe, Dave, you could also clarify for us how long the medications have been available in those two countries.

DR. HADDOX: I would have to ask my colleagues about that.

DR. GOLDENHEIM: One formulation--

DR. KATZ: Go to the mike, if you could, and introduce yourself, please, also.

DR. GOLDENHEIM: Paul Goldenheim, Purdue Pharma. A different controlled-release formulation of hydromorphone has been on the Canadian market--we will get you the exact number but I am going to guess for about six years. In terms of the United Kingdom, the same formulation that is on the market in Canada, slightly different from this one, has also been on the market, I would guess, for approximately six years.

I think that there is something also that is important to recognize, I think any kinds of

restrictions that the committee is thinking of placing on Palladone would need to be applied to all such medicines in this class and I have to say I very much fear what Herb Kleber talked about on his last slide, that we risk grave unintended consequences to patients from the kinds of things that we are talking about here.

We have a very serious approach to risk management. We want physicians to be educated. We take this responsibility very, very seriously and are very worried about the consequences of this to patients. It is not always easy to say just take two 16 mg capsules. There are some people who need three, four, five, six capsules a day. We have had a lot of negative feedback about these issues from patients and from their physicians and I think we have to proceed very carefully here.

DR. KATZ: Thank you for your comments. I think your point is well taken that for any intervention that is considered the potential downside needs to be considered as well. I think we have been hearing that for two days now. Dr. Baxter is next.

DR. BAXTER: Thank you very much. Once again, I would like to chime in that I applaud

Purdue because the RMP is very, very good and I think that the program is very good.

But I think that in order to answer this particular question we need to try to manage the risk up front and the best way to do that, in my opinion, is through the labeling, and perhaps we could add some of the suggested wording that there are some patients that are at high risk for abuse and those patients would require additional monitoring.

I like the idea of education and some sort of registration. Basically, by educating physicians or other providers and by having some form of registration, no matter how simple, we would give some would be rogue prescribers at least a moment to pause before they start writing prescriptions willy-nilly.

DR. KATZ: Dr. Bril?

DR. BRIL: I think that this is a major program as planned by Purdue and is probably unlike anything else that has been done in a roll-out to date. But what I have heard and seen from the last two days is that all of the databases and information-gathering systems have their flaws and limitations. A lot of the data was given in

numerator form so you really didn't know what it meant. A lot of the deaths were in people who had taken multiple agents so you don't really know what was causing the death in the drug overdose people for sure. You don't know if it was OxyContin or if it was the combination, or whatever they were on.

So, I am not sure that the plan will actually limit the abuse and make the slower-release form safer but at least you will get a lot of information that you haven't had to date and perhaps that will modify what happens in the future. It is a start. But I don't know how you could say that it will work or achieve its goals because there is no evidence that even education, for example, will work. So, this is a start and it is quite an intense and aggressive start, I would say, but whether it will actually work I don't know.

I don't know whether four months--I think that is very short but, I agree, and 12 months seems more reasonable. But this is quite a step forward.

DR. KATZ: Dr. Dworkin?

DR. DWORKIN: It sounds to me like there are two things we really, really know. One is that

we have no data and the other is that it is going to take DEA at least three, maybe five, maybe more years to put in place some registration system combined with education. Given that, I can't think of any reason why it doesn't make a tremendous amount of sense to have a 12-month roll-in where for 12 months all of the data that we heard about this morning are collected, RADARS etc., but that within that 12 months of the launch, as Dr. Aronson said, the first phase promotion be severely be limited to, say, pain specialists and oncologists and at the end of the year we will have all the data we have been hearing about for two days that we don't have today. Then, the next step of the launch will depend on the data.

DR. KATZ: We have heard a lot of comments on the data and concerns that it might be delayed, or what-have-you, but does anyone have any comments on whether the intensive data collection and the sorts of databases that will be developed address the issue, whether they are adequate to the task at hand? Do they give us the information we need? Dr. Gillett and Dr. Strom.

DR. GILLETT: We have an inverted pyramid here in which we are going to have a tremendous

body of data generated by a very aggressive and forthright program that I really appreciate, but it rests on the security and integrity of the formulation, which is proprietary, not well explained and certainly capable of being fiddled with--it can be fiddled with outrageously and that is where we are going to have this data, resting on the point of this pyramid. I think discussing how long we wait until the top falls over is not maybe mundane or not proper.

DR. KATZ: So what are you trying to say?

DR. GILLETT: That we really need to have a discussion of the quality of this formulation, of its integrity and how much we can rely on that to base our decision of what kind of data to gather.

DR. KATZ: I want to make sure I catch your point. Are you saying, if I can paraphrase and not to be dramatic, all the data in the world isn't going to make a difference if the formulation itself can be easily compromised and be associated with abuse?

DR. GILLETT: Yes.

DR. KATZ: That is what you are saying? Dr. Strom?

DR. STROM: Yes, I think the data that

will be gathered here is really not perfect but I can't think of anything better. I think Purdue is doing an enormous amount to do it. I think something like a year makes sense. I think the criteria should be database criteria though rather than time based, and it may be that it can be done in a year and maybe it takes 18 months or two years. If it can be done in a year, great, but if these data were gathered and available a year from now, along with an estimate of relative efficacy based on a lower dose preparation I would be much more comfortable about making a risk/benefit judgment to release it in total.

I do agree with the company that restricting one drug different from the other drugs of the class is problematic. I think a year from now or whenever those data are available, the position I would prefer would be to put this drug in line with the other drugs in the class either with all of them more restricted or this one much less restricted, depending on what the data show.

DR. KATZ: If this data is going to have implications for multiple different companies that produce these medications do you think that the burden of data collection and the resources

involved should also be shared among different companies with all the other implications that come from multiple source data?

DR. STROM: I certainly would have no problem if other companies wanted to be part of it. I don't know whether or not Purdue would want that.

DR. KATZ: Dr. Leiderman?

DR. LEIDERMAN: The question came up about experience in the U.K. and Canada and I just wanted to point out that the indication in the U.K. at least is for severe pain in cancer patients. So, it is a whole different experience.

The second sort of question I want to raise or the point I want to make is that we conceive of risks and misuse to various parties, and that includes not only the patient and this sort of mythical abuser, but there are also family members, particularly vulnerable children and adolescents. And, I want to remind the committee that there have been different kinds of tools brought to bear for similar products. For example, you have the Actiq risk management plan included in your background materials and that product has many of the same risks, and there were specific concerns about children having access to that, partly

because of the attractiveness of that formulation but also simply because of the very high dose. So, that point I think needs to be brought up.

Then, since we have alluded to the Xyrem or GHB risk management plan and discussion about that, similarly, there was very much concern about how the formulation as well as the dose, concentration, quantities factored into the risks to other household members, particularly children and adolescents. So, I want to throw that into the thinking.

DR. KATZ: So, you are asking us to consider a second category of risks. Whereas we have mainly been concerned about addiction and abuse, you are asking to consider unintentional access to children and other vulnerable individuals. Dr. Shafer, you were next.

DR. SHAFER: I would just like to mention I just looked up the Canadian doses that are available. The dose forms that are available in Canada are 12, 16, 24 and 32, the same as proposed here. I would like to chastise both the company and the FDA and DEA that we don't have six years of data on the Canadian and British experiences, which I think would be very germane to our discussions.

It would have been very nice if we had known what they actually saw with six years of experience so we could have some idea whether we are really going to have bodies on the street within a few weeks of this drug being introduced.

DR. KATZ: Before you go on, would any of the multiple corporate and regulatory agencies that were just chastised care to respond to that? Dr. Goldenheim, please?

DR. GOLDENHEIM: Yes, I am volunteering to be publicly chastised. Point well taken. I guess the reason that we didn't think about it is because it is a different formulation and typically we tend to think about these things as different formulations. It is a 12-hourly formulation, a different technology. There would be different issues with it but, nevertheless, point well taken. We will get the data to you. I don't think we know of any, but we will check, overdose deaths.

The fact though is that prescription drug abuse however, as I am sure the committee recognizes, is a different kettle of fish in this country than it is in Canada and the U.K., at least according to anecdotal reports and this is yet another area where, frankly, there is precious

little data. So, you know, bottom line in terms of safety of patients, there aren't any significant or unexpected issues. The episodes of abuse, of diversion, of overdose are few, if any but they are different environments.

DR. KATZ: Thank you, Dr. Goldenheim. Dr. Jenkins?

DR. JENKINS: Yes, just to put that in context, could you comment on what the experience has been with OxyContin in Canada so that we can understand how the relevant experience with sustained-release hydromorphone in Canada might relate to the United States? If you haven't seen much abuse of OxyContin in Canada, then the Canadian experience may not be very helpful.

DR. REEDER: Robert Reeder from Purdue Pharma. The product OxyContin is on the market in a number of countries, including Germany, U.K., Canada. The abuse pattern is very minimal in those countries. There are some episodes of abuse. For example, in Europe less than 20 on the continent. The abuse pattern is vastly different than in the U.S.

DR. KATZ: Thank you, Dr. Reeder. Dr. McLeskey, you were next.

DR. MCLESKEY: I would like to echo what has been stated by so many here today, that Purdue should be complimented for bringing this risk management program forward in its current form. In fact, I will quote Dr. Hertz who said earlier on who said that this is the best effort so far that she has seen among products with risk management programs brought forward to the FDA.

On the other hand, I would just make one comment. I believe a comment was made that if some kind of restriction is applied to Palladone that that should be, therefore, to future approval for all opioid analgesics. I would suggest, just as the data from Canada for example may not be applicable to the data from the U.S. and, in fact, it was thought to be potentially so different it wasn't presented, I would suggest we extend that information and apply it in the same context that for each of these agents, each of these new analgesics--I believe I would speak for industry at large, all the companies working in this area--that individualized consideration should be applied to each of those and an evidence-based decision made.

DR. KATZ: Dr. McLeskey has been very forthcoming about his potential conflict of

interest prior to coming to this meeting, both in writing and verbally, and maybe it would be an appropriate time for you to mention that to the group.

DR. MCLESKEY: I am happy to. I have been especially quiet during this meeting, for those of you who have seen me at other meetings, and that is because I am trying to be very respectful of the industry position in general and not represent any kind of conflicted view that might result from the efforts of my own company, Abbott Laboratories, in this particular market area in which we are also working.

DR. KATZ: Dr. Skipper, you are next.

DR. HERTZ: I am sorry, I just want to clarify--I have already been misquoted once in the "Pink Sheet" and would not like to have it happen again. I was referring only to efforts for modified-release opioid risk management programs. It was in no way a commentary on risk management across anything beyond that.

DR. KATZ: Clarification accepted. Dr. Skipper?

DR. SKIPPER: Thank you. If we are going to release this drug in the United States, it seems

to me it would be prudent to release it with the restriction that it only be used in malignant pain, as they did in the U.K. or Canada, and then advance it later if we see no problem. I would recommend that.

DR. KATZ: Thank you. Of course, that is a huge can of worms that we could talk about if we need to. I just wanted to ask one more question, before we leave the subject of the data collection entirely, to try to resolve what seems to be a paradox through this meeting. One of our primary concerns is what happens to the people that we prescribe this medication to in terms of negative outcomes, yet, I am not sure--and maybe the rest of the committee or the sponsor can help me--I am not sure that I am seeing that those patients are actually going to be monitored for the negative outcomes that we are concerned about. It seems like we are monitoring primarily abuse and negative outcomes as they occur in the community from whatever source. I wonder if individuals on the committee feel that it would be an appropriate part of a risk management program to actually monitor our patients for the negative outcomes that we are concerned about. Dr. Baxter and then Dr. Crawford.

DR. BAXTER: That is exactly what I was saying and that is what I meant. Maybe I wasn't clear enough but, certainly, those patients that are going to be put on this medication should be watched, and they should be monitored, and the form of monitoring is up for discussion. But I think that it is very important that as we begin to prescribe this medicine we watch our patients and be prepared to intervene where intervention is necessary.

DR. KATZ: Dr. Crawford?

DR. CRAWFORD: Thank you. I think not only is it appropriate, I think it should be mandatory because, as an example, I never heard an answer to Dr. Gillett's question in terms of message integrity of the patients. The proposed patient package insert says do not crush, dissolve or chew. Could it or would it be confusing to those same patients to be told that they could sprinkle it on their food? So, I think a lot of those issues go hand-in-hand.

DR. KATZ: Yes, Dr. Cicero?

DR. CICERO: I am Dr. Cicero from Washington University. I am a consultant for Purdue. Obviously I have a conflict of interest

that you need to recognize.

I think it is really important to point out there is not a blank slate here. I think we heard some comments yesterday about older, more established programs. One of those was Tramadol. It was a postmarketing surveillance program approved for Tramadol in 1984 and data was gathered systematically over that entire period of time about what constitutes a prescription drug abuser. So, there are data. There are four peer reviewed publications on this where we have documented what these people look like. So, we have those data there.

More importantly, the FDA yesterday failed to indicate that there were two additional FDA meetings after '94 in which the original decision was revisited, to take a look at the data and see if the data actually upheld the decision that was originally made. I see no reason why a similar model can't be applied in this situation. I think you can, in fact, establish programs.

The problem we have with all of the prescription drug abuse, and NIDA has put out an RFA trying to get proposals for this, we don't know what people who abuse prescription drugs look like.

We know very little about them, except that for the Ultram experience--again, published data--they have an extensive history. By and large, those who have abused it, 97 percent, have a history of strong opioid abuse. They tend to be white primarily as opposed to ethnic minorities that you see with some other drugs. They tend to be of a little higher socioeconomic class. We are beginning to understand a little bit about this patient population.

I think by extension with OxyContin the attempt was really to get some baseline information on OxyContin so that if Palladone does get released there are things in place to actually begin to look at it.

We talked about interventions today and, unfortunately, we are a little bit caught short here, just as the NIDA proposal was caught short. We don't know what we are looking yet. These are not patients generally, they are a subset of people whom we need to know how to target and how to intervene if possible. It may not, in fact, be all that easy to intervene. We won't know that until we study a little bit more about the population.

What I worry about is if we throw up our

hands and say we are not going to get anywhere with this; we don't know what is going on. We tend to be focusing on that aberrant three or four percent of the people that are suffering from the risks of it and, again, the pain patient is being ignored here and I can't help but worry about that. But, again, this isn't a blank slate. We have some information. We need to gather more information.

DR. KATZ: thank you. Dr. Dworkin?

DR. DWORKIN: Yes, I would just like to ask Dr. Cicero a question. It has been proposed here that there be a phased roll-out of the drug and that for 12 months the RADARS and all these other data be collected. Setting aside Dr. Katz' issue about a large, simple trial which I think is a complicated trial, but if we just collect the RADARS data etc., that we heard this morning, for 12 months, do you feel, based on your experience with Tramadol, that that would be enough data to provide the kind of information you have so thoroughly documented for Tramadol?

DR. CICERO: I probably won't be a consultant tomorrow so I will answer the question. Yes, I do believe that in a 12-month period of time you could get that data, particularly since we

already have mechanisms in place. This is rolling for OxyContin; it has been accumulating for six quarters now, and the whole plan was to expand it to include Palladone as it comes along. We can easily expand it and we will get data to look at within 12 months. We will have data on the Key Informant Network; we will have data on the diversion; we will have data on poison control; most importantly, where do these coalesce? Where do we see multiple signals so that we can actually go in there? I say "we" because it has to be a joint effort between the company and I think the EAB. I think it has been agreed we need to go in there, take a look at it with all the expertise we have and say, okay, we have multiple signals coming from this little metropolitan area, what is going on? Where is the drug coming on? You have heard speculation throughout the two-day meeting, it is being stolen; it is coming from script doctors. We don't know that. Everybody is making their best calculated guess. We need to find out about that.

But the way I look at this whole thing is first give us a signal that there is a problem, then let us go in and see what the nature of that problem is so we can try to figure out what the

heck we can do. Maybe we will come back in 12, 18 months and throw up our hands and just say it is an endemic problem. We don't know what has occurred. As Herb was talking about today, maybe there is something about our population that, for whatever reason, for the last hundred years we can't quite seem to get rid of this problem of prescription drug abuse.

But in answer to your question--I was expounding here a little on public health issues, but I think fundamentally, yes, we can get the data. Twelve months, I don't know if that is magical, or 18 months.

DR. KATZ: Thank you, Dr. Cicero. I hear you. Thanks. It is the ten-minute mark until the end of our meeting so I would like to turn to the FDA and ask them for their guidance on how you would like to use this time. Are there any specific issues that you would like us to focus on?

DR. MEYER: Well, I would say that we have obviously skipped over some questions related to risk management so I think if there are other elements of risk management that people would like to point out for us to consider, not just for Palladone but for all of the extended-release

opiates, it would be important for us to hear that. I am not sure we are totally done with the discussion of Palladone too, so we would certainly take more points or things that might be considered for the risk management of Palladone specifically.

DR. KATZ: So, anything specific, Dr. Meyer, or just general comments about the risk management approaches and Palladone?

DR. MEYER: Again, there are several elements of the risk management plans that were a sub-part of this question, and even some that were not actually raised or discussed yesterday, like further research needed. We have heard some questions put out today that I think would fall into that category bit since we only have ten minutes I don't want to focus it, but if people have burning things that they think are very important for us to hear, we would need to hear those.

DR. KATZ: I think what I will do then is use my discretion to pick up on something that Dr. Shafer brought up earlier, which is the potential usefulness of prescription monitoring programs. Someone correct me if I am wrong, I think something like either 17 or 19 states so far have electronic

prescription monitoring programs. Some states have more proactive programs where information is provided to physicians on the utilization by their patients of opioids from whatever pharmacy, whatever source over a certain period of time. In other states the data is only available for law enforcement.

We have heard a lot from our DEA colleagues about things like doctor shopping, multiple prescribers, things like that, that presumably could be identified through prescription monitoring programs and I wonder if people would are to comment on whether such programs could have usefulness in postmarketing surveillance efforts, or in research, or in any other application help us better understand the safety issues behind these drugs. Laura, go ahead.

MS. NAGEL: It is one of the other areas where the DEA and the FDA agree. We are both proponents of the prescription monitoring programs in each state. We feel very strongly that they have been found to assist the physicians even more than they actually assist law enforcement. They are able to give the physician some sense of confidence if he or she questions someone that

might be a doctor shopper to ensure that they are not going to several places. If law enforcement has a specific target, they are able then to go in and determine whether there is more investigation that needs to be done.

Mr. Rogers, who is here from Kentucky, put I think 10 million dollars in the budget for states to come and get grants. They feel in Kentucky that the program at the state level in Kentucky very much helped them identify their Oxy problem when they did. Without it, they think it would have gone longer and been worse. So, we are tremendous supporters and, with the FDA, intend to try to promote it as best we can state by state.

DR. KATZ: Our drug control program in the Commonwealth of Massachusetts has been one of the recipients of that Harold Rogers grant and we are just starting a project now to go through our databases. In Massachusetts, for better or worse, we only track Schedule II opioids but we are starting to work on validating algorithms to detect, hopefully accurately, some of the issues that we are talking about, as well as to monitor patients for development of untoward complications that may require further management.

There was a big discussion in Massachusetts, as you might imagine, about patient confidentiality and privacy and that whole thing, but since 1992 when the program was implemented, actually people from all different stakeholder viewpoints have been very satisfied that those concerns have not become problematic.

Any other comments about the utility of prescription monitoring programs? Yes, Dr. Gillett?

DR. GILLETT: I just wanted to encourage them to continue to evaluate these programs as they go along in ways that are open, transparent and as precise as they can be made because they are teaching a lot of people how to do something well and I think that is really important.

DR. KATZ: Dr. Shafer?

DR. SHAFER: Why doesn't the RADARS system incorporate it?

DR. KATZ: That sounds like a question for our sponsor. Dr. Haddox?

DR. HADDOX: We don't have statehood. These are legislative programs. As I answered one of the questions this morning, we have been encouraging these. We have been helping actually

with legislative language. The key here I think is well-designed programs. We believe that programs should monitor all Schedule II through V controlled substances because of the squeezing of the balloon that Dr. Kleber talked about and the paper by Weintraub that described the New York experience several years ago with some scheduling of some things and restrictions on some and not on others.

Another part of well-designed is to allow exactly what was talked about here, that is, have a provision in the legislation to allow for scholarly pursuits. This would be blinded. It wouldn't be specific information so you couldn't identify a patient but aggregate data to look at trends, and so forth, and make these things available. Some states, as Dr. Katz mentioned, are more proactive about this than others. But we do support well-designed, electronic, low barrier prescription monitoring programs for all controlled substances.

DR. SHAFER: But you don't have access to the data.

DR. HADDOX: It depends on the state. We actually have two requests in to two states right now, and we will get whatever data they will share with us. Some have issues about how they will

share the data in and out of state, etc.

DR. KATZ: Ms. Nagel?

MS. NAGEL: Just very quickly, one of the grants this year is to do an assessment of the programs and to try to check the data to see if we can come back and explain how they are good or not. So, we also feel very strongly and we need to put that forward for everyone to see.

DR. KATZ: In the two minutes left I just wanted to get one other question out for people to consider. It seems like it has been generally accepted that any good risk management effort or tool will target the problem that it is trying to target but not have an excessive negative effect on appropriate opioid prescribing. Yet, I haven't heard any suggestions and I don't think we have discussed in the last two days how we can measure the extent to which opioid prescribing is appropriate, or has been negatively impacted by any risk management intervention. It concerns me that at the end of the day we may have information on the negative outcomes we are trying to prevent but not information on appropriate opioid prescribing, which we are trying to encourage and don't want to diminish. Does anybody have any thoughts on

whether I am completely off base or whether we should consider ways of measuring the degree of appropriate opioid prescribing and incorporate that into our assessment of the overall pros and cons, overall results of any risk management effort? Dr. Rose?

DR. ROSE: Well, when I talked earlier about wanting two sets of information at the end of a provisional year, basically my assumption was that in getting information on the benefits for appropriate patients that was inherent in what I was talking about. We want to know what good does it do these patients if they are appropriately chosen; what other bad things does it do to the appropriately chosen patients. So, I think that is part of what I was saying we should expect.

DR. KATZ: Dr. Bobek?

DR. BOBEK: I was wondering if the pharmacy education piece as well as the physician education piece is being considered by the DEA. We are also highly involved in drug diversion and dispensing of these agents.

MS. NAGEL: We were targeting the physicians initially, not all registrants, which would include the pharmacies, and down to the

pharmacist.

DR. BOBEK: I was wondering if it is also possible if a pharmacy can document the indication of the opioid use at the time of dispensing, so, it is used for back pain; used for postoperative pain, and that be in your state generated database so you can actually run data to see are these inappropriate prescriptions potentially, and use that in some sort of, you know, physician education piece as well. I didn't know if that was a possibility.

MS. NAGEL: To the best of my knowledge, the indications to be included in that haven't been contemplated.

DR. KATZ: Any other comments about how one might measure rates of appropriate utilization? Dr. Strom?

DR. STROM: Yes, I think it is a great idea and makes a lot of sense, in addition to sort of a randomized trial to find out benefit, to find out from population point of view whether it works. I think it would take a lot of thought about how to do it correctly and, you know, survey kind of methods would certainly be one way to do it. Another would be, for example, to survey people who

have particular diseases that are commonly painful and look to see what proportion of them are being treated with analgesics, and then maybe survey a sub-sample of them to find out what proportion of them are being treated successfully with analgesics and, ideally, even to do this at the beginning and the end. For example, if there was a year phase-in to this risk management plan, to do it in the year when the drug isn't yet widely available and to do it a year or two later, after the drug is much more widely available. But I think the idea of having data on benefits to balance the data on risks is critically important.

DR. KATZ: I am going to take the last 60 seconds to summarize what I think we have heard in discussion, although that is not an easy job and if I get anything wrong somebody can jump up and down and correct me.

What I have heard is that it seems to be universal that people feel--well, maybe not universal, Dr. Strom, but people feel education is important and--

DR. STROM: Just a second, can I just speak quickly? I don't want to be misunderstood. Education has been shown repeatedly not to work in

voluntary education but I agree with the idea of education as part of the DEA change which, in turn, would apply to all narcotics. So, don't take me as an exception.

DR. KATZ: So, you took the words out of my mouth. People feel strongly that education is appropriate. People felt even more strongly that the real missing piece in education is some way of putting teeth into it, as you said; that it can't be escaped in order to prescribe medications. While a legislative effort might take a long time, we should think creatively about shorter-term solutions for making that happen.

Next, in terms of the labeling, we heard what seems to me a consistent suggestion that it might be appropriate to consider for the label some indication about assessment of the risk of the patient for negative outcomes, and some suggestion that enhanced monitoring for those patients might be appropriate, although collecting data on the usefulness of those interventions would be equally appropriate so that we can monitor the results of that over time.

People seemed to feel pretty uniformly that the first phase of the launch might be better

off extended. All different sorts of times came up. A year seemed to be the mode number, but I think people's real concern is that we had data on actually the outcomes of interest rather than on surrogate measures, rather than to pick an arbitrary--you know, should it be 11 months, or 9 months or 18 months.

I heard that as far as the ultimate data that is obtained from the RADARS system, it seemed like people were extremely interested in being able to know ultimately what the source of diverted or abused drugs is. It seemed like that came up as a consistent, terrible question mark that we still have and ultimately with the RADARS system or other aspect of the program we ought to be able to make statements about the actual sources so that we can ultimately, in the next iteration of this meeting, be more rational in our selection of risk management approaches.

People seemed to feel that it was appropriate to understand better another big question mark, which is what is the complication rate of these negative complications in our patients, and that any risk management program ought to not just skip over the patients to the

community but also somehow consider what is happening with the patients and we, I think, made no progress on whether that should be a large, simple trial, or a registry, or another kind of surveillance program. That is something that will have to be considered.

Also, there was a lot of discussion that, despite the fact that we are here aegis of considering modified-release opioids and in particular Palladone, it didn't seem like anybody thought that the other opioids were free of these concerns, and a number of people expressed the squeezing of the balloon analogy where, yes, we can maybe clamp down on something here but, unless we know what is happening in another part of the balloon, we may be wasting our efforts or even making the problem worse.

Then, finally, in the last waning moment of our conference we heard that prescription monitoring programs could be useful parts of risk management, both from the perspective of research and understanding what is going on, monitoring patients, monitoring for doctor shopping and other law enforcement issues, and that these will need to be explored.

Finally, the last bit was that if we are going to try to introduce measures that decrease complications, such as diversion, addiction, etc., we need at the same time to make sure those measures are not decreasing appropriate opioid prescribing. We need to consider ways of measuring that so we really do have Dr. Rose's two sides of the equation on how to do that, we did not consider in any detail but it would be worth considering.

That is what I heard. Did I get anything completely wrong or leave out anything absolutely essential? Any final comments or questions from the FDA?

DR. MEYER: I would just like to thank everybody. This has been--I guess diversity would sort of encapsulate this meeting because we have a diverse background of the rather large committee that served. We have a diverse effort on the part of the government, having folks from the DEA and several areas of HHS and even several areas within FDA. We certainly appreciate the public commentary as well. I think we got a lot of very useful discussion and advice out of it. So, we certainly thank each and every one of you, and thank the sponsor as well for your participation.

DR. KATZ: Let me add my thanks to the advisory committee for helping me get through this and get some information to the FDA, and also again to the sponsor who, I think everybody agreed, has put together the best program for this class of agents that is around. It is clearly a major step forward and I only hope that our input will help make it even better and more useful ultimately for our patients. Adjourned.

DR. DWORKIN: And I want to thank you, Nat, for doing a splendid job of chairing this meeting and keeping us all on track.

[Applause]

[Whereupon, at 5:00 p.m., the proceedings were adjourned.]

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