DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANESTHETIC AND LIFE SUPPORT DRUGS

ADVISORY COMMITTEE

Tuesday, September 9, 2003

8:10 a.m.

Holiday Inn Bethesda
Bethesda, Maryland

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Johanna Clifford, M.S., RN, BSN, Executive Secretary

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Sharon Hertz, M.D.
John Jenkins, M.D.
Deborah B. Leiderman, M.D., M.A.
Robert Meyer, M.D.
Bob Rappaport, M.D.
Victor Raczkowski, M.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. KATZ: Good morning. Welcome to the meeting of the Anesthetic and Life Support Drugs Advisory Committee the purpose of which will be to advise the FDA on risk management programs for opioid analgesics, in particular modified-release products.

My name is Nathaniel Katz. I will be chairing the meeting this morning, and my job will be to make sure that we succeed in providing all of the relevant input that has been asked to this division of the FDA.

To my right is Johanna Clifford. She is actually the real person who is running the meeting, and her job is to make sure that I do my job and that the meeting stays on track.

Now, the Division has worked very hard to create a truly interdisciplinary group of individuals representing many of the relevant stakeholders on this issue. While I have a number of ground rules for the committee that I would like to go over, what I would like to do first is begin with introductions. There are a new people on the committee and many invited guests. We don't all

know each other, so I would like to start with taking a minute for us all to introduce ourselves.

Let me just remind people from the government that many of us don't know what the specific committee or agency that you are involved with does, so it would also be appropriate for you to take a sentence or two to describe, not only who you are, but the place that you are from.

Why don't we begin at that corner, Dr. Jenkins.

Introduction of Committee

DR. JENKINS: Good morning. I am John Jenkins. I am the Director of the Office of New Drugs at the Food and Drug Administration. My office is responsible for all the divisions that review and approve new drugs.

DR. MEYER: Dr. Bob Meyer. I am the Director of the Office of Drug Evaluation II in the Center for Drugs, and my office has the Division of Anesthetics, Critical Care, and Addiction Drug Products within it.

DR. RAPPAPORT: Good morning. I am Bob Rappaport. I am the Director of the Division of Anesthetics, Critical Care, and Addiction Drug Products.

DR. HERTZ: Good morning. I am Sharon Hertz. I am the Medical Team Leader for the Analgesic Group in the Division of Anesthetics.

DR. LEIDERMAN: I am Dr. Deborah Leiderman. I direct the Controlled Substances staff within the Office of the Center Director. In CDER, we are responsible for all aspects of abuse liability assessment and interface with other federal agencies around issues of abuse and drug scheduling.

DR. RACZKOWSKI: Good morning. My name is Victor Raczkowski. I am the Director of the Office of Drug Safety in the Center for Drugs. Our office is heavily involved in risk assessment, risk communication, risk management, and medication errors. We work closely with the Office of New Drugs both before and after approval to ensure drugs appropriate use.

MS. NAGEL: My name is Laura Nagel. I am from the Drug Enforcement Administration, Office of Diversion Control. We are responsible for the enforcement of the Controlled Substance Act particularly as it pertains to legitimately manufactured drugs.

DR. CRAWFORD: Good morning. My name is

Stephanie Crawford. I am from the University of Illinois at Chicago, College of Pharmacy. I am a guest participant from the Drug Safety and Risk Management Advisory Committee.

DR. SHAFER: Steve Shafer, Professor of Anesthesia, Stanford University.

DR. BAXTER: Lou Baxter. I am Executive Medical Director of Medical Society of New Jersey, Physicians Health Program, and I am brand new. I am here and that is about all that I can tell you.

DR. GARDNER: I am Jacqueline Gardner, the University of Washington School of Pharmacy, and I also am from the Drug Safety and Risk Management Committee.

DR. ARONSON: Solomon Aronson. I am the Chief of the Anesthesiology Services for Vanguard Health Systems in Chicago.

DR. SAINI: Bhupinder Saini. I am an anesthesiologist by background. I practice full-time pain management. I am president of a 12-man group who are totally dedicated to pain management.

DR. KAHANA: I am Madelyn Kahana. I am a Professor of Anesthesiology, Pediatrics, and Critical Care Medicine at the University of

Chicago.

MS. CLIFFORD: Good morning. I am Johanna Clifford. Nat already provided you with my job description. I will be the Exec Sec to this meeting.

DR. BRIL: Good morning. I am Vera Bril. I am a Professor of Medicine at the University of Toronto with an interest in neuromuscular disorders. I am a member of the Advisory Committee.

DR. ROSE: Good morning. I am Carol Rose. I am an Assistant Professor of Anesthesiology at the University of Pittsburgh School of Medicine and University of Pittsburgh Medical Center. I am a clinical anesthesiologist.

DR. WLODY: Good morning. My name is David Wlody. I am academic anesthesiologist at the State University of New York Downstate Medical Center. I am a consultant to the committee.

DR. PASSIK: Steve Passik. I am a clinical psychologist and I direct the Palliative Care program at the Markey Cancer Center at the University of Kentucky.

DR. DWORKIN: Hi. I am Bob Dworkin. I am a Professor in the Department of Anesthesiology at

the University of Rochester in upstate New York.

DR. CUSH: Good morning. I am Jack Cush. I am Chief of Rheumatology and Clinical Immunology at the Presbyterian Hospital of Dallas and the University of Texas Southwestern Medical School in Dallas. I am here representing the Arthritis Advisory Committee.

DR. BOBEK: Good morning. I am Mary Beth Bobek. I am the consumer representative. I am also Clinical Faculty at University of North Carolina College of Pharmacy.

DR. SKIPPER: I am Dr. Greg Skipper. I am an internist and addiction medicine specialist on the faculty at the University of Alabama at Birmingham. I am also the Medical Director of the Physician Health Program in Alabama. I am here for the Drug Abuse Advisory Subcommittee.

DR. CIRAULO: I am Dom Ciraulo. I am Chairman of Psychiatry at Boston University School of Medicine. I am also on the Drug Abuse Advisory Subcommittee. I have had a long-standing interest in developing clinical pharmacology laboratory paradigms for abuse liability.

DR. MAXWELL: I am Jane Maxwell. I am a research professor at the University of Texas at

Austin and on the Drug Abuse Subcommittee.

DR. STROM: I am Brian Strom. I am Professor and Chair of Biostatistics and Epidemiology, although I am not a biostatistician, I am an epidemiologist, and I am from the Drug Safety and Risk Management Committee.

DR. GILLETT: Good morning. I am Jim Gillett. I am Professor of Ecotoxicology and Director of Graduate Studies in Risk Analysis and Cornell University. I am here as patient representative, as President of Esophageal Cancer Awareness Association.

DR. McLESKEY: Charlie McLeskey. I am the industry representative on this committee, and I am an anesthesiologist employed at Abbott Laboratories, Global Medical Director for Anesthesia and Sedation Products.

DR. KATZ: Thank you, everybody.

Ms. Clifford will read the Conflict of Interest Statement.

Conflict of Interest Statement

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

meeting.

The topics to be discussed today will not focus on any particular product or company, but rather may affect those companies that make or are developing modified-release opiate analgesic drug products.

The conflict of interest statutes prohibit special Government employees from participating in matters that could affect their own or their employer's financial interests.

All participants have been screened for interests in the products and companies that could be affected by today's discussions.

In accordance with 18 United States 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 are: Dr. Nathaniel Katz, Dr. Robert Dworkin, Dr. Steven Shafer, Dr. Steven Passik, Dr. Russell Portenoy.

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 note 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 is a shareholder.

With respect to FDA's invited guests, there are reported interests that we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Arthur Lipman has consulted for Purdue Pharma and Endo Pharmaceuticals. In recent years, he has received support from literally all the analgesic manufacturers through unrestricted educational grants and through speakers' bureaus.

In the event the discussions involve products or firms not on the agenda for which an FDA participant 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 participants, 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.

In addition, we have received a number of

letters from the public. These have been provided to the committee and are available for viewing today at the registration desk, and they will be made part of the public record, as well.

DR. KATZ: Thank you, Johanna.

Since many around the table are new to the Advisory Committee process, I wanted to take a minute or two to provide an orientation and to give a charge to the committee for our work task for the next two days. Right after that we will go to Dr. Rappaport's opening comments.

First of all, just to briefly summarize--and many of our other speakers will go into this in great detail--why we are here.

The purpose of this meeting is because it has been recognized that opioids are essential in the management of patients with chronic pain, but yet that they are associated with risks, so that individuals and sponsors have proposed risk management programs in order to diminish those risks while not interfering with appropriate medical management.

So, our task here today will be to advise this Division of the FDA and give them feedback on the pros and cons of various risk management

approaches that have been proposed, both in general today, and tomorrow with respect to a particular product called Palladone.

One of the first points I would like to make is that approval of any drug is a complicated process that depends upon a lot more than just the risk management plan, so I would like to make it clear from the outset that whether Palladone should or should not be approved will be beyond the scope of our discussion both today and tomorrow. What we will be focusing on is just one component of information relevant to that, which is the risk management program itself.

The two days will be divided into two different sorts of activities. The first will be lectures with a little bit of question and answer, and that will really occupy most of today. Then, there will be some time for discussion today and then tomorrow, there will be a large chunk of time for discussion of issues that come up both today tomorrow. That discussion will be structured in the form of questions which everybody around the table should have received and may have had a chance to look at by now.

Now, my own experience, this is the second

Advisory Committee meeting that I have chaired that relates to opioids, and my own experience both here and elsewhere is that opioids may be more be, more than many other areas of medicine, seem to create a lot of excitement and passion among the people involved in the discussion.

So, what I would like to do is to create a sense of collaboration of the people around the table. Since this is an informational meeting, it is not a requirement that we all come to consensus or agree with each other or persuade each other about our different perspectives, and furthermore, our different perspectives may be very true, but may be only true for the sorts of patients that we see or the particular area that we practice in or the sort of training that we come from or all sorts of other biases that we bring to the table.

So, our job today will be to not necessarily come to any consensus with definitive answers and everything, but at least to illuminate where there are different schools of thought, to outline the evidence based behind different perspectives on this issue, and to share the information and perspectives, so that the division can go back with all this information and make

decisions that day I need to make.

So, what will work well for us around the table will be to focus primarily on the content issues. What tends not to work as well is when folks like us start saying that this government agency ought to do this or that one ought to do that since training and the exact scope and authority of different government agencies is certainly beyond my expertise and probably beyond the expertise of many folks around the table. So, we are here to provide content information and hopefully, our collaboration will illuminate this issue more to an extent that will be helpful to the division.

Now, as far as practical details, though, there are a few practical things I just want to let you know about. In order to speak, the procedure is if you just raise your hand, Johanna will write your name down and we will try to go in more or less a first come-first serve way, but there are times where it will be important for me to violate that rule and try to foster particularly discussion that might seem productive, so don't feel like you are being discriminated against if you raise your hand next, but I am not calling on your next.

However, sometimes things come up where I can't see you, particularly the people in these corners are sometimes hard to see, so if you do feel that for some reason, we have not been recognizing you appropriately, just grab myself or Johanna during the break.

When you go to speak, turn on your microphone and when you are done speaking, turn off your microphone unless you want all of your little comments to the side to be heard by everybody.

There will be a very helpful system for speakers, as well as for people in the open public forum, and that system is called a red light. I will tell you more about that when the time comes. For speakers who are getting up, there will be both a yellow light and a red light, so the yellow light, if you are up speaking at the podium, the yellow light will come on two minutes before you are ready to stop.

Now, there has been no time for question and answer built into the lecture, so if you want to have people to have the opportunity to ask questions and to have a dialogue, when your yellow light comes on, stop then and that will give about two minutes for a couple of quick questions and

answers. Obviously, there will be ample time for discussion later.

When your red light comes on, then, you are done. So, what I really want to do is apologize to all the speakers in advance, because I will cut you off when that red light comes on, so don't take it personally, it's just for the purpose of making sure that we get our job done over the next two days, and I will cut people off equally and fairly when that red light comes on.

Another issue is that people around the table may have questions for people also around the table or for speakers or for other people sitting around the table. If you do have any questions, then, the protocol is just go through me, so raise your hand, I will address you, and if you have a question, just let me know and depending on how the meeting is flowing, we will see if we can pose those questions to other folks around the table.

If there is anything we can do to make you more comfortable, let us know.

I think those were all my procedural comments.

With that, let me introduce Dr. Bob Rappaport, who, as he said, is Division Director of

the Anesthetic, Critical Care, and Addiction Products Division, who will give us opening comments.

Opening Remarks

DR. RAPPAPORT: Thank you, Dr. Katz.

Good morning. Dr. Katz, members of the committee, invited guests, I would like to thank you at the outset of this meeting for your participation. You will be addressing an important public health issue during this session - how do we approach the issue of prescription opiate abuse while assuring the proper treatment of pain.

Prescription drug abuse is a growing problem in this country and opiate analgesics are some of the most widely abused and misused prescription products available today, however, one of the very reasons that these products have become widespread in use and availability is that for the first time in modern history, the appropriate treatment of chronic pain is receiving the acceptance and the recognition in the medical community that it so urgently deserves.

Tens of millions of Americans are estimated to suffer from chronic pain. Many of those people are appropriately treated with opiate

analgesics and for many that treatment will provide them with relief from suffering and the possibility of returning to a normal life in a manner that is not currently available with non-opiate treatments.

Therein lies a conundrum, opiates are abused and because they are abused, some prescription opiates are diverted and the more potent modified-release products that are available today are of particular interest to abusers, not only to the seasoned addict and those that hope to profit from human frailty, but also to the teenager who wants to experiment with these intriguing potions and yet may die after a single large exposure.

In our role as public health advocates, the increasing incidence of abuse, addiction and overdose in this country must concern us. These potent modified-release products are potentially dangerous even in legitimate medical practice when their unique pharmacokinetic and pharmacodynamic characteristics are not fully understood.

Overdose and death and patients being converted from one high potency, high-dose opiate to another and inappropriate use by inexperienced physicians must concern us.

Chronic pain is still undertreated in millions of patients. Misconceptions about the normal physiological dependence that occurs with opiate analgesic treatment and its role in addiction abound. Irrational fears based on myth and lore often interfere with the proper treatment of the patients most in need. Chronic pain claims a huge toll on individuals and on the American economy, and this must concern us.

How can we intervene to reduce prescription opiate abuse, assure safe use in the medical setting, and yet assure appropriate access to patients with chronic pain who need opiates for proper treatment? Risk management interventions have been touted as one of the potential solutions to this perplexing dilemma.

The Agency has implemented risk management plans for other drug products and we will attempt to familiarize you with the scope and the range of those plans today.

We have reviewed a number of risk management plans for extended release opiate analgesics that we will also describe to you, which elements of risk management work and which don't, which elements might even have a counterproductive

effect.

For the most part, that sort of data may not even exist. Do we even know the proper methodology for collecting the data? In fact, these are the very questions that we will pose to you over the next two days.

We have assembled some of the leading experts both from the government and from academic to review the extent of the problem for you. You will hear from SAMHSA representatives about the data they have collected on prescription opiate abuse and from the FDA Office of Drug Safety on the current medical usage data for these products.

Representatives from the DEA will describe their role in diversion control and risk management and their perspective on the problem of opiate analgesic diversion. The FDA Controlled Substance staff will outline the Agency's authority and responsibility under the Controlled Substances Act, and the Deputy Director of the Center for Drug Evaluation and Research will define the challenge of risk management for long-acting opiate analgesics under the authority of the Food, Drugs, and Cosmetics Act.

In addition, experts in the medical use of

opiate analgesics and their misuse in the medical setting will present the most recent information from the clinical academic community on the benefits and challenges that are inherent in the use of these products.

As this meeting is centered on the development of risk management plans for opiate analgesics, you will also hear from the Agency's drug safety staff and the New Product Review staff regarding the existing risk management plans for both opiate analgesics and other drug products.

We will define the elements of these plans for you and ask you to help assess their value, reliability, and inherent risks. We will ask you to address what role education, restricted access, surveillance, and other elements may play in the risk management of prescription opiate use, how might these elements be implemented, how can their success or failure be measured, where might those elements aimed at lessening diversion and misuse be in conflict with appropriate patient care, and what research projects should be considered to inform these programs.

Finally, during the open public hearing, there will be an opportunity for experts,

advocates, concerned citizens, and most importantly, patients from both the pain and addiction populations to speak to you about their experiences and about their concerns.

Tomorrow, we will discuss a specific risk management plan. Representatives from Purdue Pharma will review the basis for their New Drug Application for Palladone and extended release hydromorphone product.

They will focus their presentation on their proposed risk management plan for Palladone and provide data in support of that plan from a similar plan that has been designed for their other extended release opiate analgesic drug product OxyContin.

The Agency's Controlled Substances staff will provide their perspective on the abuse liability of Palladone and Dr. Mary Jeanne Kreek will provide a broader perspective in her discussion on the challenges of pharmacotherapy with long acting opiates.

You will then be asked to provide the FDA staff with recommendations regarding the Palladone risk management plan. It is important to recognize that formal risk management for pharmaceuticals is

still a young endeavor. There are no well traveled paths to follow.

As experts in the treatment of pain, in the treatment and epidemiology of abuse and addiction, and in risk management strategy and communication, we are hopeful that you will provide us with guidance and direction as we attempt to find new paths towards reasoned and sustainable solutions to a difficult and complex problem.

We know that the FDA cannot hope to implement or sustain any solution to this problem by itself. It will be of paramount importance for you to keep in mind that there are many stakeholders in this effort - other government agencies, the academic community, the pharmaceutical industry, the clinical community, and the patients and their caregivers and families.

Each of these has important, but often differing perspectives and differing roles, however, as individuals and as members of organizations and communities, we must all share in the work ahead, so that we may all share in the rewards.

Once again, I would like to thank you for being generous with your time and expertise by

participating in this important meeting.

DR. KATZ: Thank you, Dr. Rappaport.

I would like to now introduce Dr. Steven Galson, who is the Deputy Center Director of the Center for Drug Evaluation and Research, and who will be speaking with us about the FDA role in the risk management of opiate analgesics.

FDA's Role in the Risk Management of Opiate Analgesics

DR. GALSON: Thank you very much. I am extremely happy to be here this morning and I want to start by thanking the members of the committee and the Chair for your sense of public purpose and commitment in being here. I know we can't really compensate you for your time, you are all very, very busy.

We will rely very heavily on your clear-eyed and objective answers to the questions that we pose to you in making our decisions about steps to take regarding this group of products and the product that you are hearing about tomorrow. So, again thank you very much.

[Slide.]

I am here today to talk about the FDA's role in the risk management of opiate analgesics

and I want to start by taking you back to the very beginning. This is review for a lot of you, I will go fairly quickly, but just so that you understand clearly what the role of the Agency is.

The Food, Drug, and Cosmetic Act tells us that we can require from drug applicants, from sponsors, tests that are reasonably applicable to show whether or not these drugs are safe for use under the conditions for which the application is designed.

[Slide.]

But what does drug safety mean? No drug is 100 percent safe, all drugs have risks. We all know that.

We define based on the requirements of the Food, Drug, and Cosmetic Act that the benefits of the drugs that we approve outweigh the foreseeable risks for the specific indication, the medical indication, and for the specific population for which they are designed.

[Slide.]

We use a large variety of tests to assure this. We require nonclinical studies of laboratory animals, a lot of human data, which I will focus on very quickly in a second. We also don't keep the

requirements static. We incorporate new science when it has been demonstrated to help us in assisting our reviewers to look at safety and efficacy about the products in front of us.

We are continually using new information and we are not standing still.

[Slide.]

With regard to human data, we applications for drugs that have been exposed to approximately 10,000 people for varying duration and dosing. The people who take these drugs in clinical trials frequently have other concurrent illnesses.

We have the statistical power to detect an association for an event occurring 1 in 100 to 1 in 1,000 people depending on the background rate of that condition. We don't have capacity in the methods that we currently use to review and approve drugs of detecting and quantitating very infrequent events more rare than noted there.

[Slide.]

For predicting the benefit, we use randomized, controlled trials, as you all know. These, however, lack generalizability to populations that were not participants in the controls, the larger society, and, as well, these

clinical trials don't study all domains of benefit.

There may be nonquantifiable, but very important benefits to patients that aren't quantified in these studies, and we also can't predict in these studies the uncertainties of certain kinds of use and certainly not the uncertainties of abuse.

[Slide.]

So, before we approve a drug, we are assured that the benefit outweighs the risks, as you see in this simple chart.

[Slide.]

But there are lots of things that can happen after a drug is approved. Certainly, abuse, as you all know about, we may not have done a good job of predicting the risk for a variety of reasons, that some of these risks may have been unpredictable.

There may be errors involved in the way the drug is used, committed both by patients or by participants in the healthcare system, or there may be inherent risks with the drugs. We know, as I said before, that all drugs have risks, and these inherent risks may be more important than we had anticipated.

[Slide.]

Therefore, we know a drug is less safe and if it is used in a way that decreases the foreseeable benefit and if it is used in a way or in a way that increases risk of if the actual risks are greater than the predicted risks. There are a lot of different things that can, quote "go wrong."

[Slide.]

Getting more specific to the products you are interested in here, moving towards that, our goal in managing risk is to look at it throughout the product life cycle. We begin this in drug review and approval process through the methods that I have just talked about, and we use multiple risk management tools, such as the language in the drug label that is distributed with the drugs, restrictions on use of the drug or on the distribution or other special requirements to try to assure that the risks of the drug are maintained in a manageable way throughout the life cycle.

This process continues after drugs are approved. I don't have time to go into a lot of detail about this, but we conduct passive surveillance with our adverse event reporting system where practitioners, patients, and others

can send reports in when they notice them to the Agency. We keep track of those, collate them, and look at them very carefully.

There are lot of other systems to look at the safety of drugs that are on the market including four opiates, just as an example, here the Drug Abuse Warning Network, which is not run by the FDA, but detects increases in reports through emergency rooms of drug abuse problems.

We can also conduct special studies when we are concerned about a particular problem with the drug, and others in the medical community and in the research community conduct these studies for us, or may conduct them for other reasons, and we look at them to weigh all of these pieces of information after a drug is approved.

[Slide.]

So, we conduct periodic evaluation of risks and benefits of drugs that are on the market if the use changes beyond what we had anticipated, if new risk-benefit data come up through the scientific process or through another means, or if for some reason we are aware that our risk management steps have not been effective enough.

In those cases, we may make changes in the

way that the drug is labeled or in other aspects of the way the drug is used and distributed in consultation with the drug sponsors, but these changes have to be consistent with our statutes and with our regulations.

We are watched very closely in those regards, and we have a limited number of degrees of freedom that we can go in making changes to drugs once they are approved.

We also, as I think you all know, enforce advertising regulations which can be very important for this group of compounds. We also coordinate with other federal agencies, particularly with DEA, around the opiates, or other organizations to try to control risk, to try to work to mitigate information which may be incorrect about these compounds.

[Slide.]

In the special case of opiate analgesics, which you are here to talk about today, we know that these drugs are a very important part of our medical arms chest. They are safe and effective when used properly, but we do have indications that there have been increases in opiate-related abuse and deaths, and that is one of the reasons that you

are here.

The Federal Government regulatory authority and responsibility for risk management for this group of drugs is shared with the Drug Enforcement Administration, with the FDA being responsible for the items that I have talked about previously, and the DEA responsible for enforcing the regulations and the laws to reduce abuse, and you are going to hear about that from DEA speakers later in this meeting.

[Slide.]

What are our challenges in risk management of this group of drugs in 2003? We need to maintain a positive risk-benefit balance, as I have been talking about. We need to maintain access for the patients who need these drugs, and we want to be able to use the label that we approve for these drugs appropriately to foster risk management.

We need to base our decisions about changes and approval of these drugs on science, not on emotion, and we need to base them on what we can assess to be the current medical practice consensus. That is why you are here, that is why you represent different parts of the medical community, and as you know, a lot of medical groups

have been working on trying to assess what the right way to use opiate analgesics for many, many years, there has been a lot of consensus work done in medical organizations, and we need to pay very close attention to that because the medical community and the healthcare community is really one of our most important stakeholders in the Agency.

We can also consider other risk management steps, unusual risk management steps, things that haven't been tried before.

[Slide.]

What is the context under which we are asking you to be here today? The problem of opioid abuse is a complex societal problem with a lot of different causes. As you know, as scientists, any complex problem demands a complex solution. There is not a simple solution to this problem.

It is a combination of regulation, public policy, education, and research, which is being applied and which continues to need to be applied to this problem. We all recognize that it is not going to be solved overnight and will only be solved by an incremental improvement in how we manage these risks.

As I have mentioned, addressing the problem is the shared responsibility of not just the Federal Government, but of other agencies, not just the regulatory agencies, but other federal agencies, some of which are represented here, the Substance Abuse and Mental Health Administration, and the part of the NIH, NIDA, that handles drug abuse research, State and local governments, teachers, parents, nongovernmental organizations, religious groups, the Boy Scouts, et cetera. This is a societal problem, and that is the context in which we want you to look at the questions that we are asking you today.

Thank you very much again for being here. We look forward to your advice, and good luck for a good meeting.

My yellow light isn't on, so I can take any questions if folks have them based on my comments, otherwise, we will move on.

DR. KATZ: Does anybody around the table have any questions for Dr. Galson?

[No response.]

DR. GALSON: Thank you very much.

DR. KATZ: Thank you very much.

Before we go on to our next speaker, there

is a new person at the table who missed the introductions earlier, so, Dr. Portenoy, would you like to take half a minute and tell us who you are?

DR. PORTENOY: Thank you. I am sorry about being late, you know, D.C. traffic.

I am Russ Portenoy. I chair the Department of Pain, Medicine, and Palliative Care at the Beth Israel Medical Center in New York City.

DR. KATZ: Our next speaker will be Dr. Deborah Leiderman. She is the Director of the Controlled Substance staff at FDA, as you all heard. She will be speaking with us about Risk Management and the Controlled Substances Act: the FDA Perspective.

Risk Management and the Controlled Substances Act:
The FDA Perspective

DR. LEIDERMAN: Good morning.

I will be talking about risk management and the Controlled Substances Act through the lens of the FDA. Now, Dr. Galson has outlined the general framework of risk management that CDER utilizes, the Center for Drugs and FDA utilize.

In advance, I want to acknowledge that my comments about drug control and drug scheduling are from the perspective of the FDA, and that the DEA

will be speaking in greater detail about some of the law and roles that I am addressing later in the meeting.

[Slide.]

The Controlled Substances Act of 1970, which I will refer to from hereon in as the CSA, was enacted to comply with international treaties, as well as to address issues of international drug trafficking and to assure the availability of legitimate drugs for medical use.

The CSA established five schedules and level of control, C1 through 5. The major drug classes that are regulated by the CSA are the opioids, depressants, stimulants, and hallucinogens.

[Slide.]

Under the CSA, Schedule I is the most restrictive. It is reserved for drugs with the highest abuse potential and no recognized medical use. Examples of drugs within this class include heroin and LSD.

Schedules II through V are used for drugs that have medical use in the United States and have, in descending order, levels of abuse potential and restrictiveness, II being the highest

of medically approved drugs and V the lowest.

[Slide.]

The subject of today's meeting, of the two-day meeting, are, of course, the Schedule II opioid analgesics. Now, these drugs have the highest potential for abuse. Abuse potential is defined under the CSA, placement in Schedule II, means the risk is comparable to that of CI drugs. The distinction again is the medical use.

Thus, these drugs are subject to the highest level of control and, by definition, pose the greatest risk to the public health.

[Slide.]

I think, as Dr. Galson suggested, that we have to look at the use of any drug, but certainly the Schedule II opioid analgesics in the context of the larger healthcare system and the society.

Certainly, healthcare, the society have changed dramatically since enactment of the CSA. Advances in science, medicine, pharmacotherapeutics information have changed, and it can be argued that what was previously relatively limited, acute disease, often terminal, has been transformed into chronic illness. Thus, the CII drugs, the opiate analgesics, which 30 or 40 years ago, the use was

primarily confined to the hospital setting, the operating room, and the inpatient ward, have been moved, as has much medical care, into the outpatient setting.

[Slide.]

The Schedule II opioid analgesics that we are primarily concerned with, oxycodone, morphine, fentanyl, hydromorphone, again are all Schedule II under the CSA.

Now, the Schedule II designation applies to all strengths and dosage forms of each drug. The Controlled Substances Act and the scheduling designation does not differentiate between a 5 mg oxycodone and a 160 mg OxyContin, between an injectable hospital use fentanyl formulation and the 2 mg patch. A morphine 5 mg tablet is the same Schedule II as the methylphenidate 5 mg tablet.

Schedule II, thus, encompasses a broad range of drug dosages and potency, and as we will see, a broad range of drug classes.

[Slide.]

Now, this figure is intended to illustrate the range of drug classes, as well as dosages and formulations. As you can see, the opiates on the left are all in yellow, the barbiturates are in

lavender, and the stimulant drugs, on the right, are in red. Again, we can see that there are intravenous, transdermal, oral formulations in the opiate class, and that the range of strengths is quite large.

[Slide.]

Just for comparison, looking at the range of drugs controlled under Schedules III through V, we see that some of the less potent opioids, also in yellow here, are placed in Schedules III, IV, and V, and that depressants, stimulants, and other drugs, again a range of pharmacologic classes, are controlled under Schedules III through V.

[Slide.]

What does it mean for a drug to be controlled under Schedule II? Again, the DEA will go into this in much greater detail, but from our perspective, manufacturing quotas are established by the DEA with input on medical need from the FDA.

Distribution is tracked. There are import and export controls, prescribers and dispensers of Schedule II drugs must be registered, and Schedule II designation does not permit refills. That is a federal law, will not vary across states.

[Slide.]

What Schedule II does not require: physician or practitioner education, limits on the drug quantity prescribed or dispensed, nor does the CSA make any provision for or Schedule II designation mean that there will be any prescription monitoring.

[Slide.]

This is a schematic of all the parties that play a role in the regulation of controlled substances. The two federal agencies that FDA, in the left lower corner, and the DEA, with the Scales of Justice in the middle, both regulate the manufacture in the upper left corner.

The FDA, of course, is responsible for drug review, approval, and labeling. The DEA established quotas and registers manufacturers. Both federal agencies have responsibilities with respect to different aspects of inspection and compliance.

The state regulatory authorities, which are represented by the multicolored figure of the country--there is no significance to my knowledge of the particular color scheme, it is provided by Microsoft--state regulatory authorities regulate prescribers and dispensers through licensure.

The DEA also licenses prescribers and dispensers. We can see that patients and the community, represented in the right lower corner, and I have shown this with a dotted line because they are, in fact, not regulated. Prescribers and dispensers interact with the patients and the community, but essentially, they are out of the regulatory loop, that is, the federal and state regulatory loop.

[Slide.]

Again, just to briefly compare and differentiate DEA's role from FDA's role and the state role. DEA registers drug manufacturers, establishes quotas, and registers dispensers and prescribers. It does not have a role in prescriber education, any knowledge assessment of the registered prescribers or dispensers, and it does not ensure active surveillance.

[Slide.]

The FDA role, of course, again is to approve drug products and assure safety and effectiveness, as Dr. Galson described. The primary method for the Agency to communicate information to prescribers and dispensers is the drug label.

The FDA is also responsible for postmarketing safety and phamacovigilance. It is very important to note that the Food, Drug, and Cosmetics Act does not distinguish between controlled and other drug products.

[Slide.]

The State's role is primarily achieved through boards of pharmacy and medicine, that is, they are the primary regulators of physicians and pharmacy practice.

States may impose additional drug controls beyond that of the CSA. Authority, regulations, practices, and resources, however, vary enormously across states.

[Slide.]

Prescription drug monitoring programs have been introduced over the past 15 years or so as a regulatory tool for the states. They are under the purview of the states, there is no national program, and their goal is to reduce illicit use of prescription drugs through deterring and identifying so-called doctor shopping, that is, when patients obtain medications from multiple physicians simultaneously, illicit sales of prescriptions and drugs, and forged prescriptions.

Prescription drug monitoring programs--and I should note the members of the Advisory Committee did have the General Accounting Office report on PDMPs included in your background materials--these programs collect, review, and analyze prescription data from pharmacies.

These programs have varied structures, very varied resources. In 2001, there were 15 states that had active PDMPs. I believe one additional state has come on line in 2003. They vary whether they are electronic or paper, whether it's a database that can be queried or whether there is more active ongoing surveillance.

[Slide.]

Again, this schematic just to remind us of the parties that have a role in the regulation of controlled substances, and again that the patients and the community are mostly out of the regulatory loop.

[Slide.]

So, where do we stand on the issues of risk management, drug scheduling, and the CSA? I think we can see that scheduling under the Controlled Substances Act does not manage all the risks of misuse, abuse, and overdose of

prescription drugs.

Drug scheduling alone cannot address all the challenges posed by the high-dose, extended-release opioid analgesics in the context of the modern healthcare system, and it is important to remember again that Schedule II designation does not distinguish between high-dose, high- potency opioids and low-dose, immediate-release Schedule II drugs.

Thank you, and I guess I also have an opportunity for some questions.

DR. KATZ: Any questions?

[No response.]

DR. KATZ: Thank you very much.

I would now like to introduce Terrance Woodworth from the Drug Enforcement Administration, who will be speaking with us about the DEA's Role in the Risk Management of Opioid Analgesics.

FDA's Role in the Risk Management of Opiate Analgesics

MR. WOODWORTH: Well, it is much too early for this slide. Good morning.

Thank you very much for the opportunity to express some of the views of the Drug Enforcement Administration concerning the legal framework that

DEA and FDA operate under together in order to fulfill our mandate to protect the public health and safety.

Although very beneficial in the treatment of pain, recently approved potent high-dose, extended-release opioids, coupled with aggressive and persuasive marketing practices, have brought new and unique challenges to our agencies.

Dating back to the passages of the Federal Food, Drug and Cosmetic Act in 1906, the United States Congress recognized the critical importance of indicating the proven uses of prescription drugs for legitimate medical needs. It signaled its full recognition of the abuse potential of certain prescription drugs in 1914, when it passed the Harrison Narcotic Act regulating the sale of opiates for the first time.

Additional drug legislation over the years including the Controlled Substances Act has become part of Title 21, Food and Drugs. With this, Congress has indicated its full expectation of a cooperative, coordinated interagency process of reviewing a substance and its drug products, assessing that drug's safety and efficacy, and identifying whether it has an abuse potential

before permitting its marketing to the public.

FDA and DEA have collaborated extremely well in this regard for more than 30 years.

It is important to note that there are significant differences between the Controlled Substances Act and the Food and Drug Cosmetic Act with regard to drugs. One of the most fundamental is that the CSA and its controls focus on substances, morphine, oxycodone, where the FDCA focuses on products, MS-Contin, Percodan, Adderall.

The Controlled Substances Act places all substances with abuse potential into one of five schedules based on accepted medical use, potential for abuse, safety, or dependence liability.

Schedule I is for those with no accepted medical use, such as heroin. Substances with accepted medical use are in Schedules II through V, II being the most restrictive, V being the least restrictive.

When a substance is already in Schedule II of the Controlled Substances Act, and Schedule II controls are not sufficient, we must look outside the Controlled Substances Act for additional mechanisms to prevent diversion and abuse.

The substances that we are addressing

today and tomorrow are all Schedule II substances under the Controlled Substances Act, thus, there are no opportunities for increased levels of control under the CSA.

The FDCA, on the other hand, can address product (or class of product) safety needs on a product-by-product basis.

In all candor, DEA has not been able to address all of the criminal activity associated with high-dose, extended-release opioids in recent years. Compounding this difficulty are the indications that FDA's risk management plan for at least one extended-release opioid has not proven effective.

Segments of the pharmaceutical industry in certain cases have exceeded traditional drug promotion boundaries and been a significant factor in the increased abuse and diversion. State medical boards are unable to regulate the increasing numbers of dated, duped, disabled, and dishonest practitioners, and physicians themselves acknowledge a need for further information and education concerning pain management and the use of opioids.

The CSA includes seven major control

mechanisms: scheduling, registration, quotas, records and reports, import and export authorizations, security, and investigational authority.

DEA essentially controls the drug and its movement. We register all persons who handle opioids, we inspect the documentation of opioid distribution, we control and import and export. We control the amount produced, bought, sold, or otherwise transferred.

One would think with all these controls in the so-called closed system of distribution that there would be minimal risk of abuse and diversion. These controls have been extremely effective in preventing diversion at the import or manufacturer and distributor levels, however, the vast majority of diversion occurs at the retail level once the product is in the hands of practitioners and patients.

Significant weaknesses in two of the controls, quotas and investigational authority have contributed to the increases in abuse and diversion.

With regard to investigational authority, it is estimated that more than 90 percent of the

diversion occurs at the doctor/pharmacy level, however, at this retail level, it is primarily the states and the professional boards responsibility, not DEA, to regulate and oversee controlled substances activities. DEA is not directly involved in the establishment of medical or pharmacy standards, nor are we directly involved in the regulation or investigation of medical or pharmacy practice.

DEA investigates physicians who are acting outside the norms of accepted medical practice, thus, the responsibility at the retail level for controlled substances rests, in general, with a wide array of different state and medical and pharmacy boards.

[Break due to power failure.]

DR. KATZ: Our break seems to be finished, so we will continue.

Mr. Woodworth.

MR. WOODWORTH: Well, a lot of people have said DEA is in the dark on these issues, but that is a little bit much.

[Laughter.]

MR. WOODWORTH: In evaluating a physician's or a pharmacist's activities relating

to the management of pain and the use of opioids, the state boards rely heavily on the FDA approved labeling for opioids, as do physicians themselves.

FDA-approved labeling provides guidance to the medical community regarding conditions for safe use, as well as providing safety and other warnings. Labeling and risk management plans have a direct impact on the extent of abuse and diversion of opioids, but DEA has no statutory authority to participate in the development of the labeling or risk management plans except for our role in scheduling, as Dr. Leiderman mentioned.

At present, under Section 201(f), when HHS receives a New Drug Application for a stimulant, depressant, or hallucinogenic drug, and the drug appears to have an abuse potential, HHS is required to forward that information to DEA for scheduling purposes. For substances already in Schedule II, DEA has no authority to require additional controls.

The key to having the ability to further deter and prevent abuse and diversion becomes the labeling of new formulations of already controlled substances. When FDA-approved labeling indicates that extended-release forms of opioids may have

less abuse liability, as was the case with OxyContin, this significantly affects decisions of physicians to prescribe a drug, as well as the medical board's action in reviewing a physician's activities.

With regard to quotas, DEA and FDA are responsible for ensuring an adequate and uninterrupted supply of opioids for medical, scientific, and research needs of the United States. We accomplished this by establishing quotas for the total quantity of each basic class of controlled substances, oxycodone, for example, which may be manufactured in the United States on an annual basis.

The purpose of the quota system is to limit the availability of legitimately manufactured controlled substances which may be diverted into the illicit market. Increased availability and access to controlled substances are direct causes of abuse and diversion.

Quotas are established considering sales from the previous year, estimates of year-end inventory, and estimates of legitimate medical needs in the future provided to DEA by FDA.

On the surface, the quota system appears

to be an effective means of limiting the supply of opioids to what is legitimately needed for medicine and science in this country. After all, the drugs have been approved for safety and efficacy, and the pharmaceutical manufacturers have been through a rigorous FDA and DEA approval process.

However, both DEA and FDA are receiving the using incomplete information regarding what actually are the legitimate medical needs for opioids in this country. Again, legitimate medical need is largely determined by sales.

Sales are prescriptions, all prescriptions for extended-release, high-dose opioids are counted in the total sales figures to establish quotas regardless of whether those prescriptions were illegal, indiscriminate, or inappropriate.

How can the estimates of legitimate medical needs for extended-release, high-dose opioids be based on totals that include illegitimate sales, and what is the volume of those illegitimate sales?

Quotas can help limit the amount of substance that can be manufactured in a year, but quotas, nor any other control mechanism, can ensure that correct amounts of medicine get to the correct

people for the correct indications.

It is reasonable to expect that increasing availability of most, if not all, Schedule II opioids will be associated with a commensurate increase in diversion and abuse.

Finally, we get to the slides.

[Slide.]

Data available to DEA - aggregate production quotas, year-end reports, or distribution data to the retail level and IMS retail provider perspective, which are purchases at the retail level - show a consistent increase in availability for morphine, hydrocodone, and oxycodone over at least the past eight years.

[Slide.]

When availability data, as measured by total prescriptions, is compared to Drug Abuse Warning Network emergency department episodes for the same substances, it appears there is not only an increasing abuse, but increasing rates of abuse. This is particularly true for oxycodone since the introduction of OxyContin.

There are several factors that we believe have contributed to the incomplete and unreliable information that DEA and FDA are using as a basis

for prescribing and ultimately determining legitimate medical need.

These factors have led to increased availability and that has made diversion easier and abuse more prevalent.

First, the initial labeling for OxyContin allowed great latitude for prescribing, promotion and marketing of this substance.

It is indicated, as you know, for moderate to severe pain. This allowed for the promotion of the product as a substitute for products such as Tylenol with codeine, Darvocet, Vicodin, and other Schedule III and IV products.

The labeled indications also allowed for considerable interpretation regarding its use in acute versus chronic pain, postoperative pain, and other situations. It also supported promotion to all types of practitioners, particularly family practitioners and internists, not all of whom are appropriately trained in pain management and the use of these relatively new and unique products.

It was not described as a "potent" opioid analgesic as was morphine in the MS Contin labeling. This and other parts of the labeling did not convey the message that OxyContin was to be

treated as cautiously as MS Contin.

In describing the dependence, the term "psychological dependence" was omitted for OxyContin, but not for MS Contin.

The labeling also stated that controlled-release opioids were believed to have less abuse liability.

Second, unusually aggressive and persuasive marketing and promotion techniques used by manufacturers and their sales personnel.

DEA has obtained and evaluated data on the promotion of six high-dose, controlled-release, Schedule II narcotic analgesics presently marketed in the United States - OxyContin, Duragesic, MS Contin, Kadian, Oramorph, and Avinza.

The data shows that there is a positive correlation between the amount of money spent on promotional activities and the amount of sales and prescriptions. Those companies spending the most money generally have the most sales.

By far, more money has been spent on the promotion of OxyContin, as you can see in this slide, than the other products combined. There is nothing wrong with promoting a drug product in the proper context. Unfortunately, we believe that the

initial labeling allowed this product to be promoted for too large a range of conditions, to those physicians not adequately trained in pain management, and without the proper warnings about its abuse potential.

The data reviewed show the scope of medical specialty groups was widest for OxyContin. There was less emphasis on promoting to "traditional" pain specialty groups.

For example, in 2000, anesthesiologists received the most promotion dollars for Actiq, Avinza, Kadian, and MS Contin. Promotion for Duragesic was highest for internal medicine, with anesthesiologists second.

In the case of OxyContin, family practitioners and internists were in first and second positions respectively. In addition, more money was spent promoting OxyContin to nurse practitioners, physician assistants, and general practice doctors than the entire promotional dollars spent on Kadian, Oramorph, or Avinza. Unfortunately, these medical groups are not pain specialists.

Finally, we examined the message given to these medical groups. IMS Message Insight monitors

the messages being conveyed to physicians and actually provides summaries of the physicians' impressions of the sales contact.

Here, there are subtle differences, but significant, between OxyContin and Duragesic. No data was available for the other high-dose products except very limited comments for MS Contin.

The primary message that physicians received regarding Duragesic was that it should be used for chronic pain management. The few mentions for MS Contin also indicated that it was being promoted for chronic pain treatment. Physicians heard a far different message regarding the appropriate use for OxyContin.

These factors present serious obstacles to both DEA and FDA in our attempts to determine legitimate medical need, establish appropriate quotas, and conduct successful investigations. The result is our lack of success in preventing abuse and diversion of extended-release, high-dose opioids.

We have found that where companies have instituted voluntary risk management plans, and in those situations in which FDA has required them, the results have been encouraging in preventing the

excess availability, diversion, and abuse of these products.

We are also aware that the labeling for OxyContin has been changed to address some of the above concerns. Our question is would it not be more effective, considering the severe potential for abuse, diversion, physical and psychological dependence posed by these never-before-produced, high-dose, extended-release opioids, to start a little slower and more cautiously with a greater regard for patients?

It is far more reasonable to focus on patients whose needs for these drugs are already unquestioned by healthcare, regulatory, and law enforcement authorities.

In conclusion, what does DEA think will help? DEA believes that a mandatory risk management plan for these high-dose, extended-release products should include:

Some form of restriction on the distribution and/or dispensing of these products;

Secondly, limit the indications to severe pain or certain disease states, or only in certain situations where other Schedule II opiates have failed;

Three, review and approve all promotional material in advance;

Prominent warnings, such as the current Black Box on Actiq and OxyContin;

Postmarketing surveillance for monitoring the adverse events, diversion, and abuse for several years;

Physician, pharmacist, and patient education regarding the proper use and adverse effects of potent, high-dose, extended-release opioids.

DEA and FDA have worked extremely closely for decades on all controlled substances issues, but we are continuing to do so at a much closer and active pace with regard to extended-release, high-dose opioids.

We are collaborating on many issues including, as Dr. Leiderman mentioned, physician education, prescription monitoring programs, as well as in the area of risk management as far as DEA is able to go.

Our goal, together, at DEA and FDA, is to limit the diversion and abuse of opioids and at the same time ensure that the American public has an adequate and uninterrupted supply of opioids for

legitimate medical needs.

We do feel that we should limit the production, distribution, and access, promotion, and, of course, the labeling for these high-dose, extended-release opioids, and we should only gradually expand patient access as our system of standards and controls prove capable of providing for the appropriate treatment of patients by knowledgeable practitioners for accepted medical purposes.

We should not unlock the safeguards until we can adequately defend against abuse and diversion. The undertreatment of pain in this country and throughout the world is not a valid reason to wantonly increase production, availability, access to this select group of drugs that can significantly harm the public health and safety.

Government approval of a drug does not guarantee its safe use, you heard that earlier. When a potent, government-approved drug is aggressively promoted with incorrect messages about its use and indications and its legitimate medical need, it becomes an unsafe drug.

The result of such action by a drug

manufacturer, further aggravated by the drug's deliberate misuse and abuse in the illicit market, is a serious issue bearing on the American public health and safety.

With that, I see my yellow light is on and I will take any questions you may have.

DR. KATZ: Thank you, Mr. Woodworth.

Are there any questions from around the table for Mr. Woodworth? Bob.

DR. DWORKIN: Yes. You had mentioned that 90 percent of the diversion occurs from the pharmacy onwards in the supply chain.

Does the DEA have any data about what percent of that 90 percent occurs at the level of the pharmacy and what percent of the diversion occurs after a valid prescription has been filled, because those are two very different contacts, of course?

MR. WOODWORTH: That is an excellent question and extremely difficult conclusion to draw. What we have been able to do with the American Medical Association over the years is estimate, with regard to physicians, that 1 1/2 to 2 percent of physicians are dishonest, and another 5 percent are negligent.

So, then you are talking about 7 percent of the physicians. There about a million physicians registered with DEA in the United States. So, while that is an extremely low percentage, meaning that most doctors are good, law-abiding physicians, 7 percent of a million is 70,000, 70,000 physicians can account for a lot of illegal prescriptions and millions of dosage units.

With regard to diversion at the pharmacy level, most of DEA's activities have been as the result of criminal investigations, and the cases we make on pharmacies are usually associated with a physician's activities.

So, frequently, if there is a bad doctor in a town, there is one or two or three pharmacies that are not adhering to their corresponding responsibility to ensure that that prescription is issued for a legitimate medical need.

So, in order to shortly answer your question, I think the answer is there is more doctors that we have had situations interact with than pharmacies, and certainly there is a larger number of doctors than there are pharmacies. It is about 60,000 pharmacies in the United States.

DR. KATZ: Dr. Shafer.

DR. SHAFER: Thank you. A couple of questions, but the main one is, looking at your slides, you have equated DAWN emergency department mentions assays surrogate for drug abuse.

Certainly in the excellent package that we were provided prior to this meeting, there is quite a bit of discussion about the DAWN database, but it wasn't clear from anything that I saw in that packet that emergency department mentions in the DAWN database was actually a surrogate for abuse.

Can you comment on that, please?

MR. WOODWORTH: It is clearly an indicator. We feel comfortable using DAWN, not only because of its history of use, the use of emergency department mentions as an indicator of abuse, but it corresponds with all of the other data that DEA has, our federal investigations, our investigations of our state and local counterparts.

I have just thrown up a slide of our state and local seizures. This is called the National Forensic Laboratory Information System. There is about 300 forensic labs in the United States. They submit data to a database and it is collated.

As you can see, in red, is oxycodone, and in kind of a yellowish is hydrocodone. Those two

substances account for more than 70 percent in the last three years of all of the state and local law enforcement forensically analyzed exhibits, which is again a strong indication of what law enforcement is encountering on the street.

They are all indicators that are used together, so I feel comfortable drawing that conclusion.

DR. KATZ: I believe Dr. Strom was next.

DR. STROM: Thanks. Can you share with us, do you have a sense of what proportion of prescription opiates get diverted and, conversely, what proportion of illicit drug use comes from diverted prescriptions?

I am trying to get a sense of how big is the diversion problem relative to other sources of abused drugs.

MR. WOODWORTH: I am unable to quote precise statistics, but if you look at all of the accepted indicators, in addition to the DAWN emergency department mentions, the now National Household Survey, again, our National Forensic Laboratory Information System, other surveys and studies, the indications are that prescription drug abuse has been increasing for the last decade or

so, and the abuse and diversion of prescription opioids has increased at a greater rate.

DR. KATZ: Because of scheduling issues, we are going to have to curtail the discussion now. We will have time to interact with our DEA colleagues and also hear more material presented from them later in the day.

Let me thank Mr. Woodworth for coming by and hopefully, they will stick around for more questions later.

We are having a slight detour in our schedule now which I would like to describe for you. We are actually scheduled for a break, but we are not going to do that. As I mentioned earlier, we would have a number of open public hearings during the two days of our meeting, and we are going to have a portion of our open public hearing now because two representatives from Congress are here to share some thoughts with us about this issue.

So, this is part of the open public hearing and, as such, I am required to read the following statement by the FDA, which I will read before this section of the open public hearing and later in the afternoon when we have an open public

hearing and tomorrow when we have the same thing. So this is the general statement about financial disclosure and conflict of interest.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. 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 any company or any group that is likely to be impacted by the topic of this meeting. For example, the financial information may include a company's or a group'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.

So, once again, that is a general statement that I will read before all of the open public hearings.

Open Public Hearing

DR. KATZ: Now, it is my privilege to introduce Congressman Harold Rogers, who will be sharing some thoughts with us about risk management programs for opioid analgesics.

Congressman Rogers.

MR. ROGERS: Thank you, Mr. Chairman.

I have no financial interest. The only interest I have is that we have a lot of young people who are dying in my district because of addiction to OxyContin.

This is truly a life and death question that the Advisory Committee is undertaking here. I want to tell you about a couple of those types of cases that I have endured in my part of Kentucky.

Before I do that, however, Frank Wolf, Congressman Wolf and I were just chatting. Perhaps you can help me. I am trying to think of the mythological figure, the captain of the ship that was so enticed and excited by the sirens on

short--who is it? Ulysses. You get an A.

He was so excited that he had his crew strap him to the mast of the ship as they sailed past the place where the sirens, the beautiful women on shore were enticing him. It reminds me a little bit of the enticement of this wonderful drug OxyContin, which has meant so much to people in severe pain, that has been abused by users, by doctors, by companies, by pharmacies to the point that we are toying with a severe problem.

Frankly, this is the most devastating thing that I have seen in my more than 22 years now in the U.S. Congress, in my district. I have never seen anything like this. This drug is tearing apart families, it is ruining lives, it is stretching the resources of law enforcement and social service agencies to the absolute limit, and it has actually reached epidemic proportions in my district, which is southeast Kentucky.

In fact, we have become the prescription painkiller capital of the United States. An analysis of federal drug data found that on a per capita basis, our drugstores, hospitals, and other legal outlets receive more prescription painkillers than anywhere else in the nation.

From 1998 to 2001, nearly half a ton of narcotics reached seven small mountain counties. That is the equivalent of more than 3,000 milligrams for every adult who lives there. A typical pill might contain 10 to 20 milligrams.

A lot of this medication obviously is for legitimate purposes, too much of it is not. These drugs are hitting the streets, they are leading to addiction, crime, death. A public defender in one of my countries, Perry County, a small mountain county in my district, this public defender estimated that 95 percent of his clients either sell or abuse prescription drugs.

Because of this epidemic, our courts are unable to keep up with this overwhelming pace of new crimes. An eastern Kentucky court, the court dockets are jammed with these drugs cases. In recent years, charges for controlled substances have jumped 348 percent.

Our residential drug treatment centers are overwhelmed, admissions tripling since 1998. A Prestonsburg, Kentucky drug treatment program director reports that the new patients, most of whom are hooked on OxyContin, are younger and sicker than ever, and they are dying.

Nationwide, according to the statistics, OxyContin played a major role in 464 overdose deaths in the nation between May of 2000 and February of 2002. A quarter of these occurred in Kentucky and Virginia alone, and most of them were young people who were not in severe pain when they first were prescribed this medicine.

Thus, the question, should we restrict the use of this wonderful drug to those in severe pain or just moderate pain, a toe ache, a toothache, a broken arm? Ulysses.

Let me tell you about two of these people, thus, my motivation. Congressman Wolf is the Chairman of the Commerce Justice State Subcommittee on Appropriations, the committee that I formerly was chairman of.

Our two states have been impacted severely by this problem, and we first were attracted to the problem a couple or three years ago, and had a hearing. I bought up to that hearing from my district, a preacher whose son had become addicted to OxyContin, and the preacher testified, and he had his son with him, who was at the time I think 21 or so.

The son never testified. He sat beside

his father while his father described I think it was an automobile accident he had been in, the young man, and had been prescribed OxyContin and became absolutely, hopelessly addicted. He would do anything to get the drug - steal, cheat, lie, to name just a few.

The father was absolutely devastated obviously by the predicament of his son. Finally, he was able to find in Indiana, I think it was, a church-affiliated or church-related treatment center that was able finally to take the son in, in an attempt to defeat this addiction.

This was the substance of the testimony of Reverend Coots before the Subcommittee, the son sitting beside him, I will never forget the sight, because two or three months later, the young man overdosed and died.

Now, the father, the preacher heads up a group that he formed himself called Joshua's Promise. Joshua was his son's name. Now, he raises money and takes in people like Joshua into this center there in the mountains to try to help them defeat this insidious addiction.

The other death I want to tell you about is of a close personal friend of mine who happened

to have been the sheriff of my home county, Pulaski County. He was assassinated by a crazed young man hiding in the forest adjacent to a political picnic the sheriff had attended with a sniper rifle, one shot, instant death.

It turns out the shooter was on OxyContin at the time. He was affiliated with a man who was running for sheriff, against the sheriff, in a political race, all of it financed, that man's campaign financed by a drug dealer.

I had the duty to speak at the funeral of Sheriff Sam Catrin, personal friend, wonderful public servant, sheriff I think 17 years, named Sheriff of the Year, a tremendous law enforcement officer whose life and career snuffed out by a OxyContin-addicted, crazed killer.

So, I say to the committee I don't envy you your responsibility. This is a tough one. We want to believe that our pharmaceutical manufacturers do the right thing all the time. There is a real question here about the practices of overselling, overpromoting the use of OxyContin to doctors, to pharmacies, to the public because this drug is so enticing and so alluring that I think you must tie us to the mast as we pass by

this very alluring drug and restrict its use to the most severe cases, not to the broken fingers, because it is so addictive, so addictive and so devastating that we are killing our young people.

OxyContin has been overly aggressively marketed especially to rural physicians, physicians who don't have that much experience with severe pain and the way pain medications should be prescribed.

Two, OxyContin is defined as being for moderate pain, and for that reason, it has become too easily prescribed, too easily available especially to young people who crush that 12-hour time release mechanism to get the instant release.

Reverend Coots told our subcommittee that his son told him that this drug was so wonderful and the reason it was so addictive and so pleasurable to the young man, he said it felt like a constant orgasm. Thus, you can see the appeal of this drug to especially young people.

Let me give you a few examples of what corrupt doctors are doing in Kentucky. This past September, a year ago, a doctor was arrested, federal authorities, overprescribing. He had prescribed on average 800 prescriptions a month.

What is most appalling in this case is that the doctor actually expressed concern to his colleagues about the amount of OxyContin he was prescribing. Who else did he express his concern to? His Purdue Pharma sales rep, who told the doctor then, who happened to be a very top client of his, the sales rep reassured him that he was doing the right thing.

Another doctor in Kentucky prescribed more than 2.3 million pills to more than 4,000 patients over 101 days. Did you hear me? 2.3 million pills to 4,000 patients over 100 days. It's a drive-through prescription service.

Another doctor in Harlan County, Kentucky, who is now serving 20 years on a federal drug conviction, saw 133 patients in a day, in an office without electricity. He has been prescribing OxyContin and Viagra to teenage boys.

Now, we will take care of those doctors, we will take care of them, don't you worry. DEA, the other law enforcement agencies, local sheriffs, police are overwhelmed, but they are getting to them. That is not the real problem.

We have even started in my district a program we call UNITE, Unlawful Narcotics,

Investigations, Treatment, and Education. We are mobilizing the whole population to fight this insidious problem. And you know what? People are really excited about it.

We are going to bring in 30 new undercover agents, the U.S. Attorney, the local prosecutors are all plugged in. The State Supreme Court is now setting up drug courts in every one of my 29 counties as a part of UNITE.

We are trying to mobilize all of the treatment centers to try to give them new ammunition, new monies, new possibilities, some coordination, but they are overwhelmed. The State has its prescription monitoring program called KASPER.

Congressman Wolf inserted money in his appropriations bill for the Justice Department over the last two, three years, monies to help states like Kentucky start prescription monitoring programs and modernize them as we go. Those monies are being used, but that is not enough.

So long as the FDA allows doctors and endorses the practice of prescribing this insidious but alluring addictive drug for a broken finger, we will have this problem.

We cannot fight it on that end. It has got to be fought at the source. The flood is too great for us to deal with down there. It has got to be dealt with where the huge amounts of these drugs are being allowed to flow.

You must restrict, tie us to the mast, restrict the use of this insidious, alluring drug to severe pain and no more before it's too late. This is a wonderful drug for people who need it. I don't want it said that I don't want people in severe pain to have access to this wonderful released drug for severe and debilitating pain, but its use has gotten out of hand.

It is causing death and destruction and families are being rendered and torn apart. It is not just in rural Kentucky now, it has spread across the country, and unless you stop this now, it will cause many more deaths and renderings of parts of families.

I want to leave with you, Mr. Chairman, a packet of materials. These are photocopies of the stories that ran in the Lexington, Kentucky newspaper, two different series, that were absolutely accurate, as well as devastating in their investigations into the problem in our state.

If you read these stories, you will have no doubt. This will solve your perplexing question. It is absolutely devastating especially the last series that detailed how this company oversold this product, the sales reps even telling the doctor, in his notes after meeting with the doctor, saying to the effect we must push these pills more.

I will leave this with you. Thank you.

DR. KATZ: Thank you, Congressman Rogers for taking time to share your experiences with us. I can assure you that we appreciate the serious nature of the problems you are describing and we will be struggling with them over the next couple of days.

I would now like to introduce Congressman Frank Wolf, who will also share his thoughts and experience in this issue with us.

MR. WOLF: Thank you very much and I will be very, very brief.

One, I want to thank you and thank the Food and Drug Administration for conducting this important review, and I share the comments of my colleague, Mr. Rogers, on pain management drugs.

Let me begin by also emphasizing that I am not here seeking to remove OxyContin from the

market. When used correctly, OxyContin serves an important purpose in assisting those with excruciating chronic pain or those who are terminally ill. Both my mom and dad died of cancer. My mom particularly suffered. I remember at the Hahnemann Hospital, the doctor would just say we have given your mom four hours ago and we can't do it again, so I understand and I want to make it clear that I am not trying to take this drug away from people like that.

However, I believe that the Food and Drug Administration and the Department of Health Services have been slow to respond to the growing problem related to drugs, such as OxyContin, which have a darker side and can be highly addictive.

I am concerned that the powerful painkiller has increased and become a drug of choice for people who choose to abuse these drugs, for people who have no legitimate need for the painkilling drug.

FDA, I noticed, and you remember, moved quickly to address the problems with the dietary supplement Ephedra when a professional baseball player died during spring training this year. Where is the same urgency with OxyContin?

OxyContin's producer, Purdue Pharma, has spent huge sums of hiring lobbyists, slick high-paid lobbyists that are well connected to powerful people in Washington, lawyers, lobbyists, and spin doctors for a public relations and marketing campaign to defend themselves and their products.

But who represents the poor and the suffering and the Joshuas and the people like that who can't hire the big firms from New York and Washington to come in and have direct access to the prominent people who make decisions in this town?

I believe that some of that PR money could have been better spent finding ways to stop OxyContin abuse and save lives. OxyContin is leaving a trail of broken lives, murder, suicide, grieving families, and growing law enforcement problems.

Kentucky, Tennessee, West Virginia, and now my home state of Virginia have seen a spike in the reports of OxyContin. Down in Lee County in southwest Virginia, there is almost not a family that has not been impacted, either someone is using it, somebody has been robbed by it, somebody has been arrested, that has not been impacted at all

because of OxyContin.

In northern Virginia, in my congressional district, federal officials have now launched what they call Operation Cotton Candy, which has targeted between 60 and 80 people, who are believed to be involved in the illegal distribution of OxyContin.

Prosecutors claim that the amount of OxyContin improperly prescribed by this network of dealers is obscene. You probably have read the story in West Virginia, a mother was charged with trying to sell her young son, a mother, the relationship with the young son trying to sell a young son for $500, so she could buy OxyContin.

Federal officials have said that no other drug in the last 20 years has been so abused in such a short period of time. More than a hundred, several hundreds, 2-, 3-, 4-, now some say up to 500 people have died due to OxyContin.

Lives have been destroyed, and again Ephedra, they moved quickly. Big-time ballplayer, everybody knows his name, they moved. The Joshuas, they do absolutely nothing for, and I remember that hearing. The young boy had an electric blue suitcoat on, a little bit out of style, but his dad

was so proud that he was there because he had gone through this rehab program, and he thought he was cured, and then as Hal said, several months later the boy overdosed.

The FDA, and I believe all of you, and I appreciate your service here, we have a responsibility to do much more to look at why OxyContin is being abused, why is it being abused, how is it prescribed, what levels of pain require a drug such as OxyContin, what steps must be taken to halt the abuse of these drugs, so that people can stop dying.

Again, I want to thank all of you for taking the time. I also want to thank the Commission, the Food and Drug Administration for convening this. We stand ready, whatever recommendations you make to try to help you, but what you do today and what you do based on this hearing, literally will be the difference of how many more Joshuas and how many more Marys and how many more families are destroyed, and I thank you very much for what you are going to be doing.

DR. KATZ: Thank you, Congressman Wolf, for sharing your thoughts with us.

We will take a 15-minute break.

[Break.]

DR. KATZ: It is a pleasure for me to introduce our next speaker Dr. Art Lipman. Dr. Lipman is going to be particularly valuable for us today since he has been steeped in the development of pain management guidelines including guidelines surrounding opioid use for many decades and, in particular, has been a leader in taking an evidence-based approach to guideline development.

He has been involved with the AHCPR panels and acute and cancer pain, has been a co-chair of the American Pain Society Panel on Arthritis Pain Management that produced guidelines, is on the Clinical Practice Guidelines Committee at APS, and Dr. Lipman will be speaking with us about the risk:benefit relationship of opioids, and then Steve Passik, in a subsequent session, will be talking about the addiction piece of that risk:benefit equation.

Dr. Lipman, please.

Opioid Risk:Benefit Contradiction

DR. LIPMAN: Thank you, Mr. Chairman, and my thanks to the Committee and to the Division for inviting me to come and present information today.

As Nat mentioned, my interest is the

evidence-based aspect, and I speak as an editor on the Cochrane Collaboration, which as most of you know, is the international collaboration based at Oxford University on evidence-based medicine, and we have a specific pain, palliative, and supportive care group here that looks extensively at the issue of opioids in an evidence-based manner.

[Slide.]

Let me just set the stage by this quote from two of the leading pain researchers of the world a number of years ago, the late Dr. John Liebeskind of UCLA, and Dr. Ron Melzack of McGill, who said they were "appalled by the needless pain, freedom from pain should be a basic human right limited only by our ability to achieve it." Now, that was written in the year 1987, as you see.

[Slide.]

A decade later, this was the cover of U.S. News & World Report, and as you see, it reads, "Doctors have the means at hand to relieve the suffering of millions of Americans, why aren't they doing it?"

Then, in small print are the words, "New science, old thinking."

Now, all of us in our professional

education and training learn from our mentors. Unfortunately, much of what our mentors taught us was not necessarily accurate, and as we take an evidence-based approach to medicine, we recognize that perhaps we have to refresh some of our thinking.

[Slide.]

That is the reason that when Congress mandated the writing of clinical practice guidelines in the closing days of 1989, that when Secretary Sullivan, Dr. Louis Sullivan then Secretary of the Department of Health and Human Services had the mandate to create clinical practice guidelines, he immediately said he first guideline that he was going to develop was in pain because he got more calls from members of Congress about pain management than any other health-related problem on behalf of their constituents.

Now, this is a very serious issue. When we convened in this city, actually, in Washington, D.C. in August of 1990, we recognized that we could not address in a single evidence-based document all of the issues, but this document that was published in 1992, entitled "Clinical Practice Guideline Acute Pain Management," and then subsequently, the

panel was expanded from 16 to 25 members, this document that was published in 1994 laid the basis in the United States of America for evidence-based care in the management of pain.

[Slide.]

Now, what is important is we didn't take anecdote, we didn't take political perspectives, we didn't take individual cases and try to generalize them to the population, but we looked at the true quality and quantity of the evidence.

[Slide.]

As Dr. Katz mentioned, just this past year we published the American Pain Society evidence-based guideline on the management of osteoarthritis, rheumatoid arthritis, and chronic juvenile arthritis pain using the same evidence-based methodology.

I wish I had time to go into that methodology at length, but it has been generally accepted by the better people in the field as being appropriate.

[Slide.]

Of course, the American Pain Society publishes its well-respected booklet entitled "Principles of Analgesic Use in the Treatment of

Acute Pain and Cancer Pain," and what nobody else in this room knows now, but I will tell you, is that at the end of this month, the Fifth Edition, which we completed last month, will be published by the American Pain Society, and it has a lot more information on the use of opioids.

Now, what did all this evidence-based work teach us? It taught us that opioids are important therapeutic entities, but more importantly, it taught us that very few clinicians, and I suspect very few clinicians in this, and I speak as a clinician and investigator in pain work for the past three decades, very few understand the seriousness of pain and why opioids need to be used in an appropriate context.

[Slide.]

Indeed, when we convened in Washington in 1990 to be the federal panel, we were assigned a team of research librarians from the National Library of Medicine just up the street from where we are sitting now, and the world literature indicated the adverse outcomes of undertreated pain are far more serious than most of us appreciated.

We were all experienced clinicians, we were all experienced investigators. Not one of us

knew how serious pain is. The single biggest issue physiologically is catabolism. We put patients into a physiological state where they don't heal, they are weak, there is muscle breakdown, and they are predisposed to depression.

We see increased throwing of clots, we see adverse respiratory, salt, water, renal, cardiovascular effects.

[Slide.]

Beyond the physiological adverse outcomes of undertreated pain are the adverse psychological outcomes - anxiety, depression, sleep deprivation, and the serious question why I am even alive.

[Slide.]

Perhaps most interesting, and we presented more data on this at the American Pain Society meetings last year, are the adverse immunological effects of pain, work that was pioneered in Dr. Liebeskind's lab showing decreased body host defenses from pain.

Now, what does all this mean? If we are going to advocate for the American public, the good congressman said a few minutes ago who is going to advocate for Joshua, I raised my hand. I am here to advocate for Joshua. My son's name is Joshua,

it hit home. The issue is we have to look at the science, and the science tells that we based rational therapy on risk-benefit ratios.

Everyone knows that, but unless we appreciate the risk of undertreated pain, we are not going to get adequate therapy.

[Slide.]

Some of the elegant work done by Dr. Charles Cleeland and his colleagues, Charlie is now at M.D. Anderson, he was at Wisconsin when he did this work, and, of course, Dr. Cleeland developed the pain inventory with the 1 to 10 scale, well validated, with zero being no pain, 10 is as bad as you can imagine.

He actually quantified in a large series of patients the impact on their ability to function, functional outcomes, something the Agency is very interested in, according to the pain intensity.

Now, 1 to 3 is mild pain, 4 to 7 is moderate pain, 8, 9, and 10 is severe pain. Look at the impact. Ability to carry out activity, ability to work normally, ability to enjoy life are impaired at level 4, activity, mood, ability to work and enjoyment of life at level 5, sleep,

activity, mood, ability to work, to enjoy life at level 6. That is not severe pain, that's moderate pain.

Moderate pain is a bigger problem in much of American society than severe pain, because anybody in this room who has ever had an aching back for two or three days knows how that wears you down emotionally, physiologically, you don't sleep, and that is mild to moderate pain.

[Slide.]

Well, if we are going to look at this from a scientific perspective, and look at risk:benefit ratios, we have to recognize that the risk of pain is often much greater than the risk of the therapies that we are using.

There is an inherent risk in pharmacotherapy. I have always told since I started teaching medical students at Yale Medical School in 1971, I said look around the room to the third-year students in their first clinical pharmacology exposure and said somebody in this room is going to kill someone with a drug he or she prescribes, but that doesn't mean we are not going to use the medications.

Yes, there have been deaths, and, yes,

there will continue to be deaths. I strongly contest the numbers that came there because I have looked at some of the autopsy data and other issues that come out, and as I am sure the scientists and clinicians here know, many of those data are simply not accurate the way that they are presented in the newspaper and the public media.

There is an inherent risk and we must have risk management, but we also have to look at the risk of the alternatives to using opioids if we don't have opioids available.

[Slide.]

Now, the major other systemic class of medications that we are going to be using for moderate pain are the nonsteroidal anti-inflammatory drugs. We have those, we have the opioids, and beyond that we have a whole bunch of adjuncts that are very important, but we have invasive procedures, and what is being used as an alternative to opioids, invasive central nervous stimulation, invasive implantation of catheters into the central nervous system, areas where we largely have no evidence to support efficacy, where we have solid evidence for the opioids.

[Slide.]

Indeed, in 1998, the last year, before we had COX-2 selective NSAIDs, looking at the reported number of adverse drug events reported to the Food and Drug Administration, we know that NSAIDs are the number 1 category, we had over 125 million prescribed opioids, and we had major gastroduodenal and platelet toxicities resulting from these, which mandates this warning from the Agency.

[Slide.]

We are all familiar with this. It is an important warning. These drugs have real risk. They are wonderful medications, I have never said take them off the market or restrict their use. We have to use them within a risk:benefit consideration.

[Slide.]

In 1998, we had 107,000 documented hospitalizations and 16,500 deaths due to NSAID-induced gut bleeds in this country with endoscopically documented lesions.

So, the issue here comes down to risk:benefit ratio, and I believe that is the way that the committee might best look at how these opioids are going to be used.

[Slide.]

If we don't have opioids available, this is what is going to be used, invasive procedures that are not supported by evidence, and as every pain clinician knows, there are aggressive lobby groups trying to get massive reimbursement from this from CMS.

[Slide.]

Now, the opioid concerns are multiple, and my time precludes my getting into these at depth, but you have members of your committee, like Dr. Portenoy, who studied these extensively and are well aware of the fact that these are the perceived problems, but that, to a great extent, they are exaggerated concerns.

[Slide.]

Addiction in the context of pain treatment with opioids was defined in the public statement of the American Society of Addiction Medicine in its Public Policy Statement--this is on the web at asam.org--in this manner, a definition with which I think all of us can live.

[Slide.]

But what is critically important is to recognize that ASAM went on to say that patients may appear to observers to be preoccupied with

obtaining opioids, but the preoccupation is with finding relief of pain, not with opioids per se.

In 1997, ASAM endorsed the Weisman and Haddox iatrogenic syndrome that they defined in their classic paper in the journal Pain in 1989 as pseudoaddiction.

I very much appreciate the introductory presentation from CDER in which the problem was defined as complex with a very important caveat. There is no simple solution. I get very concerned when I hear individuals come up and try to propose a simple solution, a single solution, such as restriction to severe pain. Science absolutely does not support that, absolutely does not support that, or other types of restrictions that clearly would minimize availability for patients who need these.

[Slide.]

Tolerance is held up as a huge issue. In the new edition of Carol Warfield's Textbook on Principles and Practices of Pain Management just coming out this summer or actually this fall, we recognize that tolerance to analgesia is very different to the other tolerance issues. The mythology that has already been referred to by

earlier speakers is what drives so many decisions.

[Slide.]

In fact, if we look at opioids dose requirements, work that we did in England in the mid-1970s, that Robert Twycross published in the International Journal of Clinical Pharmacology, this was an individual we were treating with diamorphine, a legitimate drug in the United Kingdom, that is heroin, of course, and the dose went way up and then came down, and went up and came down before this patient with advanced irreversible cancer died.

Starting patients on opioids at whatever dose is necessary does not condemn patients to ever-increasing doses, nor does it carry the risks that we all know so well in the acute setting. In fact, again, I defer here to people like Russ Portenoy who know this field better than I do, how well patients become tolerant to some degree to respiratory effects after just five to seven days of regularly scheduled opioids.

Are people dying from misuse of substances? Absolutely. Are people dying from misuse of many noncontrolled substances? Absolutely. That doesn't mean we take the

substance away.

[Slide.]

Acutely, opioids are profound respiratory depressants. Within a week of initiating therapy, opioid tolerance is so great that in a 1996 book that Professor Margaret Batten [ph] and I published on Drug Use and Assisted Suicide and Euthanasia, we had a chapter from Dr. Steven Jamison, who studied a cohort of patients who went on to die due to AIDS, who tried to kill themselves or their partners tried to kill them, assisted suicide, using opioids, and they couldn't do it because these patients were tolerant to the opioid respiratory effect. These people were suffocated with a drycleaning bag or a pillow in some cases.

This is the type of tragedy that comes from the type of emotional mythology that unfortunately drives political decisions, but hopefully, does not drive scientific decisions.

[Slide.]

Patients skip analgesic doses. The literature on this is very clear. None of us, thank heaven, can recall the experience of severe pain. We can recall having been in pain, but we don't recall severe pain, and we have good studies

that show that patients start skipping doses.

Well, what happens? In this classic cartoon that Twycross published three decades ago, the idea was to keep the patient within the therapeutic window, shown here, but what in reality happens with short-acting medications is people having to take two, three, four doses a day, are more apt to skip doses as the number of doses per day goes up.

[Slide.]

Of course, the new science that has come out, and I have given you a couple of references here, and I have intentionally given you good reviews of the primary literature, both physiological windup, the augmented response to repetitive firing of the nociceptive neuron, and even more importantly, neuronal plasticity, the changes with the central nervous system and peripheral nervous system, but primarily the CNS, that occur in humans as a result of undertreated pain are such huge issues that we need to be more aggressive, not less aggressive in treating pain.

Has opioid use gone up? Absolutely. Is much of that opioid increased use appropriate? Absolutely. Are we using enough opioids to treat

severe and moderate pain today? Probably not.

Is there abuse? Of course, there is, but let's not look at numerator data without looking at appropriate denominators, as well.

[Slide.]

Do we need alternatives? Absolutely. Methadone clearly is the drug. When I was an investigator on the National Cancer Institute demonstration project of hospice care that we did in the 1970s, when I was at Yale, that was the one opioid that we used - wonderful medication, profoundly effective analgesic, but we had nurse investigators who visited with the patients twice a day.

[Slide.]

Methadone, as many of you know, has a biphasic elimination with very unpredictable pharmacokinetics and a serious risk of accumulation toxicity.

[Slide.]

Indeed, this is a computer-generated plot that we did in our computer modeling, in which we show the very, very long beta elimination half-life. Now, why is that important clinically? Because it will take perhaps 10 days to get to

steady-state serum levels, and the risk of accumulation toxicity is huge.

In the State of Oregon where, under CMS regulations, physicians are required for Medicaid patients to use methadone in lieu of pharmaceutically long-acting opioids, which have very different dose-response curves, there have been, I am told, and I have not seen the original data, but I have been told by physicians who I believe that there have been increased numbers of deaths due to methadone toxicity, accumulation toxicity, a far more difficult drug to use pharmacokinetically than the pharmaceutically made long-acting dosage forms.

[Slide.]

Here is a huge myth. Can patients drive safely? Dr. David Fishbain, Professor of Psychiatry and Adjunct Professor of Anesthesiology and Neurosurgery at the University of Miami, published a systematic review, and extensive valid systematic review in the journal that I edit a year ago, looking at the entire world literature, and most people taking opioids can, in fact, drive safely after they have been on consistent doses.

Of course, Professor Vainio of Helsinki

demonstrated this first in her classic paper in the Lancet in 1995. There are a dozen other papers out that I could cite, actually 27 in total. The key here is I believe that we have to put opioids in perspective.

If we start restricting opioids to a given class of prescribers, I think we will have a public health disaster on our hands. I have just finished a textbook entitled, "Pain Management for Primary Care Clinicians." A good friend of mine and of several of you on this panel, Dr. Bill McCarberg [ph], who is a family practitioner and a diplomate of the American Board of Pain Medicine, who runs the pain service and does primary care at Kaiser Permanente in San Diego, wrote the preface.

Bill emphasized in this book, the absolute importance of primary care clinicians, family practitioners, internists, physician assistants, advance practice nurses who are so licensed, having access to the right modalities to treating pain.

I appreciate what the DEA said, education is critical and many of the other things that the DEA representative said are critical, but the science and the epidemiology and the clinical need do not support restricting to any one group of

prescribers, nor to any one category of pain.

Opioids are actually safer vis-a-vis end organs than either NSAIDs or acetaminophen. Acetaminophen, as every clinician knows, has the potential of hepatotoxicity, and whether it is a COX-2 selective NSAID or a non-selective NSAID, there still are inherent risks, but there are risks with every drug.

Acutely, opioids are very toxic chronically, when they are taken within the label, are actually relatively safe. I don't believe that anyone in this room individually can prevent people from taking drugs inappropriately. We do need good risk management programs, I strongly applaud that, but I don't believe that it would be conscionable to take away access to opioids.

[Slide.]

The AHCPR, now renamed the Agency for Healthcare Research and Quality, the American Society of Anesthesiologists, the American Academy of Pain Medicine, the American Pain Society, American Society of Addiction Medicine, American Geriatric Society have all come out with documents strongly advocating the use of opioids in appropriate clinical settings, and not, implicitly

not restricting these because most of the patients who are going to be seen with osteoarthritis, a small percentage of whom will be require opioids, not a large percentage, but a small percentage, they are going to be seen by primary care clinicians, they are not going to be seen by rheumatologists.

[Slide.]

I want to save time for questions because I think this is a very important issue. I feel strongly about it, but my passion is not based upon clinical emotion, it is based upon what the evidence says.

Liebeskind and Melzack went on to say that this pain that people are suffering is needless, it impoverishes the quality of life of patients and families. It shortens life because it impairs recovery, that is the catabolism and the emotional issues.

People become depressed, they lose their will to live, they fail to take normal health-preserving measures. Before he went to prison in Michigan several years ago, Jack Kevorkian--I think everyone remembers Dr. Jack Kevorkian, the pathologist who was affectionately

known in Michigan as Dr. Death--I am told by a physician colleague, a pain specialist in the Midwest, that Dr. Kevorkian's--and this is one who has access to the information-that Dr. Kevorkian's answering service was receiving over 1,000 telephone inquiries a week before he went to prison.

Now, there were not 1,000 people looking to end their lives. These were 1,000 people who wanted to explore whether active end of life was an alternative that they should have available. What is fascinating is that the vast majority of these patients did not have advanced irreversible disease, they didn't have cancer, they didn't have AIDS, they had low back pain, they had arthritic pain, and they had headache pain.

We are talking about approximately 50 million people in the United States per year experiencing either intermittent or fairly continuous chronic pain. Opioids are not first-line therapy, we all know that, and responsible clinicians do not advocate them as first-line therapy in most chronic, nonmalignant pain.

But just as recently as a decade and a

half ago, there was general belief among many clinicians that opioids had no place in chronic, nonmalignant pain. Now, we have grudgingly seen the medical community accept, based on evidence, the appropriateness of opioids in cancer pain and in acute pain, and those are clearly documented in a searchable format in those two Department of Health and Human Services' Public Health Service Clinical Practice Guidelines.

The Cancer Pain Guideline, by the way, is under revision right now through the American Pain Society, and actually, there is more evidence to support opioids there, there is no question.

Again, I tip my hat to Dr. Portenoy for the seminal work that he did during the 1990s, getting the world pain community to look at the serious question of risk:benefit ratio of opioids in chronic, nonmalignant pain, and a large body of research that has taken place in the past decade has clearly shown that there definitely is a place for opioids in chronic, nonmalignant pain, not just severe pain.

We do not have the resources, and should not have the resources in this country, for all people who have moderate to severe pain to be seen

by pain specialists. It would be very good for my clinic and it would be very good for some of the other people here's clinics, but that is not reality.

We do need education, we do need risk:benefit decisions, and we do need risk management programs, but I am here to speak on behalf of Joshua, both the Joshua to whom the congressman referred, and to my son Joshua, who is 8 years old, and all the other Joshuas and other people in this country who at some time in their lives may require opioids to assure that we have the most reasonable dosage forms.

The pharmaceutics has improved dramatically. The entire science of pharmaceutics, of dosage form development, of making medications that will release on a consistent basis, that will give us both an immediate release and an controlled release phase, has advanced by orders of magnitude in the past 15 years, and, indeed, some of the newer dosage forms that we have are far better than some of the older ones.

The only other thing I would like to leave with the Committee from conversations that I have had with health authorities in the states that have

been impacted by some of these disastrous multi-drug, not single-drug abuse situations often leading to death, is the fact that in the majority of those cases, as I understand it, number one, there was no autopsy toxicology data, so we don't even know what the substance was, there is clear evidence of polysubstance abuse, and even when a particular opioid, be it hydrocodone or oxycodone or morphine or fentanyl, whichever one was found, as you all know, from autopsy data, there is no way to ascertain the dosage form that caused that unless we actually we find ghosts of that dosage form within the gastrointestinal system of the decedent or actually find tablets or capsules on the body, and that has rarely been the case.

So, these huge emotional extrapolations that we have seen, I think have to a great extent clouded the science, and I hope that the decisions that are made here within the tradition of the FDA and within the traditions of the Public Health Service will be based on the best issues of public health for the American citizens.

With that, I would be happy to take any questions or comments from the committee members.

DR. KATZ: Thanks, Art. We do have time

for a couple of questions. What I would like to be clear on, though, is that I think the most appropriate scope for any questions now would be on the evidence base for the use of opioids for chronic pain, and I would prefer to defer any discussion of the specifics of risk management plans, pros and cons, restricted labeling, all that thing, there will be ample time for discussion of that in the afternoon and tomorrow.

So, any questions about the evidence base for the use of opioids or alternatives in chronic pain? Dr. Shafer.

DR. SHAFER: First, thanks, I enjoyed that presentation immensely.

We have earlier today identification of specific molecule oxycodone and concerns about the risk of oxycodone. Are you aware of any data to suggest that any molecule in the Class II category has more abuse liability than any other molecule just related to the intrinsic pharmacology, not in terms of availability and distribution?

DR. LIPMAN: Yes. That's an excellent question and I am aware of the data, and the data say that that is absolutely not the case. Oxycodone is no more dangerous than morphine, is no

more dangerous than fentanyl, is no more dangerous than hydromorphone.

A very important point, however, is that Dr. Gabriel Pasternak has done some extremely important genetic research with a mouse knockout model, the Kopeki model, in which he has now demonstrated--and, Russ, you can tell me the latest number--the last time I talked to Gab, I think it was about 14 different subsets. It is higher than that, he tells me now. Well over a dozen subsets of the mu-1 receptor.

Now, what does this mean and how does it relate to your question? All of us in this room have receptors within our central nervous system at which opioids work, and the specific receptor at which a mu agonist opioid, which, of course, includes morphine, oxycodone, and most of the other Schedule II controlled substances we have discussed here today, at which they bind to give us the analgesic and other activity are mu receptors and specifically mu-1 receptors.

Now, what Dr. Pasternak's work, both as a neuropharmacologist and a neurologist, he has done elegant research, and he has shown that there are differences in the density of the subsets of the

various receptors in different patients.

Now, what this means is that I may respond more to morphine, both clinically and toxicologically, Nat may respond more to oxycodone, and someone else may respond more to hydromorphone, but it also means clinically that we need, and I emphasize the word "need," alternative opioids.

There is now a genetic polymorphism, scientific basis for serial trials of multiple opioids and not to conclude that a patient who fails one opioid will necessarily fail another even though they are both mu agonists.

As far as the toxicology on your specific question, no, absolutely not. There is no greater risk, in fact, there is less risk chronically with oxycodone than with morphine because we don't have a potentially neuro-irritant metabolite, in the case of morphine, morphine-3-glucuronide, and we only have one small percentage clinically effective metabolite with oxycodone, that is oxymorphone, and it has the same elimination pattern as the parent compound, so there is no accumulation risk. So, it is actually a safer drug from a molecular perspective.

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

DR. SKIPPER: Let's see, we were given a report from the Research America this morning, which says that a poll shows that 57 percent of Americans suffered from chronic or recurrent pain in the past year.

You showed a slide that said freedom from pain should be a basic human right. So, would we extrapolate then to suggest that we should be treating 57 percent of Americans?

DR. LIPMAN: Not with opioids.

DR. SKIPPER: So, how do we determine where the cutoff is in the interaction of other problems like depression, and so forth, that may not be due to the pain?

DR. LIPMAN: I think that is a very important clinical question and I am not here to write policy for state medical boards. I have spent a lot of time in the UK and a lot of time in Scandinavia where there are national health systems, and the Federal Government tells clinicians how to practice.

Our system works better in many ways, it also has deficiencies that they don't have, but the issue here is that's an individual clinician decision dealing with his or her patient. For most

patients with low back pain, that's myofascial, as we all know, stretching is the treatment of choice, not opioids, and I am not here to advocate wholesale use of opioids.

I am here to say that we have an epidemic, and it's not Lipman talking, David Satcher, the former Surgeon General, and Louis Sullivan, the former Secretary of Health and Human Services, just a week ago had a press conference that led to this huge issue, and you can find information on painfoundation.org on the web, the American Pain Foundation web site, saying that this is still a huge epidemic problem in the United States, chronic pain.

Opioids are one important arrow in the quiver. It is critical that we keep that arrow sharp and available. It is also critical that these be used rationally, and not in a wholesale or first-case manner, but that is an educational issue and a state regulatory issue.

Just one closing comment that I think is critical. I heard some very telling points earlier. The representative from the DEA told us that the vast majority of problems are on the local level. That has to be controlled, under the United States

Constitution, on a local level.

If we stop the source of critically needed medications on a federal level because of inadequate resources or whatever, and I don't know the answer, to solve local problems, then, I think we are doing a terrible disservice to the American public.

DR. KATZ: Again, I would like to remind the committee that I think the best focus of the discussion right now is on the clinical issues and on the evidence behind it, and we should defer discussion of the policy issues until later.

Dr. Leiderman, you are next.

DR. LEIDERMAN: I just have two questions for Dr. Lipman. One, you alluded to the immunological suppressant effects, and you said pain. The reference that I thought I saw up there was for an article entitled, "Acute and Cancer Pain." So, I had a question about whether there were data in chronic pain, as well.

DR. LIPMAN: Yes, there are.

DR. LEIDERMAN: Okay. Then, my second question is you also alluded to the high suicide rate in untreated pain, and again I wondered if you had any data on that.

DR. LIPMAN: Unfortunately, we don't have good data, I am not aware of good data in the latter area although my friend and colleague, Dr. Passik, will be speaking later, may know something, put you on the spot, Steve, because I think he has looked at these areas far more than I have.

The question you asked, though, is excellent. There is a good-sized literature that is growing rapidly now on suppression particularly of natural killer cells, but of host defenses from pain much more so than with opioids. Opioids, as you know, have a mild effect on NK cell counts, pain has a much more serious effect NK cell counts. In fact, we have a manuscript in preparation right now that will be coming out within the next six months, a systematic review of the entire world literature on that issue.

We have six different immunological indicators showing that with a whole range of human clinical chronic pain models, there are cell count shifts and other issues that do need to be looked at. If you would like details on that, just drop me an e-mail, I would be happy to share that with you.

DR. KATZ: Dr. Bril.

DR. BRIL: Thank you for an excellent presentation. I think in acute and terminal cancer pain, it is kind of easy to consider Class II drugs. My question really had to do around chronic pain models and, because of my interests, say, chronic diabetic neuropathy pain or chronic neuropathy pain, which is as severe a problem to the patients as other forms of pain.

But I wonder how good the evidence is or what the relative efficacy is of, say, a Class II agent compared to an adjuvant analgesic and how necessary this class of compound is in this indication.

I mean are there good comparative studies, what is the science that would say you would want someone chronically to take, say, oxycodone or MS Contin, or whatever?

DR. LIPMAN: No, there are not good comparative studies looking at tricyclic antidepressants versus antiepileptic drugs versus opioids. There are, however, good serial trials, and the best data set that I am aware of here is that that belongs to Mitchell Max, whose clinic is right up the street here at the NIH.

Mitchell, as you know, is a neurologist

who runs the analgesic trials clinic at the clinical center, and he has looked at a whole range of painful diabetic neuropathy and other neuropathy models.

In answer to your question, yes, there is an absolute need for opioids. Now, if you look at the paper that came out in Pain in 1988, out of Stockholm, in which Arner [ph] and colleagues said that there is no efficacy for opioids in neuropathic pain, you would recognize that that work has subsequently been refuted. It was actually a Type 1 or Type 2 error in the statistical analysis in that study, that seemingly well done study, which is why, of course, we require repeated studies of pivotal trials for any drug to be approved.

Again, I would defer to Dr. Portenoy as a neurologist. He has done some of this work and has shown that there is a clear place. Sometimes we require higher doses of opioids, and we don't really understand the mechanism. It is probably some central plasticity in these neuropathic pain models than we would in seemingly comparable nociceptive pain, but opioids are definitely effective.

We have dozens of patients on chronic opioids in our clinic including some painful diabetic neuropathy, postherpetic neuralgia, and other neuropathic pain models. What is interesting is that most of these patients are on chronically far, far lower doses of controlled release opioids than they required initially to get the pain under control, because the anxiety and all the confounds associated with the initial pain presentation often lessen once we obtain some pain control for a period of time, and particularly when we get them into multimodal therapy where they learn coping techniques and they learn some relaxation to cut down the sympathetic autonomic input, that the vast majority of patients who are on chronic opioids are on relatively low doses of long-acting opioids.

DR. KATZ: Maybe to expand on that for a second, there are actually several randomized placebo-controlled clinical trials of opioids for neuropathic pain that show efficacy, and there is now just recently published one, a study from Raja and his colleagues at Hopkins comparing, in the same head-to-head placebo-controlled trial, tricyclic antidepressant versus opioids and showing that, if anything, the opioid group seemed to have

better pain control than the tricyclic group, and both groups did better than placebo.

Now, these are short-term studies, but that is the database available to answer your question.

DR. LIPMAN: I concur with that, but I believe that some of these patients, indeed, there is clearly some patients who will respond better to opioids and others who will respond better to monoamine reuptake inhibitors.

The key is that if we are going to minimize risk, we need to be able to combine these therapies, and that is where we need a range of dosage forms, and because of the genetic diversity and genetic polymorphism, we need a range of different opioids in controlled release dosage forms.

DR. KATZ: Thank you very much for your comments. In the interest of time, I am going to have to apologize to Dr. Baxter, the second time I have cut him off, and Dr. Portenoy. We need to move along with the schedule.

I would like to introduce Dr. Gianna Rigoni from Office of Pharmacoepidemiology and Statistical Science at FDA, who will be speaking

with us about opiate use data.

Opiate Use Data

DR. RIGONI: Thank you, Dr. Katz.

Today, I would like to describe the patterns of use of immediate and modified release opioids in both inpatient and outpatient settings, to provide a context for discussions of risk management plans over the next two days.

[Slide.]

Data on drug utilization will be presented from sources FDA has available under various contracts. Outpatient data was obtained from two IMS health audits. IMS is a source of marketing data most commonly used by the pharmaceutical industry and government agencies to obtain the number of dispensed prescriptions in the United States.

Inpatient data was obtained from Premier, a group purchasing organization, for approximately 400 hospitals in the United States, and will be explained in more detail in a few minutes.

[Slide.]

First, I will present data on outpatient drug utilization. We will first examine the trends of immediate release opioids when combination

products like Vicodin, Lortab, Percocet, et cetera, are included.

Then, we will remove these products and examine single-agent, immediate release opioids. Lastly, we will examine modified released opioids and methadone.

[Slide.]

The National Prescription Audit from IMS Health measures dispensed prescriptions from retail pharmacy settings seen here in the second bullet, and only oral dosage forms were included in this analysis.

The number of dispensed prescriptions is obtained from a sample of approximately 22,000 pharmacies in the United States and is projected nationally. Mail-order and long-term care pharmacy settings were not included in this analysis since they do not capture the physician's specialty writing the prescription.

[Slide.]

Total prescriptions dispensed were selected for opioids relevant to the discussions we will be having today and tomorrow, and are presented here in millions of prescriptions dispensed. The graph categorizes the opioids into

immediate release dosage forms, represented by the blue line, modified release opioids, by the red line, and methadone, by the green line on the bottom.

Methadone was looked at on its own since technically, it is not a modified release dosage form, but i is long acting.

This graphs shows a trend of an increasing number of prescriptions dispensed in retail pharmacy settings over the past five years for Schedule II immediate release and modified release opioids, as well as Schedule III immediate release hydrocodone products. Methadone also appears to be increasing, but at a slower rate.

I will now zoom on this top line to give you a better picture of what is happening with immediate release opioids.

[Slide.]

Immediate release opioids, when including combination products, which I have mentioned before, are widely used, with hydrocodone having the most prescriptions dispensed at approximately 90 million in 2002.

I am now going to remove these combination products and zoom in even further on the immediate

release single-agent opioids to make a more clear distinction between the products dispensed in small volumes here on the bottom of the screen.

[Slide.]

When we remove the combination products, we see more clearly the total prescriptions dispensed have increased over the last five years, but at a much lower volume, about less than 2 million prescriptions per year.

[Slide.]

This graph represents the modified release opioids and methadone. It appears here also that total prescriptions dispensed have been increasing over the last five years, but again in lower volumes, less than about 7 million per year we see here, and modified release oxycodone growth appears to be leveling off as of year-end 2002.

Now that we better understand the trends in dispensed prescriptions for immediate release and modified release opioids, we need to better understand which physician specialties most often prescribe these products.

[Slide.]

The top prescribing specialties in 1998 were compared to the top prescribing specialties in

2002, and each specialty is represented by a different color bar.

Here, it makes sense to see dentistry among the top two prescribers over time since combination products are included in this table. There appears to be no significant change in prescribers over time since the same specialties remain in the top two-thirds of prescribers from 1998 to 2002.

[Slide.]

Looking at the same data, but again removing the combination products, we see that in 1998, the hematology-oncology specialty made up about 25 percent of immediate release opioids prescribers, but dropped to about 11 percent in 2002. This does not mean there have been less prescriptions dispensed by the hematology-oncology specialty, just that more physicians are treating pain in outpatient settings.

Also, keep in mind here that mail-order and long-term care data do not include physician specialty, and were not included in this analysis. Therefore, we may be underestimating prescribing by specialty, such as helonc and physical medicine in rehab.

[Slide.]

We see similar trends from 1998 to 2002 for modified-release opioids and methadone where primary care physicians constitute a majority of the top two-thirds of prescribers.

[Slide.]

Next, we examined data from the National Disease and Therapeutic Index, or NDTI. NDTI collects data on drug products and indications mentioned during office-based physician visits, in other words, a physician's treatment intention where they believe an opioid is appropriate.

NDTI provides information on trends of diagnoses, patients, and treatment patterns occurring in office-based practice, and indications as reported by the physician are linked to each drug.

Data on office-based physician visits are obtained from a sample of approximately 2- to 3,000 physicians in the U.S. and projected nationally to reflect national prescribing patterns.

[Slide.]

The following graphs display the number of visits to a physician's office where an opioid was prescribed. All diagnoses naturally fell into

these four categories - Other Pain, which includes migraine headache, fracture, dental pain, complications of pregnancy, any other pain.

The second category is postoperative surgical procedures. Third, is musculoskeletal pains, such as myalgias, lots of lower back pain, and various arthritis, and cancer-related pain down here on the bottom.

The blue bar presents the number of physician office visits in 1998 compared to the red bar, which is 2002. Since combination products make up a majority of this category, we see physician visits in the tens of millions across the five years we looked at.

Top indications for 1998 continue to be the top indications for 2002, and appear to be increasing over time with the exception of cancer-related pain, which is your last bars over there.

I am now going to take out the combination products like I have done previously in order to see the immediate-release single agent opioids more clearly.

[Slide.]

When the combination products are removed,

we see the number of physician office visits decreases into the hundreds of thousands and can see a shift in prescribing over time from Other Pain in 1998 to more cancer-related pains in 2002.

[Slide.]

Finally, we examine the most frequently occurring indications associated with modified-release opioids and methadone, and we once again see a shift in prescribing from cancer-related pains in 1998, to musculoskeletal pains in 2002.

[Slide.]

We have now seen the trends in outpatient use in opioids, we have seen an increase in the volume of dispensed prescriptions prescribing primarily from primary care providers, and immediate-release opioids use more in treating cancer-related pain, while modified-release opioids are being used more to treat musculoskeletal pain.

Lastly, we will take a quick look at the use of modified-release opioids in inpatient settings to better understand the use of these products in conjunction with inpatient surgical procedures.

[Slide.]

Premier provides information on inpatient use of drugs from approximately 400 acute, short-stay, non-federal hospitals belonging to their group purchasing organization or GPO. A GPO is an organizational unit which procures and negotiates purchase price conditions for this particular group of hospitals.

Premier data includes billing information on patients, drugs, and procedures done for every hospital discharge from 2000 to 2002. Because this is billing data, there are no direct linkages between procedures and drugs, and we can only identify if billing for a drug and a procedure occurred on the same day or the day after.

Since it was the intention of this analysis to examine the use of modified-release opioids in conjunction with surgical procedures, these data are appropriate.

Patients with a discharge diagnosis associated with any type of cancer were excluded because we cannot distinguish if they were admitted to the hospital already on opioids to treat their cancer-related pain.

[Slide.]

This graph shows the percent of all

surgical procedures associated with a modified-release opioid being billed on the day of or the day after surgery. Each bar represents the total number of surgeries performed in Premier hospitals in the following years, and the blue portion of the bar represents the percent of surgeries where modified-release morphine was used in conjunction with a surgical procedure.

The red part of the bar is where modified-release fentanyl was used. The green part is where modified-release oxycodone was used. The gray part of the bar represents the percent of surgeries where none of these three products were billed within the same time frame that I mentioned before.

We see there is a substantial use of modified-release opioids associated with inpatient surgeries over the last three years. Modified-release opioids have consistently been billed on the day of or day after surgery 50 percent of the time in Premier hospitals with modified-release oxycodone being ordered most frequently.

Next, we looked at the most frequently performed surgical procedures in these hospitals to

see how modified-release opioids were used in conjunction.

[Slide.]

These are the top three surgical procedures done in Premier hospitals from 2000 to 2002, and the percent of time a modified-release opioid was billed on the same day or day after.

The green bar represents the most frequently occurring operations in Premier hospitals, and that being musculoskeletal operations, the most common being total lower extremity replacements.

The red bar signifies second most common surgical procedures - genitourinary operations, the most common being hysterectomy, and the blue bar represents digestive system operations, the most common being cholecystectomy.

As we can see, the percent of surgery is where modified-release opioid occurred has remained constant over time, but 35 to 65 percent of the top three most common surgical procedures are associated with modified-release opioid use.

[Slide.]

Some limitations of our analysis for the outpatient drug use data are, first, data on

dispensed prescriptions include prescriptions filled in retail pharmacies only. We excluded mail-order and long-term care pharmacies in this analysis, and data from methadone maintenance clinics are not included in these data.

Second, data on indications for opioid use reflect office-based physicians' prescribing based on a small sample size of physicians, which does not mean a patient actually filled the opioid prescription, and the small sample size makes these numbers unstable.

With inpatient drug use data, because using billing of medications and procedures as proxy for actual clinical care may be imprecise, we could be over- or underestimating modified-release opioid use with surgical procedures.

Since Premier data represents only patients admitted into the hospital that have a surgical procedure, same-day surgeries are not included, which may represent a substantial number of surgical procedures.

[Slide.]

In conclusion, use of opioids appears to be increasing in outpatient settings and is widespread in inpatient settings. Primary care

providers continue to be the leading prescribers of opioids in the outpatient setting.

Indications for the outpatient use of opioids has shifted for immediate-release opioids from treating Other Pains to treating more cancer-related pain, and from modified-release opioids has shifted from treating cancer-related pains to treating more musculoskeletal pain.

Therefore, when considering risk management strategies over the next two days, we need to keep in mind that immediate- and modified-release opioids are not prescribed by any single prescriber in any single setting or for any single indication in the United States.

Thank you.

DR. KATZ: Any questions?

I have a question. Do any of the databases that were analyses that you have looked at give us any insight or give us any national projections on the number of individuals in the United States that appear to have been on long-term opioid therapy?

DR. RIGONI: That, we would require probably more of a longitudinal database. We just kind of have snapshot looks at data available to us

right now. We would have to do further analysis for that.

DR. KATZ: Any other questions? Yes, Dr. Jenkins.

DR. JENKINS: For the data on the inpatient use postsurgical, were you able to determine whether those patients were receiving the modified-release opioid before they had the surgical procedure?

DR. RIGONI: No, that unfortunately was one of the limitations of using this data. We were not able to see the drugs they came into the hospital on, which is why we excluded cancer patients because we thought that would muddy up the analysis.

DR. KAHANA: Were there any regional differences, were you able to stratify what part of the country the modified-release products were being used, are they in one part of the country, is there a specific area that they are more prevalently prescribed?

DR. RIGONI: Actually, we didn't look at that either. That is something not available in our contract with our data vendor, so we weren't able to examine that.

DR. KAHANA: So, you don't know where these patients were?

DR. RIGONI: Right, we don't. These are just national estimates.

DR. KATZ: Dr. Shafer.

DR. SHAFER: Just a follow-up to Dr. Jenkins' question. I hate to extrapolate from an N of 1 situation, but I was very surprised to see, for example, 10 percent of post-op patients getting Duragesic, because I know that in our practice at Stanford, which is the N of 1, you just don't see it because of the Black Box warning.

So, I do wonder about those post-op surgical data and I don't know if other people would have similar experiences.

DR. RIGONI: I agree with you. We really didn't have that much extra data on these patients to be able to kind of figure out if it was used for that or that they came in on a Duragesic patch for some chronic pain that they had before, so it is yet another limitation of using that data in this analysis.

DR. KATZ: Dr. Portenoy.

DR. PORTENOY: I was surprised also at the prevalence of use of the modified-release for

postoperative pain. You might not have the answers to this, but are there any other databases that might evaluate risk in that subset and help us understand what is happening with that subset of patients?

DR. RIGONI: In the hospital setting?

DR. PORTENOY: I gathered that many of those patients might have gone home with those drugs. The data only assessed whether or not a drug was prescribed the day after an operation. I would guess that many of those patients were prescribed those drugs on discharge. That seems to be a common pattern in my hospital. I would guess that is probably what happened.

But most of those patients most likely were not using opioid therapy before, so they were at a relatively higher risk of adverse events, and I just wondered whether there is any database that looks at that population specifically in terms of risk after discharge.

DR. RIGONI: Not that I am aware of. We are still exploring the Premier database in the Office of Drug Safety at FDA to see if we might be able to tease that out of that data, but we have been working with them quite closely to try to

figure out if we can determine that from their data.

DR. KATZ: Dr. Strom.

DR. STROM: Just in answer to that, longitudinal databases, like managed care or Medicaid databases, could answer that question. They wouldn't have the information on the inpatient drug use, but you would be able to look, of all those people who were discharged after a surgical procedure on long-term opiates, what proportion of them had come in on it to begin with.

DR. RIGONI: We, unfortunately, don't have some of those data available to us.

DR. KATZ: Thank you very much for sharing that data with us, we all appreciate that.

Next, it is my pleasure to introduce Steven Passik, who is the Director of Palliative Care Research--Steve, is that right--at the Markey Cancer Center?

DR. PASSIK: Yes.

DR. KATZ: Dr. Passik has been a long-standing contributor in the area of pain management and particularly in patients with substance abuse, and will be speaking with us about Misuse and Abuse of Opiate Analgesics in the

Medical Setting.

Misuse and Abuse of Opiate Analgesics

in the Medical Setting

DR. PASSIK: Thanks, Nat, it is a pleasure and really an honor to be here to put my two cents in, in this dialogue. I had a little trouble finding the room. I live in Lexington, Kentucky, and the next town over is Versailles, Kentucky, so when I asked where the Versailles Room was, I didn't get the right directions.

[Slide.]

I wanted to just say by introduction, I started out interested in this topic, I started out my career, the first 10 years of which was spent at Sloan-Kettering, I had the honor of working with Russ Portenoy, Kathy Foley, and Bill Breitbart and others, and was interested in the management of pain in addicts as the AIDS epidemic hit New York and hit Sloan Kettering.

But subsequently, as this revolution has gone on in pain management societally and medically, I became interested in issues related to how pain patients sometimes misuse their medicines and issues surrounding that problem.

I have to say that the revolution that has

happened, in my opinion, with the broader use of opioids has absolutely changed the lives for the better of, no question, millions of people, but unfortunately, I think we have too much rhetoric sometimes in the pain community, and that rhetoric has sometimes trivialized the issue of negative outcomes, and I think we need to study these issues.

I don't know personally that monitoring or restricting is the answer, I think we need more research, and I am going to walk you through some research studies that we have performed looking at this issue of noncompliance behavior in pain patients.

[Slide.]

But before I do, I wanted to first say that I am going to try to address for a moment the issues of who or what should be monitored. As we try to get a count of the problems of bad outcomes in pain management, there are several different populations that would be affected if changes in policy and changes in clinical practice were instituted.

I will admit at the outset that long-term studies of outcomes, good or bad, in opioid therapy

are virtually absent, and this is a terrible problem at a time like right now when we don't have data on patients who have been on these medicines for months or years. Most of the trials that we do have are considerably short than that.

Aberrant behaviors, or the so-called "noncompliant" behaviors, their frequency, their meaning in the clinical setting, and so on, have been poorly studied. That has been the focus of my work, and I will show you some of the results there.

Then, importantly, I think the relationship between aberrant behavior, namely, when you see noncompliant behavior in a pain patient and something has gone awry in pain management, the question is how often is that associated with addiction, and we really don't know the answer there either.

So, to the issue of who or what should be monitored, if I was better with PowerPoint, this would be a series of complicated ven diagrams with some overlap, and I will leave that to your imagination.

But when we start talking about who or what should be managed through risk management,

monitored through monitoring programs, or to whom drugs will be restricted, we are actually talking about several different populations.

I am concerned that the top group, the pain patients, would suffer if measures to stop abuse or diversion in some of these other groups were instituted. One of the problems we have when you set up a pain practice or if you are a primary care doctor who treats a lot of pain, is that some people, the people on this first line, will see on your shingle where it says, "Pain Expert," they will see hope and deliverance, and then other people will see large quantities of high-quality opioids available.

The problem is that any steps we take will impact all of these groups. All of them, in various forms, do present in pain practices from time to time, and I think it is essential really to study these bad outcomes, and outcomes related to the aberrant drug-taking behavior spectrum, that I will describe, and also better understand when those outcomes are actually related to these other groups.

[Slide.]

What do we mean by a "good" outcome? I

apologize to everybody who has heard me speak about this before, because of the fact that I have been talking about this for years now, the so-called "Four A's" of pain treatment outcomes. Some of the people who have heard me before want to add a fifth, which would be "ad nauseam."

But basically, what we have tried to teach the pain community and others who treat pain is that we are trying to get a good outcome in four areas. We are trying to provide analgesia, we are trying to improve psychosocial functioning, we are trying to limit adverse effects, and monitor and contain any suggestion of aberrant drug-related behavior.

I think the studies that I have done have shown basically that analgesia is modest, but meaningful on opioids, meaningful insofar as the fact that some 80 percent in one of my studies were rated as improved in their overall function, side effects seemed to be common but tolerable.

Then, with regard to noncompliant behavior, they are not infrequent. The problem is we don't always know their meaning, nor do we know when they are serious, and that is really I think one of the big gaps is that clinicians need more

education and more data to understand these better.

[Slide.]

When I refer to "aberrant drug-taking behavior, I am referring to something like this. This is well known in the pain field now, for some of you, though, it might be new. This comes from an observation from Russ Portenoy from many years ago, actually first, I believe in the late '80s when he was writing for Jerry Jaffe's Textbook on Substance Abuse, and this I think is really a brilliant observation that Russ had, that has led to a model that we have used in our research, as well as in our clinical monitoring of people in chronic pain who are on opioids.

What I think Russ was onto quite some time ago was that the phenomenology of the physician treating pain is not the phenomenology of the addiction medicine specialist. For example, there are many ways in which the phenomenology of the addiction medicine specialist has been highlighted over and over again as misleading in the pain treatment setting.

For example, the patient who develops physiological dependence, we know that in the pain setting, that is not associated generally with

aberrant behavior. Tolerance, to the extent that it develops, is more often than not, not associated with aberrant behavior.

So, there are some aspects of the phenomenology of addiction that don't suit the pain management setting, so sometime ago, we started writing about and researching from the point of view of articulating our own phenomenology.

Our phenomenology is very poorly studied, but basically, Russ's observation was that essentially, there is a wide range of aberrant behavior that could become evident in the clinical practice setting of pain management and that some of it is rather innocuous and some of it is very serious, and clinicians need to know how to assess and talk to patients about this, researchers need to take up the cause and try to figure out how common these things are, and so on.

I would venture a guess that there is more of a literature on noncompliance with antihypertensives than there is with opioids. There is a lot of rhetoric and there is a lot of emotion, but there is not a lot of research on what do people actually do with pain medicine when the treatment has gone awry in any way, shape, or form.

[Slide.]

One of the big complications we have, the clinician has this complication every day when he has a patient in front of him who is losing prescriptions, raising their dose on their own, doing anything of the kind.

The clinician faces this dilemma and then we, as researchers, face a dilemma when we try to understand what do we think this behavior means, because it appears in the clinical setting as the end result of multiple forces, sometimes more than one at the same time.

Sometimes when a pain patient is misusing their medicines or having a bad outcome in this spectrum, it represents addiction or abuse that is unfolding in front of the clinician's eyes. Sometimes, as Dr. Lipman said, it is pseudo-addiction and the patient is acting in an uncharacteristic fashion because they have inadequate pain relief.

Sometimes there is a form of self-medication going on or what Eduardo Bruere [ph] has termed "chemical coping" of other life circumstance and psychiatric problems, and I would venture a guess, although this has also been poorly

studied, that there are a lot more bad outcomes in this category than there are in the addiction or abuse category if you to pain specialists who treat really complicated pain patients, because of the psychiatric comorbidities and other problems that pain patients sometimes bring with them.

These kinds of problems are more frequently encountered in my practice and probably others than are out and out addiction or abuse. Then, of course, there is criminal intent. There are people who are presenting in a pain clinic with intent to divert.

When these patients are in front of us, this is our dilemma. We try to figure out what this behavior means. It is my observation clinically and through the research that there aren't really any behaviors, even the ones that are illegal on their face value, that point you in a particular direction.

For example, even the really serious ones where we wouldn't very often cut a lot of slack, I mean there are certain behaviors that really do merit a one-strike-and-you-are-out of the clinic kind of policy, like forging a prescription or where there is evidence of selling your medication,

and so on, versus simply running out a day or two early, so there is a wide range.

But I have seen prescription forgeries that were unrelated to diversion or abuse in my clinical practice - patients with personality disorder or things like that where they were angry that I went on vacation, for example, and altered a prescription as a sort of impulsive gesture.

So, I think the behaviors themselves don't help you necessarily, and this is a very, very complicated clinical phenomenon that has to sorted out with outside corroboration, urine tox screens, and a whole range of other things, but they are not all that common either. The behaviors are common, bad outcomes, truly bad outcomes, I think are not.

[Slide.]

So, what are those bad outcomes? Let's say that those behaviors are evident in the clinical setting, what might they represent? Sometimes they are going to represent abuse by the patient. We don't know how common that is in our present database.

Addiction, out-and-out addiction is probably very rare in the pain population unless people come in with vulnerabilities, but if they

are not vulnerable people when they are exposed to their opioids, whether it's oxycodone or any other one, probably they are not going to run into difficulties if they don't have some pre-existing vulnerabilities.

Then, there is chemical coping, which we also don't know how frequently this happens. What do I mean by "chemical coping"? I think we all can sort of feel what you think I mean by it, but let me just explain that there are aberrant use patterns that we see in the clinic that don't necessarily qualify as out-and-out compulsive use, nor do they qualify as out-of-control use.

They are just on the fringes of what we would consider an opioid agreement with the patient, not enough to get them discharged necessarily, but, for example, running out early, you know, every other prescription, and things of that sort.

These tend to go on in patients who fail to improve or reach psychosocial goals that have been set between themselves and their clinician at the outset. So, there is a whole range of bad outcomes with, as I said earlier, I think the third group probably being more common, and when you

have a patient who is kind of floundering, not using their medicines exactly as prescribed, not making progress towards psychosocial goals, and that medicine happens to be a controlled substance, this becomes an issue, whereas, it might not be if there was not a controlled substance and with quite the same level of acuity.

[Slide.]

So, which pain patients then are vulnerable to aberrant drug taking? Again, very little data, so this is largely unknown. We do know that exposure alone to drugs in the context of pain management is probably not a risk factor unless, for example, you had someone who had an unknown genetic risk or had a genetic risk, let's say, who had generations of alcoholism in their family, so they decide to be a teetotaler, then, they develop a painful condition and they are exposed a controlled substance for the first time in a pain management setting, and the physician fails to take a good history and doesn't implement any safeguards. That is probably infrequent, but it is feasible that that can happen, that there are people who will get exposed, but those are people, as I said, again with vulnerability.

Given that we don't have long-term outcome studies in pain management, you know, good studies heavily front-loaded for risk factors, so then we could see what predicted down the road, all that can point you in the direction that everybody around this table is well acquainted with, the traditional risk factors for addiction including genetic, psychiatric, social, familial, and spiritual risk factors.

When we assess our pain patients, there is no question that we have to assess them in these areas, because many pain patients have risk factors in these areas.

I described the kind of patient who might have a genetic risk factor, psychiatric, overwhelming, 80 percent of people with chronic pain have a comorbid depression, the social and familiar warping of their life circumstances from a year or more of untreated pain gives them risk factors often in that area, and many are spiritually bankrupt from their struggle to get their life back on track.

So, our patients have risk factors in this area. It behooves us to teach our physicians how to assess them.

But one fascinating question that my group is beginning to turn our attention to is which ones of these patients then go on to self-medicate. If 80 percent of chronic pain patients have a comorbid depression, which ones start to use their opioids to medicate that depression. We don't know the answers to questions like that.

Of those whom self-medicate, how much of that turns into abuse or addiction? Again, no answers.

[Slide.]

This is a slide just to show you that my group, both, first, when I was in Indiana, which was kind of a five-year pit stop between Sloan Kettering and Kentucky, when I was in Indiana and subsequently at UK, these are some of the studies that we published and we have been looking at these attitudes and behaviors in cancer patients and AIDS patients, and so on, and I am going to very quickly now walk you through the results that I think are illustrative of this problem although I will apologize for the methodology.

Someone said earlier that we don't even have the methods yet for really studying this. Most of our work in collaboration with Russ

Portenoy and others, and Dr. Katz, over this time has been an exploration in trying to figure out what the right methodology is to study the problem.

[Slide.]

In this particular study, the first one, actually, one of the ones down that was on that list, we just completed a NIDA-funded grant to look at aberrant drug-taking behavior in cancer and AIDS patients.

I want to point out some very interesting findings from this study to you. This not all comers with regards to AIDS patients, these are AIDS patients who were specifically chosen because of a history of substance abuse.

Both groups had moderate to severe pain. We had 73 patients with AIDS, 100 patients with cancer. One hundred percent of the substance abusers had reported past or current history of abuse. Some of the cancer patients did, mind you, a little bit higher than the national average in prevalence in substance abuse for the population especially at that age, but substance abuse predisposes to some cancer, so it shouldn't be all that surprising that it be a little bit higher. There were 101 men, 72 women. You can see the

ethnic breakdown.

[Slide.]

We threw the psychosocial medicine cabinet at them, but most importantly, from this, we have this aberrant behavior interview that Russ Portenoy and Nat Katz and Joyce Lowenson, and several others gave us some input to.

[Slide.]

With regard to the results, compared to the cancer patients, the patients with AIDS were significantly more likely, not surprisingly, to be single, male, member of a minority ethnic group, be younger, report past or present psychiatric problems, and be inadequately medicated for their pain.

So, they have lots of risk factors for aberrant behavior as compared to cancer patients.

[Slide.]

It is important to look at groups who have a different base rate in terms of substance abuse to see if they have a different rate of aberrant behavior in the clinical situation, and indeed they did.

The total sample averaged just over three of those behaviors from that earlier slide, cancer

patients just over one, AIDS patients over six. We also broke it down to the less egregious and more egregious behaviors, and you can see here that most of them are in the less egregious area, but the breakdown, this is a significant difference, more common in AIDS patients to have behaviors in this area, probably because of their undertreatment.

[Slide.]

This just represents what you have already seen, but shows you the distribution per percent of the sample for these different numbers of behaviors, and over 60 percent of the AIDS sample had five or more of those behaviors, whereas, the cancer patients were mostly down at zero and one behavior.

[Slide.]

I am going to skip ahead here to show you that, indeed, the cancer patients, using the PMI, which is a formula developed initially by Charlie Cleeland, were much more likely than not to have adequate analgesia prescribed to them, whereas, the AIDS patients were much less likely to although compared to the numbers that we saw in a study that I did with Bill Breitbart at the beginning of the AIDS epidemic in New York, these numbers actually

are improving and AIDS patients appear to be getting prescribed to in better numbers, as well, which is nice.

[Slide.]

This is probably the most important result of the study that I would like to point out to you. When you look at the AIDS patients who had adequate and inadequate analgesia according to the PMI, they had virtually exactly the same number of aberrant drug-related behaviors, and if you compare this ratio, the less severe to the more severe behaviors, it is identical in both groups, it is not affected by the adequacy of analgesia.

So, what is the take-home message there? If you have two problems, you have the problem of pain and substance abuse, your misuse of pain medicines is unlikely to be very affected by the adequacy of the analgesia prescribed to you.

So, when practitioners assess their patients, if their patients have risk factors and problems in both areas, both areas need to be addressed. Addressing the pain alone is unlikely to mitigate the risk of aberrant behavior.

[Slide.]

Just to show you very quickly, this is an

assessment tool that Russ and Nat and I, and others have had some input into, meant to design a chart note to give out to internal medicine and other practitioners who treat chronic pain, and it basically help practitioners follow people who are on chronic opioids, and it, too, is based on the four A's model.

[Slide.]

I just want to show you, in a study of 388 patients who were given opioids for nonmalignant pain, I want to show you the breakdown of aberrant behavior in that sample. This is a sample who was getting about 57 percent pain relief. Most of these patients were improving in their psychosocial functioning. They had a lot of side effects, but overwhelmingly rated them as tolerable, and I will show you the data on their aberrant behavior. This is a paper that we are just completing.

But in this particular study, 55 percent of the sample had no aberrant behavior whatsoever. Now, these are not patients separated into addition and non-addiction groups. These are just people that come in with chronic pain who need opioid therapy. Fifty-five percent of the sample had no aberrant behavior whatsoever.

I would again venture a guess, but I suspect if we were looking at compliance data with antibiotics or antihypertensives, it would probably look similar, and we wouldn't be referring to the noncompliance as aberrant either. More than likely, just over half had absolutely no aberrant behavior.

Forty-six percent of the sample, though, did, but when their clinician were asked, only about 10 percent of the individual instances of the behavior was it thought to be related to addiction or some serious negative outcome.

So, these behaviors are frequent. Remember they come from multiple sources, so in the clinical situation, we really need to educate people, not with platitudes that there is no addiction and no bad outcomes, which I think characterized our earlier rhetoric, but by saying to them as many as nearly half of your patients will have a behavior that is off the contract somehow, your job, before you can react clinically is to sort out the meaning of that behavior.

I will also point out to you that if you look at the big-time repeat offenders, remember the AIDS patients, most of them had over five

behaviors, and those were all addicts. If you look at patients in this sample, who had five or more behaviors, it is about 10 percent, which is roughly--and if this result were repeated in a better designed epidemiologic outcome study of pain management, that is roughly the percentage of patients you would expect to have a problem with opioids based on sort of the prevalence of addiction in society at large, about 10 percent.

[Slide.]

We also did one other study that recently was published in the JNCCN where, because Lexington is a referral center for eastern Kentucky, which we heard so much about before, we went into our substance abuse unit to just characterize the patients who were coming into that setting with OxyContin abuse to just try to paint a picture of who these patients were.

195 admissions in a one-year period at the height of the epidemic for OxyContin abuse. We got SCID and other medical information on them.

[Slide.]

The OxyContin abusers, many of whom were from eastern Kentucky, were using on average 180 mg per day. Most of them had a history of other

substance abuse and non-substance abuse related diagnoses, and compared to opioid abusers who were using illicit opioids, they tended to be younger, male, and from rural areas.

I think it would be an interesting question that is too afield for right now for me to speculate on, on what is it about the sociology of rural areas that the epidemic broke out in those areas. I think understanding that--and I would be happy to talk about that later because I see a lot of patients from that area--I think is a key to understanding what needs to be done.

[Slide.]

Now, this is controversial, but of those 195 admissions to our Substance Abuse Units, 60 of those patients were begun on OxyContin ostensibly in the context of pain treatment. I have to say "ostensibly" because we don't have a lot of data on their pain treatment, we did not have that available.

We are now doing a prospective study of admissions where we are getting a lot more data on their pain treatment history, and so on. But of the 60 patients who ostensibly began using in the context of pain treatment, they were treated mainly

by primary care and other non-pain experts, they had similar medical and other demographics to other OxyContin abusers, and they were equally likely to alter the route of administration with some 13 percent of these 60 reporting crushing or injecting the tablets to abuse them.

So, it is interesting. I think when I say "similar medical and demographic features," I mean to say polysubstance abuse and probably several other risk factors that were missed perhaps when those patients were started on medicine for their pain.

[Slide.]

Back to this issue of who or what should be structured or limited, should we be limiting prescribing in general? I really don't think so, because I don't think these outcomes are that common or there is that much known about them. I think we need to study them first in the pain setting especially before we start doing restrictions that will hurt the 55 or much more percent of patients who don't misuse their medicines in any way.

But I think we can teach doctors to individualize treatment plans based on a

vulnerability assessment. Bad outcomes in pain management are probably not common enough to justify limiting prescribing especially, as Art said, when you consider the numbers with 50 million pain patients and only 5,000 pain specialists.

Instead, what I have been trying to teach doctors who come to hear me speak is that we have to structure individualized treatment plans that bring in other means of structuring and limit-setting to patients who need that.

There are basically three categories. There are uncomplicated patients, there are the middle ground of so-called "chemical copers," and then there are abusers with pain. If I were teaching doctors, I would say to a primary care doctor, these are patients you can treat alone, those you can only treat with help, and those you might have to refer out right from the outset.

I think physicians can identify these vulnerabilities and triage patients accordingly. I think that is what we need to teach. What I find ironic about right now is that we are talking about limiting and being concerned about sustained-released delivery system opioids when I think some of the problems got set in motion by the

fact that rather than teaching this, at one time we were teaching that the delivery system would do the triaging for us, that sustained-release opioids would not be abused because addicts don't really like sustained-release opioids, and I think that was misguided especially when you consider that one can circumvent delivery systems.

[Slide.]

Finally, a few hundred conclusions very quickly. Patients of all types engage in some ambiguous drug-taking behavior. Substance abuse history is associated with an increased number of aberrant behaviors and with types of aberrant behaviors.

Provision of adequate analgesia alone is probably not enough to limit aberrant behaviors in complicated patients who have a history of drug abuse.

Some of the others like needing to base opioid therapy at the outset on vulnerability assessments for addiction, and so on, I think I have already kind of mentioned, so I will stop there and thank you very much for your attention.

DR. KATZ: Questions? Dr. Portenoy.

DR. PORTENOY: Thank you, Steve, I

particularly liked that presentation because of the number of times you mentioned my name. But I do have a question.

Obviously, in trying to sort through the risk:benefit calculation and decide about the extent to which a risk management plan should be mandatory or not mandatory, to which extent it should be based on education versus restrictions, one of the big problems that we have is the huge regional differences between the abuse and negative outcomes associated with prescription drug diversion, comparing your part of the country with my part of the country with respect to OxyContin, for example, dramatic difference.

So, I guess the question is from the scientific perspective, are there any data that help sort out why that might be the case, do you have any speculations about that, and from the research perspective, are there potential factors, potential variables that haven't been assessed yet that maybe need to be assessed to try to sort out why Kentucky is a problem?

DR. PASSIK: There is not a lot of research that helps me to understand that or answer it. I do see these patients in my clinical

practice, so I have some speculations, and I am kind of glad that Congressman Rogers is gone.

I mean when you look at Eastern Kentucky, I have been there, I have worked with the doctors there, I have seen patients in our cancer clinic. It is a very isolated area. There tends to be less street drugs available there than in other areas. There tend to be less pain experts, there tend to be less psychiatric consultants for the primary care doctors to utilize.

So, you have a pain revolution that shows up in an area where there is not a lot of expertise. You also have a culture that has a tremendous amount of chronic pain because of all the coal mining and things that go on in that area.

I don't mean this in a bad way, I see these patients when they have cancer, and I have understood it to be--and cultures vary with regard to this--it is a bit of a somatizing culture with regard to they don't come in and say, Steve, I have got, you know, cancer, and I am in an existential dilemma. They say my nerves, I have got nerves, you know, they experience distress physically. So, when doctors treat that distress, I think they tend to treat it medically as opposed to

psychologically, which fits because there is no resources anyway down there.

Then, finally, it is an area of making moonshine and then growing marijuana and then selling OxyContin, so there is sort of a cultural cottage industry in escapism through pharmaceuticals, if you will.

That is all my speculation. I think, you know, it is very complicated, but I think we need to understand the sociology of areas where it is a problem and design specific risk management for those areas, and education programs for those areas, that may not apply in big city settings.

Moreover, then, I also wouldn't want to develop one that hurts the law-abiding pain patient at the same time.

DR. KATZ: Dr. Dworkin.

DR. DWORKIN: Steve, I have heard you give this talk several times, but every time I learn something new, so thank you very much.

My question is, do you have any data or are there any other data regarding the question of whether these aberrant drug behaviors are more common in patients where the provider is less knowledgeable about pain? Are they less common, as

we all might imagine in pain specialists?

Of course, the point of this question is whether education of providers makes a difference. If there are no differences between relatively expert providers and relatively naive providers in aberrant behaviors in their patients, then, it would suggest to me that maybe education doesn't make a big difference.

DR. PASSIK: That is a great question, Bob. The answer about data is I don't believe that there is, and I think the data would be hard to interpret anyway because of the fact that the more difficult patients end up in the hands of the more knowledgeable practitioners more often than not.

But I will say this. I have recently had the occasion to review a couple of papers for publication that are probably in the works now, doing sort of chart reviews of aberrant behavior in big, busy clinics that treat a lot of pain, some pain clinics, others just kind of mixed.

One of the things that is associated with aberrant behavior is dose, and when you think about that, that says to me that we have been teaching this all wrong, because if we were teaching this correctly, the clinician who was appropriately

monitoring their patient would probably reserve the highest, most unorthodox doses for the model citizens--do you know what I am saying--and that you wouldn't be escalating the doses in the face of aberrant behavior.

So, what that says to me in terms of the knowledge issue, there may be some clinicians who don't have much else to offer except to titrate up when the patient isn't acting right in any way, shape, or form.

Then, the other possibility, too, is that we may have overextended a little the pseudo-addiction notion. I think the pseudo-addiction notion is very important. It is self-effacing, it takes the burden on us to do a better job of pain treatment, and not accuse everyone of being an addict in the beginning, but I think that my data question sort of, I think to some extent, the validity of pseudo-addiction in patients who are actually acting aberrantly in some instances, like in the AIDS data.

So, you know, I think we need to teach this correctly, I think there is a role for education actually because I think you are probably right, you know, in the spirit of your question,

that there is a difference, and more knowledgeable providers will recognize the behaviors and offer alternatives.

I just think that we need to readdress how we have been teaching this.

DR. KATZ: Dr. Strom.

DR. STROM: Two questions. First, in follow-up of Russ's question. Do you see the same regional variations with alcohol abuse?

DR. PASSIK: The answer is I don't know.

DR. KATZ: Does anybody know, anybody at the table know about regional variability of alcohol abuse?

[No response.]

DR. KATZ: Next question.

DR. STROM: Second, you recommend that instead of using a restrictive approach, we should use an educational approach, and we should educate docs to base therapy on vulnerability assessments.

Is there any evidence that that leads to decreased aberrant behavior?

DR. PASSIK: No. These models have not really been tested, no. I can tell you from clinical experience, though, again, my own, and I have been involved in treating a lot of patients

who are sort of castoffs from other practices for a wide range of offenses, some because they had a history of addiction, and some not, that actually, with the appropriate limit-setting, if you know how to do that, you have the time and the resources to do it, so you have to know which patients you can treat and which ones you can't, that actually, the experience has been rather sanguine, and we have had some very good outcomes.

You know, the whole debate kind of reminds me of years ago, in psychology, when they were having this big debate between the behaviorist and the personality theorist, and Don Meichenbaum [ph], who was a big behaviorist, said something like, you know, it doesn't matter if you are obsessive compulsive or hysterical, both types of people stop their car at a red light.

I think if you know how to put the appropriate structure, you can get people pain relief. I mean I have had patients where we have doled out the medication once a day and gotten them good pain relief, but they have had to get medicine on a daily basis because they needed that much structure. The average pain practice can't do that.

DR. KATZ: Dr. Baxter, did you have a response on that regional variability of alcoholism question?

DR. BAXTER: Yes, actually, there is documented data that suggests that there is geographical variations. In fact, you will find that there is a higher incidence of alcohol use disorders in the broad category, not necessarily DSM-IV, a criteria being met in mining and other areas that are more geared towards mining. North Central Pennsylvania is one of those areas.

DR. KATZ: Dr. Bril.

DR. BRIL: Thank you for a really interesting presentation. I had two questions.

My first was I was interested in the difference between the analgesia, percentage of analgesia in the AIDS and cancer patients, and I was wondering if that was related to the mean dose of whatever opiate there was, if there was a standardization against their dose.

DR. PASSIK: The answer to that is no. The PMI doesn't take dose into account. It simply matches the potency of the analgesia to the intensity of the pain.

DR. BRIL: So, we really don't know if

they were getting a similar mean dose of opiate or not.

DR. PASSIK: That's correct, and that is an excellent question given that those were addicted patients who might very well have needed higher doses.

DR. BRIL: My next question is, how does your scheme deal with, say, nonresponders? That is about outcome, too. Just people who don't get analgesia with opiates.

DR. PASSIK: Yes, good question. Well, you know, if you think about the four A's, there are multiple variations of bad outcomes that you could see. I focused on bad outcomes only in that last, the spectrum of the last domain there. But you could have a bad outcome, be a nonresponder, and everything else would be in order, but you end up switching.

You probably would rotate opioids for a while given this heterogeneity amongst individuals that Dr. Lipman talked about, but if they truly were an opioid nonresponder, you would probably move to another class of agents or type of intervention.

DR. KATZ: Dr. Aronson.

DR. ARONSON: Thank you. I appreciated your lecture, and it was the first time I heard the four A's.

What I took away are several things, but in particular is that there is a great deal of sophistication, elegance in identifying and understanding the nature of these patients.

We speak of education. We all mention our bias of how we want that to work and aren't sure that it does, but it is a very broad breadth of definition that we probably are all having when we speak of that. So, I think we need to go a little bit further.

What constitutes enough in adequate education, is it sending a pamphlet in the mail after you fill out a questionnaire and get your CME, or is it attending a conference, or is it something that is a little bit more measurable on a metric? How would you define adequate education that we would even begin to look at?

DR. PASSIK: That's an excellent question and I am not sure that I have the ultimate answer, but I think that people who prescribe pain medicines need to be knowledgeable in the complications of prescribing those medications

including a certain level of expertise in addiction medicine depending on the population they treat, or at least addiction medicine as it is applied to the pain management setting.

You know, different places have taken this on in different ways. In California, they mandated pain education CME credits that physicians have to get. I don't know that that is the correct approach, but I mean I think at the very least--and it's hard for me to gauge what the effect of this would be because, as I said earlier, I think the rhetoric and the excitement around the revolution in pain management tended to play down these issues.

So, it is not as if we have spent the last many years as this has been going on teaching about the negative outcomes and what to do and how to recognize it. There has been an effort. Some of the pharmaceutical companies have been involved in that effort to do that up until now.

So, it is hard for me to answer that question in specifics, but I think we haven't really begun the process of teaching about bad outcomes really in opioid therapy.

DR. KATZ: I am going to ask one last

question before we move on in our schedule.

Steve, it sounds like if I heard you correctly, that there really are no validated criteria in the setting of managing chronic pain to diagnose addiction or any of the other negative outcomes that you discussed. Yet, it seemed like your presentation suggested that those are important complications or concomitants that occur in some percentage of people as part of opioid therapy.

Do you feel that validation of diagnostic criteria for diagnosing these complications is essential in the safe and effective use of opioids for managing of chronic pain?

DR. PASSIK: Yes, I do, I think we need that. I think we also need validated tools. I would not refer to the PADT as validated in any way, shape, or form. We kind of road-tested it, but we did not validate it.

We tested it our for acceptability, but it is yet to be a validated tool, so we don't have validated assessment tools for studying this problem. We don't have validated criteria. Some of us in the pain field, a lot of the psychologists, psychiatrists who do pain work have

kind of toyed with the idea, and then Steve King from New York actually went to the APA, American Psychiatric Association, to try to get them interested in beginning the field trials to develop some criteria, and as far as I know, they didn't bite.

DR. KATZ: Thanks very much.

I have got good news and bad news about our schedule, mostly bad. The bad news, first of all, we are way beyond schedule, as I think everybody who has a schedule knows. The good news is that Dr. Willis has agreed to give her presentation, which had been scheduled for 11:45, after lunch. I can also see that people are getting antsy.

So, what I would like to do now is take a two- or three-minute leg stretching break, so don't go too far, then, we have three presentations from SAMHSA, that are scheduled to go for almost an hour, so I would like to try to get those presentations started after about three minutes when people have had a chance to stretch, then, we ought to be able to break for lunch at around 12:30, 12:35.

We will begin again at 1:15 with Dr.

Willis' presentation and then have the open public hearing between 1:45 and 2:00. So, I will see you all back again in about three minutes.

[Break.]

DR. KATZ: We will now have three presentations from SAMHSA, our first presentation from Mr. Gfroerer will be Nonmedical Use of Pain Relievers: Data from the National Survey on Drug Use and Health.

Nonmedical Use of Pain Relievers: Data from The National Survey on Drug Use and Health

MR. GFROERER: Joe Gfroerer is my name. I am the director of the division that runs the National Survey on Drug Use and Health. If some of you have never heard of it, that is because the survey was renamed last year. It used to be called the National Household Survey on Drug Abuse. It has been conducted for about 30 years now.

[Slide.]

Just to give you a little background on the design of the survey, actually, it has been about the same design over the entire 30-year period with a few changes now and them. It covers the entire country, it is representative nationally and also within each state, the sample is large

enough and designed, so that we can get estimates within every state and the District of Columbia.

The population coverage is the civilian, noninstitutionalized population, age 12 and older. The data are collected using an anonymous face-to-face interview with computer-assisted interviewing.

Most of the questions, in fact, all the questions on drug use and other sensitive behaviors are done with self-administration where the respondent keys in the responses on the computer.

Questions come up on the screen and also in headphones, so that they can listen, and this is to promote privacy and encourage honest reporting.

In 2002, we had 68,000 respondents.

[Slide.]

Besides the name change, there were some other changes that occurred in the survey, most importantly was that we started paying incentives to respondents. Every person who participates in the survey is given an incentive payment. Unexpectedly, this turned out to actually affect the reporting of the various behaviors on the survey, so the 2002 data represents a new baseline for the estimates that we produce. These estimates

from the 2002 survey are not comparable for trend purposes to the earlier surveys.

[Slide.]

The nonmedical prescription drug use data that we collect is based on this definition. Of course, the survey focuses mainly on marijuana, well, it focuses on all substances, marijuana, cocaine, heroin, and also tobacco and alcohol, but there are also a series of questions on prescription type drugs using this definition, prescription drug that is not prescribed for you, or you took the drug only for the experience or feeling it caused.

This is within the context of the entire survey asking about all the other illicit drugs. So, we are not picking up legitimate use, and we do exclude over-the-counter misuse, as well as use.

[Slide.]

The way the data are collected it we focus on major categories of drugs, and what we have defined as pain relievers looks like this. It is primarily opiates, but the way we ask the questions is that we use a pillcard like this with pictures of really the most prevalent pain relievers, and use this as a memory jog for the respondent.

The main purpose is to initially identify if the have ever used any of these substances, and then if they have used at least one. Then, we go into more detailed questions about current use and frequency of use and problems associated with the group pain reliever, so we only get, for these specific drugs shown on this pillcard, we only get whether they have ever used that drug.

The way it is done here, it is also important to note that above the red line here on the pillcard, you have these three major categories, and there is a question for each of those - did you ever use Darvocet, Darvon, or Tylenol with codeine? Yes/No. So, that is asked for those three, and those three cover a large percentage of all the pain reliever abuse that we pick up.

Then, there is another question that asks if they have used any of the other pills shown on the card below the red line, and then they just check off which ones they have used, so we don't go through each of these specific drugs, all 21 drugs, and ask about whether they have used them.

So, what we have, again, this is used as a memory jog, it is not intended to provide the most

precise estimates for the use of each of these substances. We know that this method of asking about some of these drugs at the bottom of the chart is going to be giving us conservative estimates because there will be some drugs that won't be reported.

[Slide.]

Here is the estimate of lifetime use that we get from using that pillcard. You can see the top three are those three above the red line, the Darvocet, Darvon, Tylenol with 18.9 million lifetime users, and you can see the other drugs - codeine, hydrocodone, demerol, morphine, OxyContin at 1.9 million, Dilaudid at 1.1 million.

[Slide.]

Here is what the pain reliever data looked like when we put all those lifetime measures together and asked the more specific questions about use of pain relievers in general. Overall, about 29.6 million, which is 12.6 percent of the population 12 and older, have ever used any of those pain relievers nonmedically, and 10.9 million was 4.7 percent had used in the past year, and 4.4 million in the past month.

Then, we also have a series of questions

that try to get at DSM for dependence or abuse. For anybody who has used any of the pain relievers nonmedically within the past year, they go through a series of questions asking about the DSM criteria, and then we classify people as to whether they are dependent or abuse.

Here we have an estimate of 1.5 million, which is 0.6 percent of the population.

[Slide.]

Just to put that in context, here is what the dependence or abuse estimates looked like for all the substances we asked about, of course excluding alcohol, which would be way off the chart, but marijuana is at 4 million, 4.2 million, and pain relievers and cocaine are about at the same level, at about 1 1/2 million, higher than tranquilizers, stimulants, hallucinogens, heroin, inhalants, and sedatives.

[Slide.]

Now, the trends, even though I told you we can't compare to the earlier data, what we have done here is we have constructed trends just from the new data from the 2002 survey by using the responses to the questions on age at first use, so if we know that somebody has first used 10 years

ago, you can back date when they were a lifetime user and correct for their age.

So, we construct these trends based on that and it shows substantial increases in nonmedical pain reliever use. This is looking at the 12 to 17 age group and the 18 to 25 age group.

[Slide.]

Also, looking at some of the specific drugs, we can see the OxyContin trend here, which we saw up through the 2001 survey, basically doubling each year from around 200,000 up to 400,000 and then up to about a million in 2001. I wanted to show what the 2002 data looked like.

I made it a different color with a different label and put a line down the middle just to make the point that these are not really comparable, but on the other hand, none of the comparisons we have made, none of the effects of the change in the survey were this large, so I think it is safe to say that the estimate is higher or the number of users of OxyContin is higher in 2002 than 2001 although it may not be at this level doubling.

[Slide.]

Another way we can look at the trends

besides looking at lifetime use is to look at how many new users each year, how many people first tried pain relievers for the first time in that year, and here is what the trend looks like there.

There is a small dip at the end there of that curve which is not statistically significant, but basically, it does show that not only was there an increase in initiation of pain reliever misuse in the '90s, in the late '90s, but it is still at a high level of over 2 million new users each year.

[Slide.]

Now, one thing we can do to look at what the--even though we only have the lifetime use of OxyContin--if we want to see what effect, how that trend in OxyContin misuse is related to the overall pain reliever trend, and is it driving that trend, well, here, we are looking at the recent new initiates to pain reliever abuse.

In other words, on this chart here, if you look at the last three data points, those are the recent new users, and it's about 7 million people. So, we take that population and look at what other drugs they have used, and you see that most of them, 75 percent have used marijuana, 46 percent hallucinogens, 32 percent cocaine, 3 percent

heroin. Only 9 percent ever used OxyContin, so it doesn't look like, from those data, that the increase in pain reliever misuse is being driven by OxyContin use.

[Slide.]

Another way to look at it would be to look at the 1.9 million OxyContin users, nonmedical users, and just see what other drugs have they used, and you see 98 percent have used some other pain reliever nonmedically, 98 percent have used marijuana, 89 percent hallucinogens, and cocaine and heroin, as well. So, clearly, the people who are using OxyContin are coming from a group that are already using other illicit drugs.

[Slide.]

This shows that first group in more detail. Again, this is the lifetime OxyContin users looking at what other pain relievers they use, and it's across the board, 80 percent with the Vicodin, Lortab, Lorcet, and high percentages of all the other pain relievers from that pillcard.

[Slide.]

These next few slides take a look at the demographics of the OxyContin users, the lifetime OxyContin users, comparing them to the demographics

of overall pain reliever abusers. This would be the population with dependence or abuse on pain relievers on the left compared to the OxyContin users, just to look at the shape of the curve and whether there is a different population with OxyContin use.

This is certainly a similar pattern here with the younger age groups having the higher rates, but among the OxyContin users, that 18-to-25-year-old group really dominates much more than it does for the pain reliever dependence and abuse.

[Slide.]

Looking at it by gender, there is really no difference in the rate of dependence or abuse on pain relievers between males and females, but OxyContin users are more likely to be male, 1 percent versus 0.6 percent.

[Slide.]

This looks at race/ethnicity and you can see that the OxyContin users are much more likely to be white and much less likely to be black or African-American or Hispanic.

[Slide.]

This breaks it out by--it is not really

rural areas, but you are looking at, in the blue bar there, the nonmetropolitan areas, we don't have enough data to break it out into true rural areas, but it does show that the rates are about the same in the nonmetropolitan and the large metropolitan areas, but it is the small metropolitan areas, those would be metropolitan areas with less than a million population that have the highest rate of dependence or abuse on pain relievers, as well as lifetime OxyContin nonmedical use.

[Slide.]

Finally, this slide looks at the dependence or abuse on any pain reliever depending on whether the person has ever used OxyContin or not, and also Dilaudid at the bottom. You can see that of the pain reliever users who have used OxyContin, 20 percent have dependence or abuse, and only 4 percent of the other pain reliever users have dependence or abuse.

Similarly, for Dilaudid, the Dilaudid users are more likely to be dependent or abusing than users of pain relievers that did not use the Dilaudid.

[Slide.]

Just to summarize the conclusions of these

data, first of all, there is significant increases in nonmedical use of pain relievers and OxyContin in particular. The nonmedical OxyContin users are primarily coming from a population who are already abusing other drugs, and the OxyContin and Dilaudid users are more likely to have dependence or abuse on pain relievers than other nonmedical pain reliever users.

That's it. Thanks. I will take questions, I guess.

DR. KATZ: Actually, I think it would be better to hold questions until after all three SAMHSA presentations, so if I could ask people to just jot down their questions and save them for the end.

Thanks. Hopefully, you won't go too far and we can hear from you.

Our next speaker is Deborah Trunzo, who is the team leader of the Office of Applied Sciences at SAMHSA, who will be presenting Data on Treatment Admissions for Opiate Abuse.

Data on Treatment Admissions for Opiate Abuse

MS. TRUNZO: I am going to be talking about data from the Treatment Episode Data Set, specifically, treatment admissions for the abuse of

opiate analgesics.

[Slide.]

The Treatment Episode Data Set, or TEDS as we call it, consists of client-level information on admissions to substance abuse treatment. This is information that is routinely collected by states by monitor their individual substance abuse treatment systems. So, as a consequence, TEDS includes data primarily from treatment facilities that receive public funds.

TEDS is a very large data set. We get about 1.7 million admission records annually from the states, and I should add that at any given time, virtually all the states are participating in TEDS.

Selected data items from the individual state data systems are converted to a standardized format consistent across the states, and then these standardized data are what make up TEDS.

[Slide.]

The TEDS data elements include demographic variables, such as age, gender, race, and ethnicity, but the heart of TEDS is formed by the data elements on drug use. For each admission, the primary, secondary, and tertiary drugs of abuse are

identified along with route of administration, frequency of use at admission, and the age at which the client first used each drug.

The treatment variables in TEDS include the type of treatment service to which the client is admitted, whether methadone is planned as a part of the treatment, the number of prior treatment episodes, and source of referral.

[Slide.]

TEDS is sort of a strange beast and has quite a number of features and limitations that are important to understand before getting into the actual data.

First of all, it is important to be aware that TEDS is an admission-based system, it does not count individuals, so, for example, a person admitted to treatment twice within a calendar year would count as two admissions, not as one.

Despite its size, TEDS does not include all admissions to treatment. Because the data comes from state systems, admissions to federally-owned facilities, such as VA facilities, are not included, and also, as a rule, admissions to private for-profit facilities are not included.

So, in terms of absolute numbers, TEDS

underestimates the scope of the problem. We estimate that TEDS probably covers about 80 percent of the nation's substance abuse treatment admissions.

Another important factor to keep in mind is that TEDS reports on the top three drugs of abuse at time of admission. It does not include all the drugs that the client may have abused prior to admission.

Also, substances of abuse are reported to TEDS in generic categories or classes. My particular this morning or this afternoon, I should say, will be on a group of drugs in TEDS classified as "Other" opiates. By that, I mean other than heroin and other than nonprescription methadone.

This category, by elimination, consists of opiate analgesics. TEDS has some very limited data on specific drug within this group, but even so, TEDS is not able to identify specific formulations or brand names.

[Slide.]

I think for the purposes here today, it is important to realize that TEDS is not an early warning system, in fact, it is the opposite. Typically, there is a lag of some years between

first use of a substance and admission to treatment for abuse or addiction of that substance.

Unfortunately, there is also a considerable time lag between treatment admission and when we receive the admission data records from the states. This delays the release of TEDS data at the national level, so much of the data that I will be showing you in a minute is for the year 2000.

However, having said all this, TEDS data does have predictive value. The nature of addiction is a constant, so knowledge of past patterns of abuse that have led someone into treatment can be useful for assessing future risk.

[Slide.]

Now, for some of the data. As indicated by the small red sliver on this pie, admissions to treatment for primary abuse of opiate analgesics made up a very small proportion of the 1.7 million admissions to treatment reported to TEDS in the year 2000, but in terms of absolute numbers, even 2 percent represents a significant problem. This is around 30,000 admissions.

[Slide.]

In 2000, there were about 50,000

admissions to treatment where the primary, secondary, or tertiary substance of abuse was an opiate analgesic. For half of these admissions, narcotic analgesics were the primary substance of abuse. The other half represented dual addictions, such as abuse of opiate analgesics in addition to abuse of another substance. Most often this was alcohol or heroin.

[Slide.]

TEDS has been producing data since 1992, which allows us to look at trends. As shown here, the number of treatment admissions in which opiate analgesics were involved was relatively stable between 1992 and 1997, but this increased sharply in 1998, 1999, and 2000. So, the question is what is behind this dramatic increase.

Unfortunately, TEDS cannot answer this question conclusively, but the beginning of the sharp rise does follow the introduction of OxyContin. This suggests that we may be seeing the early part of the wave of OxyContin addicts. If this is the case, we would expect the increase to continue as the wave has some more time to build.

[Slide.]

The data appear to bear this out.

Although national data are not yet available for 2001 and 2002, at this time, we do have preliminary data from some states.

Five states were responsible for 40 percent of all admissions involving opiate analgesics in 1999 and 2000. These states are California, Florida, Massachusetts, New York, and Pennsylvania. These states have reported their preliminary data for 2001 and 2002. In each of these states, the dramatic increase in the number of opiate analgesic admissions continues into 2001 and 2002.

[Slide.]

The five states in the previous slide accounted for large numbers of admissions, but there may be other states where admissions for opiate analgesics are occurring at an even higher rate.

This map shows the rate of admissions involving these drugs by state for the year 1992. This year was used to set benchmarks for comparison with subsequent years.

The five red states represent the top 10 percent of reporting states' rates in 1992. In these states, admissions for opiate analgesics were

at least 24 per 100,000 population.

The brown states have rates in the top 11 to 25 percent, and the yellow states have rates in the top 26 to 50 percent. The pale yellow states are those in which the admission rate was below the median for all states combined.

[Slide.]

By 1997, rates had increased in a number of states. There are now 11 states with admission rates of at least 24 per 100,000 population.

[Slide.]

By 2000, 22 states had opiate analgesic admission rates of at least 24 per 100,000. Rates were particularly high in the New England States ranging from 75 per 100,000 in Connecticut to 150 per 100,000 in Maine.

[Slide.]

The increase in admissions involving opiate analgesics between 1992 and 2000 was much larger than could be accounted for by an overall increase in treatment admissions. In TEDS, the total number of treatment admissions increased by 15 percent during these years.

In that same period, admissions for primary heroin abuse increased by 64 percent.

Admissions for primary abuse of opiate analgesics increased by 181 percent, and the number of admissions involving any primary, secondary, or tertiary abuse of these drugs increased by 143 percent.

[Slide.]

A group of 10 states collect data on the specific opiate analgesics responsible for treatment admissions. In the three years from 1997 to 2000, treatment admissions involving narcotic analgesics increased by 49 percent. Specific drugs had increases that were much higher, 391 percent for oxycodone, 257 percent for propoxyphene, and 172 percent for hydromorphone.

[Slide.]

The characteristics for admissions of abuse of narcotic analgesics did not change much between 1992 and 2000. Just over half were male, and over 80 percent were white. About three-quarters were 30 years old or more. Referral to treatment through the criminal justice system was relatively rare as most admissions were self-referred.

The major change between 1992 and 2000 was the substantial increase in the proportion of new

users of opiate analgesics, and we define new users as those entering treatment within three years of first use. The proportion of new users increased from 27 percent in 1992 to 41 percent in 2000.

[Slide.]

This slide compares for the year 2000, all admissions involving opiate analgesics and new users of opiate analgesics. Their demographic characteristics are similar with the exception of age. The new users are younger, 12 percent are under the age of 20, and 40 percent are under the age of 30.

[Slide.]

As mentioned before, in 2002, treatment admissions involving opiate analgesics were overwhelmingly white.

[Slide.]

In this slide, 1997 admissions are depicted by the green line, and 2000 admissions by the red line. The number of admissions involving opiate analgesics increased for all ages during the three-year period, but the largest increase was among young people.

[Slide.]

This slide shows the same information by

sex from 1997 to 2000. There were increased numbers of both male and female admissions involving opiate analgesics. The increase was especially pronounced among young men.

[Slide.]

Finally, this slide shows the trend in median duration of use before first treatment in the five large states that I had mentioned earlier, that is, California, Florida, Massachusetts, New York, and Pennsylvania.

Between 1997 and 2002, the time between first use of opiate analgesics and admission to treatment for abuse of these drugs had declined by half. In 1997, the median duration of use before treatment was eight years. By 2001, it was only four years.

Contrast this with earlier years in which the median time before treatment was 10 years. Again, the question is raised what are the causes of this shift in behavior amongst abusers of opiate analgesics, and again, a plausible hypothesis, given other evidence, is that OxyContin may be a factor.

That is all that I have to present this morning. Our 2001 report with national data will be

coming out shortly, and I encourage you all to check out the SAMHSA web site, click on Statistics and Data, and you will find more information on TEDS and the specific states that are involved.

Thank you.

DR. KATZ: Thank you very much.

Once again, we will just hang onto your questions until the end of the next presentation, which will be by Dr. Judy Ball, who is the team leader of the Office of Applied Sciences at SAMHSA who will be presenting Opiate Abuse Data for us.

Opiate Abuse Data

DR. BALL: I am not going to go through much of the methodological detail that was provided in your briefing book in the interests of time. I am, however, going to talk today about immediate- and sustained-release opioid analgesics as shown in the DAWN data.

[Slide.]

All of the findings that I am presenting today will come from the national probability sample of hospitals. In 2002, we had 437 hospitals that participated in DAWN. It's a representative sample of hospitals for the 48 states. We also collect data on drug abuse related deaths that are

reviewed by medical examiners and coroners. That is not a national database, and I will not be presenting any of that information today.

[Slide.]

DAWN cases, it is important to remember that a DAWN case is a patient who is between the age of 6 and 97, who was treated in the emergency department. The visit is related to drug abuse, and that is defined very narrowly as the patient intended to use the drug for dependence, or psychic effects, or for suicide attempt or gesture.

During the period of the data I am showing you today, DAWN did not collect anything that did not meet this narrow definition of drug abuse.

[Slide.]

The drug detail in DAWN is quite varied. We collect data on illicit prescription and over-the-counter drugs, but the specificity of that drug information is dependent on what is contained in the medical record. So, sometimes we get brand names, sometimes we get chemical names, sometimes we get generic, sometimes we only get classes of drugs, and that is a particular challenge in looking at the opiates for this presentation.

The drug mention is simply a unit of

measurement for individual drug. Most visits involve more than one drug, 1.8 drugs on average. So, each individual report of a drug is referred to as a mention.

[Slide.]

To put the opiate data into context, this chart compares estimates for 1994 and 2002. The 2002 bar is the pink one, 1994 is the gold one. This shows that the opiates, the top set of bars there, other than heroin, grew 2.7 times over this nine-year period. Marijuana, the third set down, grew nearly 3 times, but cocaine, heroin, and the benzodiazepines grew less than 50 percent over this time period.

The bottom line is that by 2002, the opioids were as frequent in emergency department visits related to drug abuse as heroin or marijuana, but they were less frequent than cocaine.

[Slide.]

This shows you a breakdown of the opiates and opioids in DAWN. Thirty-five percent of the mentions are due to an unnamed ingredient. Virtually all of these are reported to DAWN simply as opiates. It is very likely that this is

information that is coming from laboratory tests that may not have had confirmatory testing.

The four named opiates that we are focusing on today, hydrocodone, oxycodone, morphine, and fentanyl make up about 44 percent of mentions of opioids, and the other 21 percent come from the various others, codeine, and so forth.

[Slide.]

Now, for this analysis, we can break the various opioids down into those that have immediate release type, sustained release types, and, of course, in DAWN, we always have to contend with the types that are unspecified.

So, for the unnamed, for example, they would always be unspecified. Hydrocodone or hydromorphone, because they only occur in immediate release products, can all be classified as immediate release, but fentanyl, morphine, and oxycodone can be divided between immediate release products, sustained release products, and those products that were reported to us without specifying the formulation.

[Slide.]

So, to look at trends for each of these groups, we will first look at the unnamed opiates,

which are, in fact, the most frequently reported opiate, but we can't ignore them because they are the most frequent.

Over the nine years, there was 400 percent increase, and we have seen a one-year increase from 2001 to 2002 of 31 percent.

[Slide.]

For hydrocodone, which is available only in immediate release forms, it is the second most frequently reported opiate in DAWN. In 2002, there were over 25,000 mentions, and the nine-year increase in hydrocodone was 170 percent. The recent increases from 2001 to 2002 are fairly moderate at 17 percent. The two-year increase from 2000 to 2001 was 25 percent.

[Slide.]

Hydromorphone. These numbers are much smaller. Where we were talking in the tens of thousands previously, now we are talking in the individual thousands. You will see that for hydromorphone, I do not have an estimate here for 2000, 2001, or 2002.

The reason is that the relative standard errors on these estimates--don't forget these are all estimates that are produced from sample

data--so there is sampling error surrounding all of the estimates.

Estimates for these three years for hydromorphone had relative standard errors that exceeded 50 percent. That, in essence, means that the estimate may not be significantly different than zero, so we do not report them because we don't trust them.

The other years that you see here, there is still a fair amount of variation. Only two years, 1995 and 1996, had relative standard errors below 30 percent, so there really isn't a whole lot that we can conclude from the hydromorphone estimates.

[Slide.]

Fentanyl. It does have an immediate and a sustained release product, but the numbers in DAWN are such that if we break them apart, we run into precision problems, so they are all combined here, all different types.

What we see with fentanyl is an interesting pattern. From 1999 to 2001, that two-year period, we saw more than a doubling in mentions, and then in the last two years, 2001 to 2002, we see another more than doubling, but the

numbers here are so very small, the estimate in 2002 is 1,506 mentions. It is really quite tiny.

[Slide.]

For morphine, again, there is an immediate release, there is a sustained release, but when we break them apart, the estimates aren't precise enough to present, so this is all types.

Morphine has been behaving quite differently than the other opiates in emergency department mentions. We do see a significant increase of 126 percent. That is more than doubling from 1996 to 1998, a 71 percent increase from 1997 to 1999, but in recent years, although the bars look like they are different heights, those are not significant differences. Those variations that you see there are within the margin of error.

[Slide.]

Now, for oxycodone, the numbers are large enough that we can, in fact, split them into immediate release, sustained release types, and types unspecified, and this is the first set of bars for the types that are unspecified.

The numbers are fairly low. I was actually surprised when I looked at this at how low

they were. You don't see a bar in 1995 because the estimate had a relative standard error of greater than 50 percent, but the other years, the estimates are within reasonable ranges.

We do not see an increase when we look at the last two years, from 2000 to 2002, or 2001 to 2002. The only significant increase we see in these actually occurs between 1996 and 1998.

[Slide.]

For the immediate-release types of oxycodone, the numbers here are considerably higher than the unspecified ones. We do see a significant increase from 1996 to 1998 of about 37 percent, another significant increase from 1999 to 2001 of 59 percent, but the estimates for 2000, 2001, and 2002 are essentially stable, there are no significant differences there, and this is all of the immediate-release types of oxycodone.

[Slide.]

For sustained-release types, this is largely OxyContin, the OxyContin was first approved I believe in 1995. We saw the first mention in DAWN was actually in 1997, but the numbers were so small, you can't see them. Since then, the increases have been quite dramatic.

By 2002, we see over 14,000 mentions of sustained-release oxycodone in DAWN nationally, and the one-year increase was 41 percent. The two-year increase, though, is quite shocking because it's over 400 percent, but we are also talking about starting out with numbers that are very small. When you are working with small numbers, you get really big percentage increases very easily.

[Slide.]

So, if we put the three types together for oxycodone, the trend looks like this. Here again, the sustained-release is the yellow, the intermediate-release is the pink, the unspecified types, the blue.

The nine-year increase overall is about 450 percent. The one-year increase actually here between 2001 and 2002 is not significantly different, and it is because of the modulating effects of the immediate-release here, but we do see a doubling in mentions over the past two years, between 2000 and 2002.

The total number of mentions in 2002 for oxycodone here is over 22,000 mentions, and since 1998, we have seen a doubling every two years in those mentions.

[Slide.]

This is going to show you the proportions across time as the sustained-release versions of oxycodone have become more prominent. It starts out at zero in 1997 and goes to 63 percent of all the oxycodone mentions by 2002.

[Slide.]

My colleagues have talked before about the issue of multiple drug abuse, and we certainly see the same in DAWN. I took all of the DAWN episodes that involved a mention of the four major drugs that we are looking at here - fentanyl, hydrocodone, morphine, and oxycodone.

I didn't do the hydromorphones because of the precision problem, and looked at these in terms of visits, not in mentions, and then looked within the visit that involved one of these index drugs of what other drugs were there.

The findings were quite interesting. We find that the fentanyl numbers are a little different, but we see quite consistent patterns for hydrocodone, morphine, and oxycodone. More than two out of three of the visits involving one of these drugs also involved other drugs.

A large share of them, about 4 out of 10,

involved a major substance of abuse, and "major substance of abuse" in DAWN lingo are the standard alcohol, cocaine, heroin, marijuana, amphetamines, methamphetamines, and the less frequent drugs of abuse, such as the club drugs Ecstasy, JHB, and so forth.

We also see that there is a moderate share, we see here 13 to 26 percent of visits involving these drugs also involve a benzodiazepine, and then when I actually looked at these drugs and then looked to see if there was more than one opiate in the particular visit, I find a surprising number, from 14 percent to 27 percent of the visits involving these drugs also involve another opiate.

So, the idea of the polysubstance abuse that comes out in each of these data sets, I think is really quite remarkable and confirmatory.

[Slide.]

Let me remind you again the limitations of the DAWN data that we are looking at here. These are reportable cases of drug abuse based on the patient's intent as documented in the medical record. Patients are never interviewed, so this information has to be gleaned from a retrospective

review of charts.

We do have variable reporting of nonspecific terms, and it is possible that a chart could indicate that a patient took OxyContin, and they took some other form of oxycodone. How many times have you heard people misuse the two terms? That is possible, and it is not something that we can quantify.

It is also not possible to distinguish from these data, diversion versus abuse of these drugs from people who have legitimate prescriptions, it is simply not possible, and for the period of time that these data cover, we actually collected, except for knowing that the person was in the emergency department for some treatment, we don't have any information about the health condition that brought them there.

I am happy to say that starting in 2003, we are correcting that and making headway on many of these other limitations, as well.

Thank you. I will be happy to take our questions, as will my colleagues.

DR. KATZ: Thank you, Dr. Ball.

Let's go ahead and take questions. Dr. Shafer, you had one from before. Do you still have

a question?

DR. SHAFER: This is a question for Ms. Trunzo. You showed us data that use of narcotic analgesics from 1997 to 2000 had gone up 49 percent, and then specifically, cocaine had gone up 71 percent, hydromorphone 172, oxycodone 391 percent, but I didn't see anything going down, and all of the individual components have gone up much more than 49 percent.

So, my question is what went down during that period of time?

MS. TRUNZO: That is a fair enough question. There is a large component of "Other," other opiates that we can't sort out, we don't know what has gone into that pot, but amongst the ones, the specific ones that are identified, they had gone up, the oxycodone and hydromorphone and propoxyphene had gone up the amounts that I had said.

But in terms of numbers, the ones in the "Other" category far outnumber the ones that we can't identify in the "Other" category are by far in the largest pot, so the average then is brought down to 49 percent overall.

DR. SHAFER: So, some of the increase is

then just simply reclassifying "Other" into these other categories.

MS. TRUNZO: Yes, right, it is a small portion of the total "Other."

DR. KATZ: Dr. Strom.

DR. STROM: I think between what we heard in the first of the presentations and what we heard before from the Office of Pharmacoepidemiology have the answers to the question I asked earlier, but I want to nail that down to be sure.

If I understood correctly, it sounds like the proportion of all of the drug abuse underway in terms of lifetime nonmedical use which is due to modified forms of opiates is actually very small and most of that is associated with polydrug use.

Another way of look at it is proportion of prescriptions. So, of the prescribed drug, what proportion ends up being misused, and if I understood these numbers correctly, that may be fairly high.

The question is really to Mr. Gfroerer and Dr. Rigoni to make sure I have got the numbers right. If I understood the numbers correctly, basically, there is roughly 2.5 million new users each year of nonmedical use of pain relievers in

recent years. Roughly 10 percent of that would be OxyContin, so that is about 250,000 people.

The total number of new prescriptions for OxyContin in the recent year was about 6 million. Even assuming that the average person on the drug got two prescription, that drops it down to 3 million. That is 250,000 divided by 3 million or were approaching 10 percent of the prescriptions are associated with nonmedical use.

Are those numbers correct?

DR. KATZ: Who wants that one?

[Laughter.]

MR. GFROERER: I certainly can't speak to your data on prescriptions, but the numbers that you cited on the OxyContin and the nonmedical pain reliever use were correct, about 2 to 2 1/2 million new users each year. Now, we don't know how many of those were OxyContin new users. We can't tell which was used first, whether they first used OxyContin and then moved on to other drugs.

We only know that of those 7 million new users within the past three years of the pain relievers, about 10 percent, well, I think it was 9 percent had ever used OxyContin. In total, about 1.9 million have ever used OxyContin nonmedically.

DR. STROM: So, that 9 percent, because it comes from lifetime use, and given the time trends we are seeing, might actually be an underestimate if we had data available from 2001 as opposed to lifetime use.

MR. GFROERER: It is 9 percent of the new users, not 9 percent of all lifetime, because there is 29 million lifetime nonmedical users. It is only those 7 million are the recent new users, and 9 percent of those had used OxyContin.

DR. STROM: So, then, of the 250,000 users--

MR. GFROERER: I don't have that number. What is the 250,000?

DR. STROM: I was looking at your graph before that and it was roughly 2 1/2 million new users and roughly 10 percent of those, 9 percent.

MR. GFROERER: Over the three-year period, those 7 million new pain reliever users, nonmedical users, 9 percent, which would be about 700,000 ever used. I don't know that it was 250,000 each year.

DR. STROM: These are close enough as approximations, I am just changing it to annual numbers, so that it is roughly 250,000. What are the total number of ideally newly prescribed

patient getting OxyContin each year? As far as I can tell from the NPA data, it looked like there were 6 million prescriptions.

MR. GFROERER: I can't answer that one.

DR. RIGONI: Because the DEA does scheduled opioids, every prescription would be kind of representative of a new patient to therapy, so it is hard to tell from the NPA data because it's not longitudinal how many people are actually new to opioid therapy, because everyone would be new.

DR. STROM: How about from the NDTI data, though, you could tell what proportion of prescriptions are new versus refills?

DR. RIGONI: Technically, no, because there are no refills for Schedule II opioids, so they wouldn't be counted as refills, they would be all counted as new prescriptions.

DR. STROM: But my 6 million is a correct read of your data there?

DR. RIGONI: Right, and also it is kind of hard because it is comparing apples and oranges, where we have medical use of opioids and NPA data, and they are actually finding out about nonmedical use of opioids, so it is kind of hard to compare.

DR. STROM: But it sounds like my

calculations are correct, that given OxyContin is a chronically used drug, if there are 6 million prescriptions written for it in a recent year, if you even assume the average person got two prescriptions, which may be an underestimate if a lot of these people are on chronic therapy, then, you are talking about 3 million users in that year, new users, sorry, users in that year, and you are talking about 250,000 people who used it for nonmedical purposes to compare that to, comparing the two data sources.

DR. RIGONI: I guess I would have to look at more longitudinal data to see if that is correct, two prescription per year assumption, but I don't know that off the top of my head.

MR. GFROERER: Just to follow-up, though, in terms of the 250,000 calculated new users, those people could be users the next year. The new use doesn't mean that is the only year that those people used, so they could be users the next year and the year after that.

DR. ARONSON: I have a question for Ms. Trunzo and I promise you it won't involve numbers.

I noticed on your graphs that there is clearly a regional difference in the absolute

number of admissions to the treatment and episodic data set. Was there an equal, if you will, propensity of increase over the years even though the absolute number was different? Did you see a regional difference in the change, if you will, the slope of increase over the years?

MS. TRUNZO: I haven't looked at that.

DR. ARONSON: The reason I ask is that you showed a graph where you mentioned the narcotic analgesic admissions in some states.

MS. TRUNZO: Those were rates.

DR. ARONSON: I noted that California was particularly flat relative to the other states on your graph. Can you speak to that?

MS. TRUNZO: Only to say that their rate probably has remained stable as indicated in the graphic, however, I included that their preliminary data in the slides for 2001 and 2002 because they account for such a large number of admissions.

DR. ARONSON: The corollary to that, and it's an observation I had with some of my colleagues during the break, was that California, I would note, has enacted some educational, if you will, linkages to pain management to their CME expectations, and I just wished to make that

observation.

MS. TRUNZO: As I also said in terms of discussing TEDS' limitations, it does not include all admissions, and the proportion of admissions that it might include would vary from state to state depending on the individual system, so it is possible that in California, some of the admissions are not being reported to TEDS that might affect the rates had we known about them.

DR. KATZ: Dr. Portenoy.

DR. PORTENOY: I guess I am coming at this from where Dr. Strom is coming at it and just trying to understand it, because we have had the marked increase in the medical use of controlled prescription drugs in the last few years, which some of us who do pain management think might be a good thing given the base rate of undertreated pain.

Clearly, the data together suggest that there has been an increase of abuse and the adverse outcomes associated with abuse, and it is a whole lot of numbers. I mean I did try to focus and I probably absorbed about 3 percent of them, and I am just trying to understand you who work with the numbers all the time if you could help us interpret

what we are looking at in terms of the change over time in the abuse indicators that you all work with given the limitations with respect to this issue of change in controlled prescription drug abuse and adverse outcomes.

It is obviously a noticeable change, the graphs all changed, the curves are all going up, but have we seen historically other drugs that look like this? Is there some sense, regionally speaking, that it is linked to where the largest increases of controlled prescription drug for medical purposes is happening? Is there any way of interpreting these data other than just a conclusion that, yes, at a time of increasing medical use, you are also seeing some increased abuse, which is like no surprise?

MS. TRUNZO: I will speak first for TEDS. Changes in TEDS tend to occur very gradually, so whenever we see a sharp increase, I think that something real is going on there, however, as Judy mentioned in her presentation, other opiates represent a very small percentage of TEDS' admissions, so the numbers are small. So, therefore, it is easy to see a large percentage increase when there is an increase in the numbers.

However, you know, the trend has been consistent since 1997. It's not going like this that might make you think some sort of error was creeping in.

DR. PORTENOY: Just to follow up on that, is there any way from the data to sort out the difference in the adverse outcomes that would originate from diversion, diversion to the illicit market versus what is actually being prescribed by doctors speaking to Brian's point?

MS. TRUNZO: No, we can't do that.

DR. KATZ: Dr. Maxwell.

DR. MAXWELL: This is a little bit off topic, but there was one thing in Mr. Gfroerer's presentation that caught my eyes, because often we don't associate hallucinogen use with the use of other opiates, but the National Household Survey is showing 89 percent of the OxyContin users also used other hallucinogens.

Did you break out which hallucinogens are most associated with it? This is kind of an interesting change in who is using it. It's club drug users?

MR. GFROERER: Well, I don't have that data. It is possible to look at that, though, we

could look at the specific hallucinogens and see which ones are associated with OxyContin, but I don't have it now.

DR. KATZ: Dr. Gillett.

DR. GILLETT: Thank you. It strikes me that veterans are rather ignored here. They are either institutionalized and excluded or somehow not counted, and I was curious as to how you tapped into that population, which has a history of drug abuse and other issues critical to their health.

MS. TRUNZO: In TEDS, admissions to Department of Veterans Affairs facilities are excluded, however, the data might include veterans who were receiving treatment at state-funded facilities. They weren't broken out in my presentation although we could do that. There are quite a few veterans in the TEDS database, but the federally-owned facilities simply aren't part of it.

DR. GILLETT: Along that same line, how does that work with rural communities which are not served by emergency rooms, do we undersample, underreport, ignore, what?

MS. TRUNZO: I will turn this over to Judy in a minute. TEDS, as a rule, does not include

emergency rooms, it includes specialty treatment facilities or substance abuse treatment units within a hospital.

DR. BALL: The DAWN sample of hospitals is designed, so that we can produce estimates for the nation as a whole, and we have oversamples in 21 major metropolitan areas that we can produce estimates for each of those areas.

The challenge of collecting data on drug abuse in rural areas, and certainly Joe can probably talk about even more than I, but basically, it is not feasible for us, given the constraints of budget, to produce rural estimates from emergency department sample in DAWN.

Rural areas are included in the national estimate, but all the metropolitan areas are, as well. One of the ways that we are beginning to try to get a handle on this is on the medical examiner side of DAWN, that the medical examiner data, too, has been sort of skewed toward metropolitan areas in the past.

We have begun an initiative to bring on some statewide medical examiner systems, and many of these come from states that have substantial rural populations, so we are sort of looking at the

state initiative as a way of trying to get some comparable data on drug abuse in rural areas, and that is beginning this year.

DR. KATZ: Thanks, everybody, especially our colleagues from SAMHSA for pitching in right before lunch.

Two announcements before we adjourn for lunch. First of all, we will regroup here at 1:45 to start the afternoon session. Secondly, any speakers for the open public forum, please, as we begin our afternoon session at 1:45, situate yourselves here in this seating area to my left, so that we can bring people up and down relatively efficiently when we get started.

Thanks, and I will see you at 1:45.

[Whereupon, at 1:00 p.m., the proceedings were recessed, to be resumed at 1:45 p.m.]

A F T E R N O O N P R O C E E D I N G S

[1:50 p.m.]

DR. KATZ: While the slides are being queued up, let me introduce Dr. Elizabeth Willis, who is the Chief of the Drug Operations Section of the Drug Enforcement Administration, and she will be addressing us on Diversion of Prescription Opiates.

Diversion of Prescription Opiates

DR. WILLIS: Good afternoon. I would like to thank this committee for the opportunity to address you regarding DEA's concern on the control of opioid pharmaceuticals and our specific concern with the diversion of high-dose, single-entity prescription opiates.

The Controlled Substances Act of 1970 assigned the DEA the legal authority to regulate controlled substances. Through this legislation, DEA is mandated to prevent, detect, and investigate the diversion of legally manufactured controlled substances, while at the same time, ensure that adequate supplies are available to meet legitimate domestic medical and scientific needs.

The CSA established a closed system of distribution of controlled substances that requires

the registration of all handlers of these drugs including manufacturers, distributors, importers, exporters, pharmacies, and practitioners.

Production quotas, as well as recordkeeping and security requirements, are designed to enable DEA to track and safeguard potentially dangerous controlled substances as they are transferred from the manufacturer to the ultimate user.

However, despite these controls and our best efforts, the diversion and abuse of pharmaceutical controlled products continues to pose a significant problem. New, higher dose, single-entity products, particularly opiates, are of particular concern given our experience with OxyContin.

For the sake of clarity, DEA defines diversion as the movement of a controlled substance from the legitimate distribution chain into the illicit market.

Why are prescription drugs so popular with the drug abusing population? There are several reasons for this. Number 1 is quality and quantity. Abusers know that prescription drugs are manufactured under strict government control. They

know the drugs do not contain adulterants or contaminants, and they know the exact dosage they are taking. These assurances are not available on street drugs.

In addition, the amounts of the drug found in the new high-dose opioids makes these drugs particularly attractive to narcotic addicts.

Second, there is the belief that if my doctor prescribed it for me, it can't be bad, and most often this is true as there is no question that pharmaceutical drugs are beneficial when used appropriately. However, care must be taken that the right patient gets the right drug at the right time and in the right dose in order to ensure its efficacy.

Also, there is the belief that if the user does not inject the drug, he is not truly a drug abuser. In U.S. society, the stigma of being an I.V. drug abuser often does not carry over to those who swallow a pill.

There is also the cost. When controlled substances are obtained via a prescription, oftentimes the cost is covered by health insurance or by Medicaid, which makes the cost to the user minimal. However, on the street, pharmaceutical

controlled substances command a very high price and this encourages the diversion of these drugs.

Sometimes the abuser will turn to prescription drugs when street drugs are not available, or they will use prescription drugs in combination in order to potentiate the effect of street drugs.

Finally, prescription drugs are readily available and distributed through open commercial markets unlike street drugs, which are distributed through a series of illegal and underground trafficking networks.

Today, the vast majority of diversion of controlled substances is at the retail level, which includes diversion by practitioners and pharmacists and consumers. The means used to divert prescription opiates are those typically used by diverters of all pharmaceutical controlled substances and include illegal and indiscriminate prescribing by practitioners. This includes the four D's previously referred to as the doctors who are duped, dishonest, disabled, and dated.

There is also illegal dispensing by pharmacists. Pharmacy theft is another common method of diversion including armed robbery, night

break-ins, employee theft, and customer pilferage. There are forged and fraudulent prescriptions.

There are patients who go to doctors claiming false medical needs. There are doctor shoppers who travel from doctor to doctor looking for an easy mark who will readily write prescriptions or who can be duped by false medical records and illnesses.

There is foreign diversion and the subsequent smuggling into the United States. There is also in-transit theft of controlled substances during the transportation process from the manufacturer to the retail pharmacy. In fact, during this past year, we have experienced several armed hijackings of entire tractortrailers of controlled substances. This has been a rather unusual event and one that we are particularly concerned about.

There is also distribution through the internet. Many internet web sites advertise and sell controlled substances with little or no oversight to encourage or ensure that the drugs are being used for a legitimate medical purpose.

In order to keep abreast of diversion trends, the DEA Office of Diversion Control gathers

information and intelligence from several sources. The DEA's automated reports and consolidated order system, known as ARCOS, was developed to monitor and maintain current and historical records of selected controlled substance inventories and transactions from the point of manufacturer to the point of retail sales where it is dispensed to the ultimate consumer.

The DEA gathers drug exhibit data from state and local forensic laboratories through the National Forensic Laboratory Information System. Intelligence is also gathered from other federal agencies, state and local counterparts, and regulatory agencies.

In addition, the DEA is alerted to possible illegal activities and abuse by family members, local law enforcement, and state authorities. Through these sources, DEA finds that while there are some unique drug trends in each geographic area, overall, the abuse and diversion of controlled substances is consistent throughout the country.

I would now like to take this opportunity to identify for you some of the prescription opiates that DEA finds to be commonly abused and

diverted. In many of these cases, these drugs are abused in combination with each other and with other types of controlled substances, such as benzodiazepines. This polydrug abuse makes successful treatment even more difficult and contributes to overdoses and death.

Historically, DEA has found that the immediate-release opiate products of hydrocodone, hydromorphone, and oxycodone are among the most diverted prescription drugs. Once diverted from legitimate channels, these drugs can be used as a substitute for illicit narcotics and are frequently trafficked on the street by individuals and structured organizations.

The costs of purchasing these prescription drugs on the illicit market vary from drug to drug and from geographic area to geographic area. Most often, recognizable brand names are preferred over generics and command a higher price on the street.

Hydromorphone has been one of the most diverted and abused prescription opiates for the past 30 years. Hydromorphone 4 and 8 milligram tablets are the most subject to diversion and abuse. As far back as the 1970s, Dilaudid has been known on the street as "drug store heroin."

Current street prices for a single 4-milligram Dilaudid tablet, the most preferred strength, range from $5.00 in the Milwaukee area to as high as $80 in Richmond, Atlanta, and San Diego. The nationwide average price for a single 4-milligram Dilaudid tablet is $40 per tab.

Oxycodone immediate-release combination and single entity products are also very popular among the narcotic-abusing population. The most common and popular combination oxycodone products are Percodan, Percocet, and Tylox. Diversion of these products occurs in every area of the country and the street price runs between $10 and $30 per tablet.

For the last three years, DEA's National Forensic Laboratory Information System reported oxycodone and hydrocodone account for approximately 70 percent of all narcotic analgesic drug exhibits analyzed by state and local forensic labs.

The DEA Quarterly Reports indicate that hydrocodone products are the most sought after licit drugs and are diverted in every geographic area of the country with street prices averaging around $5.00 per tablet.

As a group, hydrocodone products are the

most prescribed and the most diverted of the opioids. Because they are Schedule III controlled substances, hydrocodone can be telephoned in to pharmacies and can be refilled, so they have a higher association with doctor shopping and fraudulent prescriptions.

The most popular brand names of hydrocodone products diverted include Lortab, Vicodin, Lorcet, and Tussionex. Because there is a steady increase in abuse and diversion of these products, DEA is currently reviewing hydrocodone drug products for possible control status change from Schedule III to Schedule II.

The new generation of high-dose, single-entity controlled-release products, or sustained-release products, such as MS-Contin, Duragesic, and OxyContin pose special problems for law enforcement.

The problems associated with OxyContin have been particularly devastating. OxyContin is a valuable and efficacious drug when used properly, however, the abuse and subsequent diversion of OxyContin has increased dramatically since its introduction into the market.

Once word of this product made its way to

the street, its popularity skyrocketed. DEA has never witnessed such a rapid increase in the abuse and diversion of a pharmaceutical drug product, and we believe there are a number of reasons for this.

OxyContin is marketed in 10, 20, 40, and 80 mg tablets. While the higher dose of active ingredient facilitates continuous and effective pain relief, it also makes the product more attractive to drug abusers. In simple terms, the drug abuser gets more bank for his buck by buying one OxyContin 80 mg tablet than in one Percodan tablet containing 5 mg of oxycodone.

Put another way, the abuser would need to take 16 Percodan tablets to get the same effect or the same quantity of narcotic as found in one 80 mg OxyContin tablet. In addition, when the sustained-release formulation is compromised, the entire dose of active ingredient is released at one time, thus creating a potent narcotic high. This immediate release of the active ingredient can have deadly consequences for opiate-naive users whose bodies have not developed a tolerance to the narcotic.

The DEA also believes that the original marketing of OxyContin contributed to its abuse and

diversion. OxyContin was promoted to a wide range of medical specialties for a variety of indications. Many of the physicians were family practitioners and internists, not all of whom were trained in pain management regarding the proper use of such a high dose narcotic.

Because OxyContin contains the active ingredient oxycodone, it was frequently equated with other products such as Percodan. But as stated before, OxyContin contains 2 to 16 times the dosage of oxycodone as Percodan. The effects of taking such a potent narcotic were not fully recognized by either physicians or consumers.

Problems with OxyContin occurred relatively soon after its initial marketing.

[Slide.]

By the year 2000, DEA noted a dramatic increase in the illicit availability and abuse of OxyContin. By mid-2001, OxyContin reached record levels of diversion and abuse. Initially, diversion was noted in rural areas of the eastern United States, particularly in parts of Appalachia and New England.

It very quickly gained popularity among prescription drug abusers, and it was not long

before OxyContin abuse and diversion spread to other parts of the country including South Carolina and Florida.

While at first the abuse and diversion of OxyContin seemed to remain east of the Mississippi River, within the past couple of years, DEA has seen an increased diversion spread into western parts of the country including Alaska and Hawaii.

Street names for OxyContin include C, OC, Ox, and Execution. Drug abusers quickly found the means to compromise the time release mechanism of OxyContin by removing the coating or by crushing the tablet which allows for the complete dose of oxycodone to be administered at one time by swallowing, injecting, or snorting.

Its abuse has led to an OxyContin subculture with the manufacturer's promotional items often found for sale on E-Bay.

[Slide.]

In one DEA investigation, a defendant was found to have this tattoo on his arm. When asked what the tattoo stood for, the defendant stated that by taking an 80 mg and a 40 mg tablet together just one time, the user would be hooked for life and his life would be hell.

DEA field offices report that the 40 mg OxyContin tablet is the most popular dose sold on the street and that all dosages sell for an approximately $1.00 per milligram.

Methods of diversion of OxyContin run the full spectrum of those previously identified. Illegal and indiscriminate prescribing by unscrupulous medical professionals, doctor shopping, and forged prescriptions are common methods of diversion.

DEA investigations have also uncovered organized rings of individuals obtaining OxyContin by fraudulent means of doctor shopping or prescription forgery. Oftentimes these individuals use some of the drug themselves and then sell the remainder on the street to cover their own drug habits.

Other investigations have found drug organizations that traffic in illicit street drugs, such as cocaine and Ecstasy, are now also trafficking in OxyContin.

In South Carolina, a group of seven physicians was investigated and indicted for the illegal distribution of OxyContin. The investigation found that patients would wait up to

four hours to see one of the physicians who would write prescriptions for OxyContin for nonmedical reasons. Patients traveled from all parts of South Carolina and from out of state in order to get their OxyContin prescriptions.

The prescriptions were then filled in nearby pharmacies and taken back to local communities where they were sold on the street. The DEA determined that the physicians diverted in excess of 1,080,000 tablets of OxyContin.

As a result of this investigation, the physicians are currently awaiting sentencing for the illegal distribution of OxyContin. Regrettably, one doctor was so despondent over his involvement that he committed suicide.

When interviewed by the DEA, the primary target and owner of the clinic said that his only goal in the operation of the clinic was to make as much money as possible without getting caught. He admitted that all he and his colleagues did was distribute narcotics.

His hiring process started with seeking out desperate and willing doctors for job placement and he instructed the placement agencies to only refer those doctors who would write large amounts

of narcotics.

His pain protocol was that everyone coming to the clinic would receive a narcotic and if the patient did not want narcotic, they could go elsewhere. The clinic also had a "don't ask, don't tell" policy about histories of drug abuse and patients were deliberately not asked if they had drug problems.

[Slide.]

The chart on the screen shows the distribution of OxyContin in the State of South Carolina for the years 2000 to 2002. While DEA cannot avow that the drop in OxyContin distribution wa due solely to the closing of this clinic, it is interesting to note the sharp decline beginning in June 2001, the same time that the clinic was shut down.

In many parts of the United States, thefts of OxyContin through armed robberies and night break-ins of pharmacies have increased over the past three years. The violence typically surrounding armed robberies is of particular concern to DEA and other law enforcement agencies.

In the year 2000, DEA received reports of 43 armed robberies of pharmacies nationwide where

OxyContin was taken. In the year 2002, there were 277 such armed robberies. Particularly hard hit has been the State of Massachusetts, where almost 250 armed robberies were reported in an 18-month period.

Due to the large number of robberies throughout the state, many of the pharmacies in Massachusetts discontinued selling OxyContin. Others hired armed security guards to patrol their premises during business hours.

The pharmacies were not the only targets for armed robberies. In one particularly heinous incident, two armed men entered a nursing home in Massachusetts at 1:30 in the morning. They held 6 nurses and 40 patients at gunpoint and demanded all OxyContin be turned over to them. Fortunately, once they received the drugs, the armed gunmen left and no one was physically harmed.

I would like to share with you the experience DEA found in Southwestern Virginia regarding the abuse and diversion of OxyContin. Due to the devastation that OxyContin abuse was having in this area, DEA conducted a threat assessment of the problem in 2001.

This study found that OxyContin abuse in

Southwestern Virginia exhibited a sharp rise beginning in the spring of 1999. Considerable law enforcement resources were devoted to curb the OxyContin diversion including the creation of formal and informal drug task forces combining federal, state, and local resources.

Through these combined efforts, several OxyContin trafficking organizations were identified and disrupted. However, the area then experienced an increase in the number of pharmacy armed robberies. In addition, homes were broken into for the sole purpose of stealing OxyContin from legitimate pain patients.

As a result of this crime, many local jails were filled to double their capacity and reported that more than half of their inmates were incarcerated due to OxyContin related crime.

The study also found that drug treatment centers in Southwestern Virginia were experiencing an increase in the number of intakes due to OxyContin abuse. One treatment facility stated that in 1999, they had treated 18 patients for prescription narcotic addiction. However, between March 2000 and January 2001, the facility had treated more than 1,000 patients, with over 98

percent of the patients stating OxyContin was their drug of choice.

Less than 2 percent of the patients reported a preference for heroin. One OxyContin addict interviewed related some of the desperate lengths abusers will go to in order to get their fix, including using water from mud puddles in order to inject the drug, or using needles previously used to vaccinate dogs.

[Slide.]

In response to growing concern among federal, state, and local officials about the dramatic increase in the illicit availability and abuse of OxyContin, DEA initiated its OxyContin Action Plan in May 2001 as a comprehensive effort to prevent its diversion and abuse.

This was the first time that DEA had found it necessary to take such a comprehensive approach to a particular brand name controlled substance drug product. These efforts are not intended to impact on the availability of OxyContin for legitimate medical use.

The OxyContin Action Plan is ongoing and has four primary elements. Individually, the elements will not result in success. To succeed,

we must have cooperation, coordination, support and participation from all four of the following elements:

First, the four elements are enforcement and intelligence, which includes coordinated investigations targeting individuals and organizations trafficking OxyContin.

Regulatory and administrative, where DEA and other regulatory agencies utilize all of our means to prevent and pursue action necessary to make it more difficult for abusers to obtain OxyContin.

We also seek industry cooperation. DEA has sought increased cooperative efforts with all aspects of the pharmaceutical industry, and we view voluntary compliance from industry as the key to this element.

We also participate in Awareness/Education and Outreach Initiatives. This includes participation at several levels including town-hall meetings, demand reduction presentations to parent groups, and cooperative efforts with ONDCP. In addition, DEA includes information on OxyContin abuse on the Office of Diversion Control public web site at www.deadiversion.usdoj.gov.

Since the OxyContin Action Plan was initiated in mid-2001, DEA has conducted over 400 investigations of the diversion and trafficking of OxyContin. Well over 110,000 work hours have been spent on these investigations with the result of almost 600 individuals arrested.

Approximately, 60 percent of the cases initiated were in the retail profession including doctors and pharmacists. Doctor shoppers, forgeries, and individuals arrested in armed robberies and burglaries accounted for 40 percent of the investigations.

There has been concern expressed by some pain physicians that they could be investigated by DEA or have legal sanctions placed on them by DEA or state medical boards simply because they prescribe OxyContin or other strong opioids.

I would like to assure you that the intent of DEA is to target the illicit diversion and abuse of controlled substances. We recognize the place that pharmaceutical controlled products have in the treatment of a variety of medical needs, including pain management, and we work closely with state medical boards and associations to ensure our investigators are up to date on the latest

guidelines.

In conclusion, I would like to say that DEA is committed to protecting the American public's health and safety from the serious and negative consequences associated with the diversion of pharmaceutical controlled substances.

In this effort, we will not be deterred. DEA has seen firsthand the devastation that all drug abuse, including prescription drug abuse, can wreak on our fellow Americans. Lives can be lost and families can be destroyed.

During the past few years, DEA and the entire healthcare community have learned new lessons on the damage a prescription drug can do when not appropriately prescribed or used.

From our experience with the diversion of OxyContin, we have found that a targeted effort to eliminate diversion of particular products, such as our action plan, may be necessary and that it can be an effective weapon in the fight against drug diversion.

However, as always, prevention of drug abuse is the most effective tool against diversion. The devastation wrought by the abuse of OxyContin has been a hard lesson for all of us. We must

learn from this experience that once a drug has gained popularity among the drug-abusing population, there are few actions that can dramatically alter the demand for the drug on the street.

Law enforcement efforts are, in reality, simply clean up of a problem that has gone out of control. Steps must be taken to ensure that comprehensive risk management plans are in place before any new high-potency narcotic is approved for release to the American people.

Thank you. I think I have time to entertain a couple of questions.

DR. KATZ: It is still yellow. We have time for a question or two. Dr. Dworkin.

DR. DWORKIN: Does the DEA have any data regarding what percent of diverted drug remains local and what percent, if you will, crosses state lines and ends up being used elsewhere?

DR. WILLIS: I don't have data to that effect and it just depends on a case-by-case basis. We do know of many examples where we have very organized criminal rings that will traffic from Florida up to New York, for example. We had an example of that recently.

Some of the local doctor shopping and prescription forgery remains local area. I am afraid I don't have those specific statistics for you

DR. KATZ: Dr. Crawford.

DR. CRAWFORD: Thank you. In a similar vein, can you quantify for us and estimate how much of the problem may be due to the rogue internet sites out where it is out of the United States, not based in the United States?

DR. WILLIS: Well, foreign internet sites are a particular problem, and DEA is very aware of this issue. We are working in several different arenas with our foreign counterparts. It is difficult to investigate and curtail the smuggling or diversion of these drugs from foreign sources, simply because we do not have immediate control over these sources.

We are putting a lot of effort into identifying them. As far as quantitating how much is coming in, no, I am afraid I can't do that. There are new sites that come up on the web every single day. We do know that probably the drugs that are most purchased or available over the internet as far as controlled substances would be

weight control drugs and hydrocodone, but there are a number of web sites that advertise the higher schedule narcotics also.

DR. CRAWFORD: And a very quick question. We have been told this morning by Mr. Woodworth that DEA establishes quote limits on the manufacture of the products. For any of these predominant products we are discussing today, have any of the manufacturers met or approached their limit, are they well below those limits?

DR. WILLIS: Well, the quotas are based also upon estimates submitted by the drug manufacturers as to how much they will be producing each year, so the vast majority of them produce what they submit.

DR. KATZ: Dr. Shafer.

DR. SHAFER: I heard two different kinds of diversion problems and to my mind they are quite different. One is clearly criminal diversion, hijackings, home invasions, thefts, or physicians who are basically running criminal enterprises to make drugs available.

The other is diversion I would say at the level of the individual patient, who may be doctor shopping because they are addicts, but they are

essentially seeking drug for their own use. I somewhat despair as a physician of being able to give you any guidance on, you know, hijacking trucks. It is just not an area that I have a lot of expertise or experience with.

How much of the diversion is frankly criminal activity and how much of it is something that happens as an adverse outcome of routine clinical care?

DR. WILLIS: Well, it is difficult really for me to quantify that. DEA, we expend most of our resources at the criminal level, so I can address as far as the number of investigations we have had and the number of defendants we have arrested, the number of armed robberies, and that type of thing. We do not have the resources to fully investigate diversion through doctor shopping and prescription forgery. We work primarily in concert with our local law enforcement agencies, and they are the ones that primarily do the doctor shopping and prescription forgery.

So, I don't have available statistics as to how much is associated with criminal versus individual patients. What I can tell you is that physicians and obviously it's a small number of

physicians who are involved in criminal activity, we recognize that the vast majority of doctors are very law-abiding and only want to help the public, but a single physician has an unlimited ability to write prescriptions, and until law enforcement or the regulatory boards catch up with their activities, so one physician can do a lot more damage than a dozen prescription forgers.

DR. KATZ: Thank you. I just can't help but emphasize the importance of that question about how critical it is to design any rational program to combat prescription opioid abuse without knowing what proportion of the cases of prescription opioid abuse arrive to it from different pathways, it is impossible to rationally construct methods to reduce the ultimate problem not knowing which pathway to reduce.

DR. WILLIS: That has been a problem we have been dealing with for years.

DR. KATZ: So, I would just submit to the committee, since one of the aspects of our agenda in this meeting is to decide what data we need in order not only to construct a risk management program, but to monitor the results of the program, I would ask the committee to keep this question in

mind as we get to that discussion later today or tomorrow.

I have got a couple of people ahead of you, Dr. Gillett, but I will put you right on the list.

Dr. Cush.

DR. CUSH: I haven't seen any information on the use of taggers or tracers, or anything like that in these batches. Do they do that or is that confidential?

DR. WILLIS: That type of thing would be proprietary information.

DR. KATZ: Dr. Portenoy.

DR. PORTENOY: I am just look at this problem as you presented it, as one that would have to include law enforcement, the availability of treatment, demand reduction, and then some controls on the prescriber side.

I am just wondering whether DEA collects data about whether or not the regional differences, the regional distribution in abuse may correlate with the availability of treatment, the differences in the availability of treatment in different states, or the expertise of local law enforcement in different states, or educational programs

directed toward the public for demand reduction in different states, whether you collate any information that could help us try to understand the regional differences.

DR. WILLIS: I am not aware that we have any information at the moment, but I think that would be a very interesting study for us to undertake. Particularly, we do have all of the distribution data through our ARCOS information system. We have treatment information as to where the narcotic treatment programs are located and some type of correlational study would be interesting to do.

DR. BRIL: Along these lines with differences in regions, I was wondering if the DEA has any information on the use of, say, OxyContin in--is it the Netherlands where opiate use is decriminalized, the European country where it is not a crime, I guess, to use these drugs?

DR. WILLIS: I don't have information on that available, but we could try to find some out and get back to you.

DR. BRIL: That would be kind of answering the question directly about what comes from prescription use and what comes from recreational

use if you had numbers from a country where it wasn't criminalized to take these drugs.

DR. KATZ: Dr. Ciraulo.

DR. CIRAULO: I have just a couple of comments really related to the experience that we have had in South Boston, which is a small community. One of the things I would like to point out is it is not as simple as an OxyContin problem.

The problem started several years ago with actually a heroin problem, that the heroin entered the neighborhood in such a cheap and pure form that adolescents were able to get it. What we saw is a decline in cocaine use, then using heroin, then, a switch to OxyContin. So, I think it is a complicated problem, it is not just an OxyContin problem.

The second problem is a real concern about the level of resources that are being put into stopping the diversion. I can go into South Boston and identify, and I know the police can go do the same thing, who is pushing, and what happens when they identify these folks, they keep on moving farther south and farther south, but we have seen 30 overdoses of adolescents in the past month on a mixture of heroin and OxyContin. So, I am

concerned.

Are there resources at the state level? You saw Massachusetts was one of the ones way up there. Are there enough resources and what can we do to--

DR. WILLIS: Well, I don't think there are enough resources nationwide to combat the problem. Certainly, there aren't at the federal level, and the state and local police departments are stretched to the limits also. So, no, I don't think there are enough resources.

I don't think it's a matter of not wanting to work on this problem. It's simply a matter of not having the budget and the resources available to address the problem the way it should be.

I also agree with you in your first part of the comment about it isn't just an OxyContin problem. It is a very complex problem. One type of drug abuse leads to another type of drug abuse and experimentation. When the heroin is not available on the street, they will turn to the pharmaceutical narcotics and vice versa, so it is a very complex problem.

DR. KATZ: Thank you very much, Dr. Willis, for sharing your thoughts with us.

Open Public Hearing

DR. KATZ: We are moving on to the open public hearing section of our afternoon now. First of all, let me just say that anybody who is planning on speaking during the open public forum now, please come up from wherever you are and have a seat in that section to my left.

I promised that I would read this announcement about financial disclosures before every open public forum session, so I am going to keep my promise right now. This is for the speakers to pay attention to.

Both the FDA and the public believe in a transparent process for information gathering and decisionmaking. 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 any company or any group that is likely to be impacted by the topic of this meeting.

For example, the financial information may include a company's or a group'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.

So, here is what that all boils down to. When you get up, just say who you are, where you are from, and financial disclosures that you have. You have got five minutes. The yellow light goes on at four, and the red light goes on at five, and then I will interrupt you and it will be time for the next person. So, hopefully, that makes it more clear.

The first speaker will be Barry Cole. After that will be Jeffery Ebel, if you would like to put yourself on deck.

DR. COLE: Thank you very much. Barry Cole with the American Academy of Pain Management. In the last year, myself or the American Academy of

Pain Management have received funding from Abbott and G.W. Pharma, Jansen, Ortho-McNeil, and Purdue Pharma.

[Slide.]

This is about education I would say more than anything else. That is what is really important. We understand that today, that there are still tens of millions of people suffering that can't get lost in any debate that we talk about.

[Slide.]

Why we are really here is how to stop substance abusers from dying. We are at an interesting position, we don't really have a product defect per se, we have a defect in the end use of the product, and perhaps practitioner education can address that problem.

However, there will always be public policy implications for every choice we make. What I worry about is that pain patients will have decreased access to practitioners. Already many people tell me it's just too much trouble to deal with these kinds of patients, there will be more barriers thrown in their way, there will be mandatory police checks, there will be increased costs that somebody is going to get stuck with.

There will be more administrative burden, and I can't even guarantee that the patients will fare any better, while I can't absolutely guarantee either that abusers won't stop dying. The problem here is that they will still abuse product just like criminals still can obtain guns even with gun control legislation.

We have always used education as the remedy in medicine. The half-life of medical information is about five years. Every physician expects to go back and retrain. We have used the model in California where the Academy is located now of having a mandatory 12-hour educational requirement to allow for relicensure of California physicians. There is something that the Federal Government could do - look at DEA's certificate renewal on a three-year basis as something that could be contingent on continuing education.

The kind of education that needs to be addressed is what kind of patients are we putting on medication and when do we make these choices. It is about medical history taking. It's about risk assessment. It's about doing a physical examination, something that often isn't done that well.

It is about developing a plan of care with measurable, behaviorally measurable goals, getting informed consent, maintaining an ongoing monitoring relationship with the patient, establishing some way of seeing that therapy works, and obviously, staying in compliance with rules and regulation.

I can't tell you how many charts I have reviewed where it appears that my colleagues don't believe that the DEA's rules specifically apply to them. They have found loopholes, but they thought they could exploit.

Roles for simulation-based opioid education, this is something that I don't think very many of us have thought about. Most of us went to medical school, nursing school, pharmacy school. We sat like sponges in a room and they presented a lot of information.

I have recently been working with a group called Digital Think out of San Francisco to see if there is a way to creatively solve this problem through on-line education, creating an environment that would actually immerse practitioners in real decisionmaking processes and allow them to fail safely, be able to identify what they don't know and provide education to them on a real-time basis

and hopefully, teach them something along the way.

[Slide.]

The U.S. Military loves this idea. If you think about it, because the consequences of bad decisions are literally lethal and also they have to make decisions often with imprecise information in a very short period of time.

[Slide.]

The difference between our traditional educational models and where we might want to go is being able to get past the consequences of bad decisionmaking from a paper and pencil test to showing what really could happen. I guess you could have a model where there is an electronic DEA agent who actually kicks down your door and you can see your hands being handcuffed to do the perp walk. That is possible.

Knowledge being tested doesn't always seem relevant when you do a paper and pencil test. It would seem a lot more relevant when you are actually doing a computer simulation and certainly you would be able to see its applicability in real time, and obviously, passing tests doesn't prove you really know anything, it proves you passed a test.

Working in a simulation model, we hope would actually lead to behavioral changes on the job.

[Slide.]

The Academy, like many other pain-related organizations, really is hoping that we can all work together. This is more than just about my organization or anyone else's. It involves law enforcement, it involves professional societies, the addiction community, the patients themselves, and even regulatory authorities.

I am a former state administrator for Nevada, a place that has been described as the most behaviorally adverse state in the Union. I was the Director of Mental Health, very strange job.

I think we really can work together and make a lot of good things happen. Don't be too draconian too quickly.

Thank you.

DR. KATZ: Thank you, Dr. Cole.

Jeffery Ebel, you are next, and on deck is Dr. Van Zee.

So, once again, who you are, where are you are from, any financial disclosures, yellow at four, red at five.

DR. EBEL: Good afternoon. My name is Jeffery Ebel and I am President of Clint Pharmaceuticals. Clint Pharmaceuticals is located in Nashville, Tennessee. We are a distributor of injectable medications to physicians, hospitals, clinics, pain control centers, and to surgery centers.

We distribute these products that we have, are distributed, all have FDA approval. We get the products in from the manufacturer, and we do not alter them or do anything with them in any way. We simply get them in and then re-ship them out.

The product I am going to talk to you about is called Celestone Soluspan. It is a product that we do benefit from financially when the product is sold.

I will just lay this up here for Exhibit A. However, the competitive products to Celestone Soluspan, Kenalog and Depo Medrol, we market those equally as well, and if a physician does not have access to the Celestone, they can order the Kenalog or Depo Medrol, and we would benefit from that. So, we really don't have in a way a horse in this race.

Clint Pharmaceuticals works with many

specialties, such orthopedics, rheumatologists, dermatologists, et cetera. One of these specialists we work with is anesthesiologists or pain care physician.

We plan to work with the ASIPP in getting Celestone Soluspan available to their patients. I have a letter here that I am submitting as an exhibit from the ASIPP, which is the American Society for Interventional Pain Physicians.

Celestone Soluspan has not been available to the physicians and has been in an extreme back-order situation for the last two years. It was developed in 1963 by Schering-Plough. Clint Pharmaceuticals has distributed many doses of this product over the last 15 years without even one incident of adverse reaction or fatality reported to our company.

The anesthesiologists or pain management physician uses Celestone Soluspan in epidural injections to reduce the pain in their patients. Celestone Soluspan has not been available due to complications with the FDA and Schering-Plough, the manufacturer.

The lack of access, of patient access to Celestone Soluspan, has spawned fatalities and

adverse reactions across our country. These adverse events are due to the pain physicians having to resort to using compounded steroids in treating their patients.

I have Exhibit B, a list of various sightings where these fatalities and adverse reactions have been reported.

We have, however, no idea how extensive these incidents are because compounding pharmacies are not regulated. They do not have to report adverse reactions, compounding pharmacies do not have to comply with good manufacturing practices.

There are only two other commercially available long-acting repository steroid suspensions available to the interventional pain specialists. One is Kenalog and the other is Depo Medrol, which I showed to you earlier.

Many times these commercially available steroids are unaccessible to the interventional pain physician. Kenalog, for example, has benzyl alcohol. Benzyl alcohol as a preservative is known as a neurotoxin. Depo Medrol contains polyethylene glycol, which has been implicated in arachnoiditis.

DR. KATZ: I need to ask you to finish your sentence and your time is up.

DR. EBEL: I am requesting that you put this product on an emergency use for the pain interventional physician as you have with the Ob-Gyn patients as this product is being used with the Ob-Gyns in fetal lung maturation and is available to them. I would like to have this product available to the interventional pain physician.

DR. KATZ: Thank you.

Dr. Van Zee.

DR. VAN ZEE: My name is Dr. Art Van Zee. I have no financial disclosures. I guess I should disclose that I grew up in Nevada.

I am a general internist that has practiced the last 27 years in a small coalmining town in Southwest Virginia. What has brought me to these issues has been the OxyContin abuse problem.

It would be hard to overstate the devastation that this has brought to Central Appalachia and now a number of other areas of the country. There are literally tens of thousands of new opioid addicts in Central Appalachia stemming from the use and abuse of OxyContin. Many of these are good kids from good families who recreationally used OxyContin and became rapidly addicted.

Most of the OxyContin issues have to do with chronic noncancer pain issues. The noncancer pain market, if you will, constituted 85 percent of the total opioid market in 1999, and Purdue Pharma has aggressively promoted opioids in general, and OxyContin in particular, for chronic noncancer pain.

What do we know about the risks and benefits of opioids in chronic noncancer pain?

The risks of diversion have certainly been much higher than expected

This map is from IMS Health that documents OxyContin prescriptions per capita, highest and lowest states in the year 2000. The thing that this speaks to I think and some of the subsequent slides, graphic slides, to some of the questions raised about regional variation, variability of OxyContin abuse.

For those of you familiar with the OxyContin abuse problem, if you made a slide of those areas that were affected by that problem in the year 2000, it would virtually superimpose over these areas here.

I want you to note that Virginia appears as a normal area, normal kind of prescribing area

for OxyContin.

If you look at more detailed data, and this data comes out of the ARCOS system through the DEA's Office of Diversion Control where they are able to track opioid distribution down to the retail level, one can see on this slide, the year 2000, OxyContin distribution per 100,000 population, the red being over national average prescribing.

You can see this remarkably high area in Southwest Virginia. This is all Southwest Virginia area and this is where we have had extensive OxyContin abuse problems, and it is not just that this area is a higher prescribing area, but a very higher prescribing area.

These counties range in OxyContin prescribing anywhere from 300 to 600 percent higher than national averages.

Other states involved in the Central Appalachian OxyContin problem have similar demographic information in terms of high OxyContin prescribing and high use. East Kentucky, as you have heard about today, has had a terrible problem.

Maine, West Virginia, Alabama, the story is much the same, and, to me, this information

would suggest that the high availability of OxyContin was associated with high abuse rates and, not surprisingly, reinforce the old idea that a highly abusable drug, if widely available, will be widely abused.

What do we know about the risk of addiction for treating chronic noncancer pain? We don't have a definite answer about that. There are some studies that looked at the risk of addiction in treating acute pain setting, and those were somewhat reassuring.

There are a number of studies that looked at prescription opioid abuse behaviors, and that is not to be equated with addiction, but they can certainly run around together and these are oftentimes an indicator of addiction problems.

Dr. Portenoy, at this same committee hearing a year and a half ago, said that quite frankly we really don't know what the risk of addiction is in treating patients with opioids for chronic, nonmalignant pain.

What are the benefits of using opioids for treating chronic, nonmalignant pain? Again, there is very limited data on this. In the handouts, I referenced eight studies that were prospective,

randomized, double-blind, placebo-controlled studies lasting at least four weeks in duration, and if you take those studies as a whole, you will see that the efficacy is certainly there, but it's a very thin to modest amount of efficacy, and the functioning is essentially not improved.

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

DR. VAN ZEE: So, in conclusion, I would say there has been great harm, pain, and suffering from the OxyContin abuse problem in areas that have been affected. Its high availability seems to correlate with high abuse. From my point of view, it is very problematic in a risk-benefit analysis of opioids in chronic, nonmalignant pain when we really don't know what a lot of the risks are involved including addiction and diversion.

Thank you.

DR. KATZ: Thank you, Dr. Van Zee.

Siobhan Reynolds is next and Gregory Walter will be after her.

MS. REYNOLDS: Good afternoon. I am Siobhan Reynolds, Executive Director of Pain Relief Network in New York City. We don't have any relationship with pharmaceutical companies of any

kind.

We are a national patient and physician advocacy group dedicated to making pain care available to Americans. I would like to tell you, if I might, how I came to sit before you today.

I married a man, Sean Greenwood, who developed severe chronic pain as a result of a congenital connective tissue disorder. We were married for 11 1/2 years, we had a son, and I continued to care for him.

As a result of the damage he and our family suffered because we were unable to find pain care, I became an advocate on behalf of all Americans in pain. I became familiar with the inner circle of cutting edge pain care and was invited to participate in an internet listserv discussion on the issues confronting physicians who treat pain.

One by one, I watched as several of our most prominent members were arrested and charged with murder or subjected to accusations of violating the Controlled Substances Act. I knew, as I watched this, that something was going terribly wrong.

I am trained as a film-maker, so I set out

with my camera to find out what the stories were behind the attacks. What I found will soon be a film, but it also brought me before you here today.

In my travels, I came across Dr. Deborah Bordeaux as she was about to stand trial in the trial that this lady was referring to, in South Carolina, for writing prescriptions for pain medications outside the course of professional practice and without legitimate medical purpose.

I sat alongside here and two other doctors tried on similar charges. I was shocked and dismayed to learn that the Justice Department was bringing out-of-date, anti-scientific and prejudicial testimony into a U.S. courtroom in the hopes of convincing the jury that by prescribing medication in conformity with the actual up-to-date standard of care, the standard I am familiar with, that the doctors had done something shameful, something unspeakably wrong.

I have since watched the U.S. bring such cases all around the country. I began PRN and hired nationally renowned counsel to take up Dr. Bordeaux's appeal, partly because I wanted to save this innocent woman from federal prison, but also because I wanted to figure out what was going on

here. How could it be, I asked, that in an area of medicine so central to the physician's role, that of relieving suffering, could find itself so thoroughly overwhelmed, so unable to develop its own methods and clinical practices in the communities, as any other area of medicine is allowed to do.

As it turns out, the red flags that the government uses to determine if a doctor appears to be diverting drugs rather than practicing medicine are, for all intents and purposes, identical with the markers I or the healthcare professionals I know would identify as signs that good progressive medicine is being practiced.

In other words, what we have is a perfect storm created by the collision of the development of progressive pain care with the application by Ashcroft's Justice Department of a now hopelessly out-of-date Rosen Rules.

As a result, hundreds of physicians have been misidentified as being in violation of the Controlled Substances Act and have borne the full brunt of Justice Department drug prosecutions aided by determinant sentencing laws that have become so draconian that even the Supreme Court Justices

Rehnquist and Kennedy have moved to speak out against them.

Physicians all over America have been induced to take plea deals or to walk away from medicine rather than face what Dr. Bordeaux currently faces. Having been convicted by a lay jury of violating the CSA, Dr. Bordeaux's OxyContin prescriptions, 270 pills in total, were weighed up as though they were heroin, and the probation department has recommended that she spent 100 years in prison.

Since the committee, this committee cannot be moving to further manage the risk of Palladone, as a result of objective evidence of harm, because the only evidence we have actually disproves the DOJ's claims of hundreds of deaths summarily, and you cannot be concerned on the basis of any finding by any court that Purdue Pharma has been negligent, because they have been beating all these claims against them without exception, I must conclude, therefore, that your perception of the risks posed by Palladone is created at least in part by the astonishing increase in physician prosecutions recently reported by the Justice Department.

I am here to tell you that a terrible

misunderstanding has occurred here and the public health has been inestimably damaged. All over America, doctors have simply put down their pens, patients in pain have returned to their beds or committed suicide. The suffering and destruction of innocent life is unimaginable.

PRN is therefore calling for you to suspend your cooperation with the DOJ and to stand solely for your primary commitment to safeguard the public health. The public and the compassionate physicians have been badly let down by our Federal Government, a Federal Government which seems to have lost its way.

We hope you will join us in our call for an open and frank congressional investigation in what has happened here before you resume your collaboration with the DOJ.

The damage done will only come to be known as we uncover the deaths and listen to the stories the American, the stories the American people, the people have to tell.

You can find--

DR. KATZ: Ms. Reynolds, you need to wrap up.

MS. REYNOLDS: You can find our web site

at painreliefnetwork.org and thank you very, very much.

DR. KATZ: Thank you.

Gregory Walter is next and then Mary Baluss.

DR. WALTER: Good Afternoon. I just have a few things to say. I am an emergency physician in South Georgia. I have been an emergency room physician for 20 years. My wife of 10 years has been a chronic pain patient.

I think it's appalling the way we treat our chronic pain patients in this country. I have sat in emergency rooms with her for five hours to have her declared a drug addict, a drug-seeking individual. I have had her denied care time and time again.

I have had a personal perspective that not too many people have had. I, for 20 years, have had drug-seeking people come to me, and I have had to make the decision whether they are diverter or not, and I have done this to the best of my ability with all the skills I possess.

I have also worked in this pain clinic in South Carolina for six months, which the DOJ has declared a hell hole, and I just wondered when the

DOJ was going to tell you that there were only two pain clinics in all of South Carolina, so the patients have to drive for four hours to get pain medications.

Then, I was wondering when they were going to get to the fact that after they closed the two, not one, pain clinics in South Carolina, how the numbers dropped, but then the whole entire State of South Carolina has no place to go.

I thought the DEA was going to tell us that they were going to make sure the patients had a place to go, but when they closed those two clinics and confiscated all the patients' records, where were these patients to go?

That's all I wanted to say.

DR. KATZ: Thank you, Dr. Walter.

Mary Baluss and next will be Bruce Canaday.

MS. BALUSS: Good afternoon. My name is Mary Baluss. I am the Director of the Pain Law Initiative. I am also speaking today on behalf of the National Foundation for the Treatment of Pain. I am also the Chairman of the Maryland Pain Initiative.

I, myself, have received a grant from

Purdue that allows me to buy two medical journals a year, and that's it, and as far as I know, and I just don't know for sure, there is no industry funding for the National Foundation for the Treatment of Pain.

However, I am here today to talk to you a little bit in reactive mode. I would say that my message to you is do not restrict the availability of OxyContin to particular specialties. The specialty of the anesthesiologists doesn't want to use OxyContin because, in part, procedures are so much more profitable.

The other specialties, which are not so overtly associated with pain management, see the great bulk of American patients, and I assure you that in the rural areas in small towns, they see the people with serious chronic pain.

So, I would say please do not restrict the specialties. Doctor education at every specialty level is a wonderful idea. It should be based on clinical experience and clinical data, and not on scare stories.

Do not restrict OxyContin to severe pain even if you can figure out what that means. Pain is subjective, it takes everybody, as we have seen

data today, it takes everybody differently, our little bundles of nerves react differently to different stimuli and to different pain medications.

By the time a person gets to the privilege of being tried on opioids, they have usually had or been asked to have every intervention that could possibly be dealt out. The ones who haven't had those interventions are the people who can't afford it, and this is another reason not to restrict the medical pain management modality is because the poor people cannot afford your procedures, and they are the people who worked in the coal mines and the other aspects of Appalachia, and they hurt, and that suffering is so palpable.

I get a lot of phone calls and I don't charge my clients who are pain patients, and I don't charge the doctors that I help out, but I get calls almost every day and sometimes several day which basically say my doctor dumped me, what am I going to do. Where do you live? Well, I live in a little town near Des Moines or a little town near Columbia, South Carolina, or a little town near New Orleans.

Some of then live in big towns, but mostly

they live in little towns, and their doctors have decided it's not worth the trouble, it's not worth the fear of investigation, it is not worth hassling with pharmacists. This is why we need doctor education, not to reduce the prescribing, but to make it as intelligent and as clinical as possible.

Now, the DEA--and I didn't come here to mix it up with the DEA today, but they sort of started it--the DEA's Risk Management Program is based on two things--three things. One is the criminalization of prescribing to people who are lying to you.

Another is the expectation of perfect prognostication on the part of any doctor, so that he knows when he is being lied to.

Thirdly, they have conflated the notion of legitimate medical purpose with the notion of illegitimate medical procuring on the part of would-be patients, and you can't do it that way.

We need more data on outcomes, we need more research, we need more funding for drug abuse, for people who are addicted, but we don't need the DEA's suggestions that were made today.

Finally, Dr. Willis started this. I, like Ms. Reynolds, was very close to and sat through the

entire trial of South Carolina doctors. The only people testifying against those doctors were themselves plea bargaining felons.

The doctor who testified against them was a specialist in nothing. He had no board certifications, never taken a pain management certification, and I know you are going to tell me to sit down. So, thank you.

DR. KATZ: Thank you, Ms. Baluss.

Next is Bruce Canaday and after that Arthur Horn.

DR. CANADAY: Thank you for the opportunity to present the views of the American Pharmacist Association.

I am Bruce Canaday, clinical professor with the University of North Carolina, and Director of Pharmacotherapy for the Coastal Area Health Education Center in Wilmington, North Carolina. I am also a member of the APHA Board of Trustees and appearing today on behalf of the Association.

In the interest of full disclosure, I have on occasion been involved in project funded by pharmaceutical manufacturers, and APHA commonly partners with federal agencies, consumer groups, the pharmaceutical industry, and others to develop

educational tools for pharmacists and consumers.

Neither I nor the Association received any funding to participate in today's meeting. The views I am presenting today are solely those of the Association and its membership.

As the medication use experts in the healthcare team, we would like to share our experience with risk management programs, offer our perspective on program design, and provide recommendations on the development of risk management programs for opiate analgesics.

Before you can discuss the design of risk management programs, there is a few fundamental questions to be addressed. First, what is the specific risks identified, is the risk to manage the potential of adverse events or contraindications, or is it product abuse and diversion? Very different things.

It is equally important to establish the metrics of success. If the risk is diversion, does success mean a reduction in diversion or zero diversion, and what numerator do you use, what denominator?

These questions should be at the forefront of considering risk management programs for any

product. Pharmacist participation in risk management programs have grown significantly in recent years. Despite the additional steps that participation requires, we would rather work to mitigate product risk than lose a tool in our armamentarium for curing patients and helping them.

Patients must not lose access to opiate analgesics because of failure to reduce risk or prevent misuse. While pharmacists want to participate in risk management programs, our experience has not been very positive to date.

We are often not provided with the opportunity to help shape the programs we are then responsible for implementing. In some cases, in fact, pharmacists are excluded from participating all together. APHA has significant concerns with these restrictive distribution programs. Any pharmacist should be allowed to participate in a risk management system.

While it is understandable that participation may require that the providers meet certain requirements, providers who meet them should be allowed to opt in the program, and not be automatically excluded.

To increase the effectiveness of risk

management programs, pharmacists must be involved both in the development and implementation. The current product-by-product approach to risk management is frankly a bit of a morass.

The risks are identified with a product, a new program is developed to address that risk which may bear little or no similarity to currently existing programs. APHA strongly supports utility or a systems-based approach to risk management, this approach, create a prototype system that includes standard tools.

As products are identified that require special attention, the program is built with the appropriate tools from the prototype system. This would provide consistency, limit administrative burden, increase program efficacy and effectiveness, and allow providers to place greater focus on patient care.

As you discuss opiate analgesics, I would like to highlight three areas for your consideration. First, when preparing for this meeting, it was unclear if the Agency is seeking a new program for one new drug product, or group of similar products, or an entire class of drugs.

We have concerns if the Agency targets one

specific pain relief product for a risk management program when other products have similar risk. If all the products in class have similar risks, the risks could be managed in a consistent manner, otherwise, providers will migrate to products of similar risk with frankly less hassle.

Second, if the goal is to limit diversion, it must be very carefully considered. Opiates are under the spotlight already. A program to reduce diversion could not only restrict access to appropriate pain medications, but really significantly compromise the entire system.

Finally, controlled substances are subject to state oversight and federal DEA rules. You need to be sure that we are not in conflict with existing laws. The agency should consider what diversion programs are already in place or under consideration. I know Florida and Virginia are putting together their own programs, which are going to make it a bit challenging to deal with another set of regulations.

We welcome the opportunity to work with the Agency. We recommend that you consider a utility approach in risk management, managing products with similar risks or similar systems to

help providers navigate the system, and to allow us to focus on what we should be, the patient and appropriate medication use.

Thank you.

DR. KATZ: Thank you.

Would anybody from FDA care to address the question about whether the FDA is seeking risk management, the device for a single drug or for the entire class of drugs?

DR. RAPPAPORT: This particular meeting is about Palladone, it's about a risk management plan for Palladone. There is a possibility that this could be expanded to apply to other similar products in the future, as well. That is not the topic of this specific session.

DR. KATZ: Arthur Horn and next is Jan Towers.

DR. HORN: Good afternoon. My name is Arthur Horn. I am a physician in Hagerstown and Frederick, Maryland, just down the road.

I have come today because Congressman Wolf asked me to come and share some of my feelings about narcotic therapy. My practice consists of chronic pain management. I have been doing so ever since I came to Maryland back about 14 years ago.

I don't have to bestow the virtues narcotic therapy has really changed over the past couple of years, particularly the last 10 years. Patients have definitely benefited from that. There is an improvement in function, there is certain more functional standpoint that we are able to find with these individuals.

But one of the tools that we have used, OxyContin is a double-edged sword. Although it works well, well tolerated initially, has been a problematic drug particularly over the past couple of years with all the notoriety that we have seen.

I would like to make some suggestions as a doctor in the trenches, you know, a doctor who basically treats patients every day including my daughter, she has a complaint every day also.

I am very concerned about the increase equivalent amount of morphine that patients receive on a daily basis, and that clearly has been escalating, and not only has that been escalating as newer products have come out, but as these patients stay on longer as your tolerance builds up, sometimes they can be receiving whopping doses of narcotic therapy on a daily basis.

That leads me to the second problem with

OxyContin, which is the street value. I went ahead and I went to a pharmacy, and I asked to weigh out 40 mg tablets one ounce of OxyContin. That turned out to be 210 tablets. Retail cost was $1,040. When I calculated it out on my little calculator, that came out to 2 1/2 ounces of gold.

When I converted that to the traditional sale of OxyContin, which is $1.00 a milligram, that came out to $8,400 for that one ounce of OxyContin, which equals 21 1/2 ounces of gold. Again, this is part of what I think is the motivation for some of these diverters.

Once again, we do want to treat these individuals, they have clearly responded favorably, the people that take the medication appropriately, but when you are looking at such a marked profitability in terms of a single one prescription, it is really an attractive nuisance as far as I am concerned, and, well, once again, leads to further problems.

In addition, I think most of the doctors that treat chronic pain and that prescribe chronic opioid therapy really are effective at what they do. They really try their best, they try not to give patients medications for abuse or diversion,

but as we saw, there is a small number of doctors that really stick out, that are really running prescription mills, and there are some doctors that just aren't as careful as they should be.

I am concerned about the doctors in the middle, the ones that may suspect a patient is abusing medication, but are not willing to really do anything about it. Those are the ones that really need to be watched, because I think they are very pervasive throughout the entire medical community.

My suggestion is, as was brought up, a bar code on tablets or a tagon [ph] put inside. I would like to see that traced back from the apprehended products on the street, and find out where that came from, find out whether it was stolen from a truck or which doctors and which patients were involved.

The reason why is because we really have to control this to get some effective use of this medication without fear of reprisal, but on the other hand, we have to take these bad guys off the street.

Another issue, and I would only like to throw it out, I don't know how realistic it is,

that perhaps when patients take a medication, such as OxyContin, which has a 20 to 30 percent immediate release within the first two hours, this may represent a public safety issue in terms of driving, you know, operating equipment and things like that, and that certainly is another consideration to be given.

Ultimately, in conclusion, I believe that OxyContin has been very helpful, but on the other hand, it is a problematic drug, which does have its problems in terms of euphoria and this large amount of narcotic therapy.

I think if we can identify the abusers that are involved or the people that are helping this, I think we could make a difference in continue to improve our patients with chronic pain's lives.

Thank you.

DR. KATZ: Thank you, Dr. Horn.

Jan Towers and next with be David Joranson.

DR. TOWERS: My name is Jan Towers. I am the Director of Health Policy for the American Academy of Nurse Practitioners. I have no direct financial relationship with any pharmaceutical

companies, but our organization does accept unrestricted educational grants for many of our activities from a variety of pharmaceutical companies.

The American Academy of Nurse Practitioners is the full service national organization representing advanced nurse practitioners from all specialties. Advanced practice nurse practitioners practice in a variety of settings where it is necessary to prescribe and manage opiate analgesic drug products for the patients under their care.

These sites range from pain management clinics, hospice and oncology practices to acute care facilities and primary care practices. Nurse practitioners also practice in settings where they are working with patients to deal with addictions associated with misuse and abuse of these same drugs.

The comments made here are considered in the perspective of nurse practitioner experience with the management of patients in all of these settings.

As we review materials to be used in the consideration of a framework for a risk management

plan for extended-release opiate analgesics, there are a number of SDA, risk management activities that we feel are particularly applicable to authorized prescribers and dispensers of these drugs.

While the DEA has responsibility for dealing with the illicit use of these drugs, we feel the FDA's responsibility centers around the safe and effective use of these drugs in legitimate patient care settings. In this context, we would suggest the following.

First, in addition to clear product labeling that includes descriptions of the drug structure's actions and interactions, side effects, contraindications, documented studies in dosing, we encourage the inclusion of high-quality patient education information focused on increasing patient knowledge and hence, appropriate compliance by patients for whom these medications are prescribed.

Second, we endorse the concept of additional education and outreach to healthcare professionals and suggest that this concept be extended to consumers, that is, patients, as well. Studies have shown that the most effective

treatments are those where providers and patients are well informed and share in the therapeutic process.

In the area of tool development, we would suggest that contributions to the development of tools be broader than what is in your document that you have today, physicians, pharmacists, patients, and insurers.

We further suggest that the target groups be broader than physicians and pharmacists as listed in the FDA concept document. Advanced practice nurse practitioners, for instance, can make a viable contribution to the development of educational and outreach tools focusing on these drugs.

We suggest that you seek their input in your deliberations and in the development of processes adopted by the FDA to assure the safe and effective use of these medications. With their focus on the total patient and his or her environment, and the provision of care to patients with acute and chronic pain, and with their additional expertise in patient education and counseling, input from advanced practice nurse practitioners regarding these issues as they apply

to both patients and providers would be an asset to the development and implementation of risk management programs centering on these medications.

In addition, we would caution you not to take steps that would limit needed patient access to these medications prescribed and dispensed by authorized prescribers and dispensers in all healthcare environments.

We would suggest that educational and outreach programs also be explored and developed to assist providers, patients, and patient support systems in recognizing and managing patients with addiction problems, and we endorse the evaluation process suggested in the concept paper.

While problems have arisen with the use of opiate analgesic drugs, the use of these medications, particularly in the management of chronic pain, has demonstrated their worth. We suggest that a well-informed provider-patient and public population can facilitate the safe and effective use of these particular drugs.

We thank you for the opportunity to speak with you today. The American Academy of Nurse Practitioners is interested in working on these projects with you and with the Food and Drug

Administration. You have our contact information.

Thank you.

DR. KATZ: Thank you.

David Joranson, you are up, and Daniel Carr, you will be the next and final speaker.

DR. JORANSON: My name is David Joranson. Our published work has been supported by grants from the Robert Wood Johnson Foundation. Our group at the University of Wisconsin has also received unrestricted grants from Purdue, Jansen Pharmaceutical, Ortho-McNeil, and I have received some honoraria from time to time for occasional lectures. No company paid for my trip here today.

The title of my talk is Use the Principle of Balance to Evaluate Risk Management Strategies for Opioid Analgesics.

Mr. Chairman, committee members, the task of developing risk management strategies for approved opioid analgesics is essential to good public health policy. The appropriate medical use of opioid analgesics is absolutely essential for many patients because adequate pain relief restores quality of life and saves lives.

However, there are still many barriers to the appropriate medical use of opioids. Opioids

also have an abuse potential. Drug abuse destroys lives and diversion of prescription pain medications from legitimate medical channels to illicit uses should be prevented, but efforts to prevent the abuse of opioid analgesics should not interfere with their use in legitimate medical practice and patient care.

This is a principle called balance, and achieving the right balance between these two public health objectives, that is to say, preventing abuse and ensuring patient access is the subject of my statement and I think the mission of the Committee, as well.

FDA and the Committee can use the principle of balance to evaluate various risk management strategies. There are two tests for balance. One is that the strategy should have a high potential to prevent diversion or abuse, and, two, that the strategy should have a low, perhaps zero, potential to interfere with legitimate medical practice and patient care.

For example, balanced strategies to address diversion and abuse would include measures to prevent pharmacy theft, to identify employees who divert medications, to identify doctor

shoppers, making sure to distinguish them from inadequately managed pain patients, to educate physicians about how to identify at-risk patients or to formulate products to reduce their abuse potential.

These strategies are balanced because they address the sources of diversion and abuse directly without interfering in legitimate medical practice or patient access to needed medications.

In contrast, unbalanced approach would be physicians who stop prescribing to all patients or who refer all their patients to specialists, pharmacists who refuse to stock needed medications, insurance companies that restrict reimbursement or agencies that restrict the amounts that physicians can prescribe to patients.

These are unbalanced because they are not aimed directly at the source of the problem, and they have a clear potential for interfering in medical practice, interrupting patient access to pain relief, and increasing the burden on health professionals and patients.

As the Committee evaluates risk reduction strategies, I ask that you consider the extent to which crime is the source of the opioid analgesics

that are abused. Large and as yet unknown quantities of prescription pain medications are diverted each year, are abused, and thus, contribute to the drug abuse statistics that you study.

This particular chain of events begins with criminal rather than medical or patient behaviors. I am referring to pharmacy theft, forgery rings, doctor shopping by non-patients who feign painful illnesses in order to obtain prescriptions.

It is important to note that in the 1980s, at the urging of the country's pharmacists, Congress made pharmacy theft of controlled substances a federal criminal offense, however, little is known about how this law is enforced in the country.

It is important for the Committee to realize that risk management strategies that you may develop for use particularly within the healthcare system are independent of, and may not affect, the abuse levels of medications being diverted by criminal activities. In fact, statistics are available to quantify diversion from pharmacy thefts, and I would urge the Committee to

obtain these data and factor them into your understanding of the numerators and the denominators.

We respectfully recommend that FDA and the Committee use the principle of balance to evaluate risk management strategies. A balanced approach is consistent with good medicine where we aim to do no harm and where we avoid cures that are worse than the disease.

A balanced approach is also completely consistent with international, federal expectations of what amounts to good drug regulation.

I have attached a bibliography to my statement and I will be pleased to provide any other information that the Committee may require.

Thank you.

DR. KATZ: Thank you. It may be worth pausing for a second since Mr. Joranson has proposed a relatively simple lens through which we can look at any proposed risk management strategy, and since that is what we are doing for the next day or so, the strategy being to simply look at to what extent they are likely to impact upon the problem we are trying to impact on, namely, diversion and abuse, and then to what extent they

may interfere with normal medical practice.

Does anybody have any questions for Mr. Joranson about that principle of balance and about his experience in implementing that policy and evaluating regulations? Russ.

DR. PORTENOY: Just to clarify a point. The aspect of balance that relates to the negative side, what we would like to try to deal with in terms of the positive outcome of risk management program relates to reducing diversion, reducing or limiting the adverse consequences of addiction, and then there is this gray area of misuse where physicians who don't have adequate skills may use these medications inappropriately.

Several of the speakers have addressed that and obviously, for those of us who are pain specialists, it is a very problematic thing because we try to educate physicians in order to treat pain more effectively, to use these drugs more effectively, and it is quite clear that some physicians can be trained well and some physicians cannot be trained well, and the ones who are not trained well can become part of a problem, not only in relation to the problem of iatrogenic addiction, which is probably less common, but in the problem

of not treating patients up to the standards of care where patients' function declines and they don't do well as a result of continuing access to an opioid drug.

We don't have much data about this, and I just wondered how you would put that piece of it, that issue of misuse, that gray zone in that misuse category, how you would put that into the balance equation.

DR. JORANSON: Could you clarify what you are defining as misuse?

DR. PORTENOY: Yes. What we would like to do, the lens through which we would like to evaluate the risk management program might be that we don't want to do anything that would reduce effective good medical care with respect to opioid therapy. We don't want any management program to make care less good.

At the same time, we would like to target these risk management programs to try to reduce bad outcomes. So, under the bad outcomes, we have diversion into the illicit marketplace, we have the development of iatrogenic addiction.

Do we also have a responsibility there to talk about the inappropriate use of opioid therapy

by physicians who aren't adequately trained to provide these drugs or to monitor these drugs with sort of a broader negative than just the possibility of diversion?

DR. JORANSON: Dr. Portenoy, I think the brief answer to your question is that good pain management is always going to require a large investment in education especially now that we know that very little about pain management was taught at all or perhaps not even accurately in past generations.

We have got problems in knowledge to overcome, as well as teaching new knowledge. In some countries, doctors are so afraid of prescribing opioids that if you make them available to them, they won't prescribe them because they are too afraid.

In this country, there are some doctors, as we know, that don't have that problem. My sense is that as a matter of public policy, education can be encouraged and perhaps at the state level it can be required as a continuing education piece as some states are, but it's experimentation at this point to learn what the effect of this kind of education will be on practice.

But I don't think that we should rely on education to solve problems of deliberate misuse or diversion area activities. I think that is a job that we should focus on and clean up. We have done it a couple of times in past decades, and I don't think we should get those two things mixed up.

If we can separate out the problems of diversion, target those and deal with them, it will be a lot easier to deal with improving the educational level of practitioners and many regulatory agencies, including the state medical boards, are eager to be involved in that process. About half of the state medical boards have adopted a policy statement that encourages increased education for any physician who makes pain treatment part of his or her medical practice.

DR. KATZ: Dr. Passik, question?

DR. PASSIK: We have a lot during the day today, a lot of statistics indicating, you know, curves going up, and as Russ said earlier, all we can really extrapolate from that is more availability, more abuse, but we haven't, other than Dr. Van Zee's comments in the open forum, really seen a big correlation between medical use and abuse, geographically or otherwise.

I think that is one of the biggest problems we face is we don't know how much of it is coming. Of the 90 percent of diversion that was talked about the first thing this morning, we don't know how much of it is coming from medical use with pain patients.

I wanted to ask David if he could amplify because he added another unknown, which is the whole issue of pharmacy theft, and I just wondered if he had any comments about that, because we have heard that 90 percent of the abuse happens there, but you have added yet another unknown, which is how much is being diverted from pharmacy theft as opposed from patients and doctors.

DR. JORANSON: Well, obviously, the reason that you want to know how large that source is, is so that you can begin to factor out whether it is doctors and patients that are the problem, or whether it is criminals, so to speak, that are responsible for putting the drugs on the street.

Of course, the short answer is that it is both, but we need to know a little bit more about the proportions, and I think this is also going to vary regionally. For example, I think DEA mentioned a high number of thefts in the Boston

area, and that has been in the newspapers hundreds or more. It is possible to determine the amount of all prescription controlled substances that were stolen in those thefts. There is a form that all the pharmacists have to fill out, the DEA-106 form, and presumably that data could be available and could be studied, and would add some perspective to the total quantities. These would be objective measures of diversion, not indicators. They are actual measures. That could happen for any pharmacy theft anywhere in the country.

DR. PASSIK: Do we have that data and when was the last time it was available?

DR. WILLIS: We could get that for you.

DR. KATZ: Many people didn't hear that response, but the bottom line is that that data could be made available to the Committee.

Dan Carr, you have got your five minutes in the sun.

DR. CARR: Thank you very much, Dr. Katz, and the distinguished and erudite members of the Committee for giving me your attention.

I recognize first that the issue of risk management is fraught with complexity and therefore, I have chosen only to identify two

specific comments to leave you with amidst an ocean of greater complexity.

I also point out that nobody paid for me to be at the meeting today. By coincidence, I had to be in Washington yesterday because the American Academy of Pain Medicine unveiled a new internet-based educational effort, a part of which encourages appropriate use of opioids, and tomorrow, the Institute of Medicine has a program on encouragement of clinical research.

On the other hand, that educational program, and hence my airline ticket, was supported by Purdue very indirectly

[Slide.]

If we were able to deal with all the complex issues of risk, and we tackled them capably, we might produce an ideal world in which there is prospective identification and planning for patients who are both at risk of undertreatment of pain, as well as the adverse effects of such therapy.

There would be prompt, perhaps even preemptive, individualized antinociceptive and palliative interventions including adjuvant medications. We would deliver effective treatments

based upon rigorous evidence, and we would capture data about the effects and adverse effects in a standardized fashion.

We would do so in a supportive climate with respect to policies, payment, and attitudes, and there would be recognition at the system level that the disease burden of undertreated pain far outweighs that of abuse, addiction, and diversion.

One reference I could think about right off the bat that you could go to is the WHO global burden of disease web site to see numbers to support this. There would also be recognition at the system level that people have always and will always treat their pain by whatever means is available to them.

There would also finally be recognition at the system level that the adverse effects of these treatments often preclude adequate pain control.

[Slide.]

Personal experience includes doing many systematic reviews and meta-analyses, some of these over the years funded by the government.

[Slide.]

Having looked at the evidence, there are a lot of problems with the evidence, and this

evidence is evidence relevant to the formulation of policy concerning management of risk.

Randomized, controlled trials are a tiny fraction of the literature and most of the literature is observational or describes a technique. There clearly are very important elements of data that would be important to formulate a rational risk management policy, not only for the single drug Palladone, but for all drugs which are lacking.

Even in the randomized, controlled trials, a pervasive problem is underpowering. In fact, if one is assigned to pool the available data and construct a pooled efficacy estimate for various classes of drugs including opioids, it is an almost impossible task because of the heterogeneity of diagnoses, patients, and outcomes.

There is a proliferation of instruments that have been employed, and that is for pain, and the picture is even worse for non-pain symptoms, such as fatigue.

A 2003 systematic review commissioned by the American Pain Society on treatment of opioid side effects, which can be looked at in the Journal of Pain by McNicol, et al., was hampered by the

lack of focus to date on the side effects.

[Slide.]

What the two points I wanted to make? Well, in formulating a risk management policy, one dimension of risk simply has to do with adverse effects. These are very important in the real world.

Eric Mannheimer of the Cochrane Collaboration has pointed out that the assessment of effects and side effects in drug trials to date have proceeded as if they were two different dimensions or different universes.

While for most of the effects, we capture these prospectively, seek them deliberately, and we use instruments that at least have some likelihood of reflecting consensus, thus far to date, the majority of trials, even randomized, controlled trials, have captured side effects only if volunteered or if prospectively, in an ad-hoc way.

Given the importance clinically of side effects, and the fact that in the real world, they contribute to risk, consensus instruments and methods should be encouraged and possibly required.

I know that I am echoing what many people around the table or in the audience have said,

Mitchell Max, for instance, has a manuscript about this point, but I think this is an important opportunity in formulation of a risk management policy.

Further, if instruments are standardized, this will allow pooling of data which is not currently possible.

[Slide.]

Now, looking at another dimension of risk, which is the societal dimension, I think we have heard from many of the speakers that discouraging clinicians from prescribing, controlled substances worsens the situation that is well documented of undertreatment of pain.

Therefore, in the formulation of a risk management policy, adding to risk management burdens may increase the global aggregate societal risk from undertreated pain or the reliance upon unregulated analgesics. That might include street drugs, alcohol, or over-the-counter NSAIDs, which themselves carry considerable risk.

I wanted to emphasize the point that the true systemwide risk is aggregated and it is distributed, much as one might imagine the process of treating pain as consisting of a flow of fluid,

let's say, through a series of spigots. The spigots represent the choices of therapies, and if shut one spigot or make one element less available in a multi-spigot system, that has two effects.

First, you increase the aggregate resistance slightly and you shift the flow to be through other spigots.

So, I wish you would keep these two points in mind, and thank you for your attention.

DR. KATZ: Thank you, Dr. Carr.

Our next presentation will be from Ann Trontell. The open public hearing session is over. She is Deputy Director of the Office of Pharmacoepidemiology and Statistical Science at FDA, and will speak to us, giving us an introduction to the goals of risk management plans and also non-opiate risk management plans.

After this presentation, we will have a break.

Existing Risk Management Plans

Introduction: Goals of Risk Management Plans/

Non-Opiate Risk Management Plans

DR. TRONTELL: Good afternoon. I am going to be providing a broad and general overview of FDA's experience to date in risk management

programs and our evolving guidances on the topic of risk management.

[Slide.]

FDA's involvement with risk management is longstanding and derives from the Agency's role in weighing the risks of drug products along with their benefits in making decisions about drug approval.

The nomenclature of risk management per se was probably introduced in 1999 when the FDA Commissioner released a report on managing the risks of medical products.

[Slide.]

With the passage of the Prescription Drug User Fee Act last year, FDA's role in risk management was formalized. The Agency was asked to develop three interrelated guidances on risk management and to do so by September 30th of next year.

The topics for these three guidances were premarketing risk assessment, postmarketing pharmacovigilance and pharmacoepidemiology, and risk management itself.

[Slide.]

FDA gathered its preliminary thoughts in

these three areas and published and presented concept papers on each in April of this past year, and solicited public comment. Draft guidances based upon these concept papers and the commentary received upon them will be published later this fall. There will then again be another opportunity for commentary.

[Slide.]

As a consequence, this presentation will be focusing both on FDA's experience with risk management, as well as the concepts that were articulated in the concept paper entitled "Risk Management Programs." I hope you understand I am giving you a snapshot of what is a very rapidly evolving approach to drug safety by the Agency and our many partners.

[Slide.]

The Risk Management concept paper discussing risk management programs focuses on risk minimization efforts. These efforts are termed "risk management programs" in the concept paper. The risks are, in fact, identified using practices that are described in the other two PDUFA3 documents on risk assessment in the premarketing and postmarketing areas.

[Slide.]

Important concepts, as Dr. Galson told you this morning, include our concept of safety, which is that it means for us, on balance, that beneficial actions of a product outweigh their harmful or undesirable side effects. It does not suggest that risk itself is absent.

A risk management program was defined in the concept paper as a strategic safety effort to reduce risk and that that effort entailed one or more risk reduction goals and the use of one or more interventions or tools other than the package insert.

The package insert, or PI, refers to the professional package insert or what you may know as FDA-approved labeling. This is not considered in the concept paper to be a formal risk management program in and of itself.

[Slide.]

As I stated, part of the definition of a risk management program is that it have one or more goals. The goals of a risk management program would, in FDA's concept paper, be tailored to a product's specific risk concerns and describe the ideal product use scenario or the desired end

result of the risk management program.

It would include a vision statement, if you will, of the optimal drug use scenario. Examples may illustrate this. For the drug product thalidomide, a known teratogen, the vision statement might be described as no fetal exposures. For clozapine, a product associated with agranulocytosis, the goal might be stated no agranulocytosis.

[Slide.]

In the concept paper, FDA discusses when a risk management program might be appropriate. The Agency describes in its concept paper that this might, in fact, occur whenever risk reduction needs emerge during a product's lifecycle, and this might, in fact, be initiated by a drug company's sponsor or by the Agency.

The language proposed in the concept paper was in instances "when the number or severity of a product's risks appears to undermine the magnitude of benefits in an important segment of actual or potential users."

[Slide.]

The challenge is how to assess, in fact, whether or not risks undermine benefits, and that

will likely be much of the topic of further discussions here today and tomorrow.

There is no simple formula that compares risks and benefits. They are measured in different units and they are of different types. As such, FDA stated in its concept paper that it anticipates case-by-case judgments will be made by the company's sponsor or by FDA on whether or not to develop, submit, or implement a risk management program.

At the same time, the Agency acknowledges that for most drug products, that these will be handled sufficiently and well by the package insert without the need of a formal risk management program.

[Slide.]

Now, to turn to risk management program tools, which again were part of the definition, these we defined as a process or system intended to enhance safe product use by reducing risk. The choice of tools can be influenced by the severity of the risks, its reversibility or its rate.

[Slide.]

It may be useful for discussion purposes to talk about three categories of tools that can be

used in current risk management programs. These include education and outreach, so-called "guiding" systems, and restricted access.

[Slide.]

First, education and outreach. As I stated previously, in the concept paper on risk management programs, the Agency specifically excluded the conventional professional labeling, or package insert, acknowledging, in fact, that this is the standard mechanism whereby the Agency, with drug company sponsors, communicates risks and benefits.

Instead, education and outreach would describe those that go beyond the package insert, and might include, for example, the issuance of Dear Healthcare Practitioner letters or other public notices, training programs or offerings of continuing education, or patient-oriented labeling, such as medication guides or patient package inserts, or PPIs, which I will now describe.

[Slide.]

Medication guides are a form of FDA-approved patient labeling that have been regulated since 1999 with the reference given to you here. These patient labelings are, in fact,

required to be dispensed by pharmacists with each prescription to a patient.

They are intended primarily for outpatient prescription products that pose serious and significant public health concerns, and at the time this regulation became effective, it was anticipated that this form of patient labeling would be applied on average to 5 or 10 products on an annual basis.

[Slide.]

Medication guides have, as part of the regulations, the requirement that they meet one or more of the following criteria set within regulations, the first being that patient labeling could help to prevent the occurrence of serious adverse events; the second being where there might be serious risks associated with the use of a product or the patient should be informed in order to make a decision whether or not to initiate or continue use with that product.

The third triggering criteria was instances where patient adherence to therapy and to directions was crucial to effectiveness, particularly for life-threatening conditions. Again, the regulations for medication guides set

forth a standard format and content for these materials.

[Slide.]

Depending on how you counted, there are now approximately 13 medication guide texts that cover approximately 22 different products.

They cover a wide array of risks, and the risks are not in any way constrained by regulation. They include, but are not limited, to issues of hepatotoxicity risks, teratogenicity, abuse and diversion, and the potential for overdose.

[Slide.]

Patient packaging inserts, or PPIs, are yet another form of FDA-approved patient labeling with some important differences for medication guides. In the instances of products that contain estrogens, they are, in fact, required for distribution to patients, much like medication guides, but otherwise, PPI distribution is optional.

In instances where PPIs may be used as the brief summary for direct to consumer ads, they are subject to FDA regulation, as listed in this slide.

[Slide.]

Many patient package inserts follow the

medication guide format on FDA's encouragement that this format may well promote consistency in patient adherence with patient labeling.

In fact, as many products are increasingly packaged in unit-of-use packaging where PPIs may be contained, they may function similarly to a medication guide and that each patient would receive a PPI.

[Slide.]

But to draw the distinction clearly, medication guides are required to be dispensed with medications to patients. For other than estrogen-containing products, PPIs are optional. In instances where generic products may enter the marketplace, they conform to the same labeling requirements as the innovator drug, and the medication guide requirements convey then, as well.

[Slide.]

Turning now to the second broad category of tools are those that we call systems that guide prescribing, dispensing, and use.

The purpose of these systems is to assist individuals in following appropriate prescribing practices or stated in alternative terms, to make it difficult for individuals to forget important

safety processes.

These may use a variety of reminders or prompts.

[Slide.]

Examples of these might include the use of patient agreements, sometimes called informed consent, or practitioner certification programs. There have been a number of special conditions of dispensing that have been put into practice.

These include special packaging, limitations on the supply of the drug product, or the inability to obtain refills. In some instances, check mechanisms have been put in place to assure that appropriate prescribing has taken place.

[Slide.]

An example of special packaging would be the drug product Lindane, also known as gamma-hexachlorocyclohexane. This product is now limited in its dispensing to one or two ounce aliquots due to the risk of seizures and death with overdose from this product.

[Slide.]

Yet another product, in this case having multiple guiding systems, is the drug product

alosetron, known perhaps to some of you as Lotronex. For this product, there is a patient agreement. There is physician attestation to knowledge of the disease irritable bowel syndrome and of the attendant product risks in using this.

The physician then obtains stickers which are affixed to prescription. These indicate then the physician's expertise, appropriate patient selection, and signing of the patient agreement.

Pharmacists look for these stickers on prescription prior to dispensing. This system depends then upon individuals being aware and informed about its existence.

[Slide.]

Turning to the third category of tools are restricted access systems. These systems link drug product access to compliance with risk management program elements. An example would be the drug product clozapine, or the expression is "no blood, no drug," the reason being that proof of adequate white cell count is necessary for pharmacists to dispense this product.

Restricted access systems often limit prescribing and dispensing to selected healthcare practitioners and pharmacists and may require

documentation of safe use conditions, such as laboratory tests or monitoring, before dispensing to patients.

[Slide.]

One example of a restricted access system is the thalidomide program, known as STEPS, standing for the System for Thalidomide Education and Prescribing Safety. I will be describing only a component of this, it is actually quite complex.

But in the thalidomide system, this product is shipped only to pharmacists who are registered with the program, and these pharmacists can dispense the product only if the following conditions are met: that both the patient and the prescriber are registered with the program, necessary documentation is in place for that, and that, in fact, there is some receipt of centrally authorized information indicating both the provider and the patient have been compliant with the program features to assure that the product isn't given to anyone who is pregnant.

[Slide.]

In its concept paper, FDA set forth three considerations in the use and development of tools. The first was that stakeholder input be solicited

on the feasibility and acceptance of the tools, and this would include all manner of prescribers, pharmacists, patients, and payors, and yet other parties perhaps we haven't named.

The Agency also set forth the value of consistency in selecting and developing tools since we think it is important to look to existing and well-accepted tools to minimize confusion and burden upon the healthcare community.

The Agency also indicated the value of evidence of past effectiveness of a tool in a similar product or in a similarly related safety objective in order again to make use of the most effective tools.

One comment received by the Agency at its public meeting in April, and also in the written commentary that came after that, from the public, was that another important consideration needed to be stated explicitly. That was preserving patient access to the benefits of drugs at the same time that risks were minimized.

[Slide.]

It is important to make some mention here of Subpart H, which is a regulatory approval option available to FDA to be applied in instances where

we have used surrogate endpoints or in instances where the Agency deems it important to have restrictions to ensure safe product use.

Subpart H may include restricted access.

[Slide.]

However, restricted access or distribution can be done without approval under Subpart H approval provisions. Subpart H affords FDA the opportunity of more rapid product withdrawal if that should be necessary, and also gives FDA an opportunity to review promotional materials prior to their publication.

[Slide.]

The FDA concept paper on risk management programs states as one of its important principles that it feel risk management programs should be evaluated. The Agency feels it is important to measure the effectiveness and value-added of tools and to use this information to assess progress toward attaining goals and any changes in health outcomes that might be attributed to the program.

It would also allow the modification, as necessary, of a risk management program to ensure that goals and health outcomes are, in fact, being met.

[Slide.]

In talking about evaluation, the risk management program concept paper has some overlap with the concept paper on postmarketing pharmacovigilance and pharmacoepidemiology. Active or targeted surveillance systems may, in fact, serve as means for measuring whether or not risk management program goals or objectives have been met and may, in fact, determine whether or not the overall risk management program itself is effective or needs modification.

[Slide.]

So, in summary, risk management programs, as they have been put into practice to date, and as FDA is stating its guidance to the industry over the coming year, these are sparingly applied interventions that have been intended to minimize identified risks and that are goal-oriented in terms of their purpose.

Risk management programs use tools that are commensurate with the risks and benefits of the products, and that they merit evaluation.

[Slide.]

Let me summarize and expand the three categories of tools that I have described, the

first being education and outreach. Education and outreach can take many forms, and the Agency and sponsors have had experience with these categories of interventions for many years. They can be general or targeted and applied to many drugs.

They are perceived by many as being limited in their intrusiveness on conventional prescribing, dispensing, and use processes. Data on the effectiveness of these interventions is, in fact, limited, and the data that are available are mixed with evidence of low to moderate influence upon actual prescribing behaviors.

[Slide.]

The category of risk management program tools that I described as guiding systems are more limited in number than education and outreach. These are perceived to be moderately intrusive on conventional prescribing, dispensing, and use processes, and as yet, we do not have evidence on their effectiveness, but evaluations are planned for several of these programs.

[Slide.]

Lastly, the category of risk management program tools described as restricted access are, like the guiding systems, applied really to a small

number of drugs and only a small number of systems are currently in practice.

They have been applied to date for products that have limited therapeutic alternatives and which themselves are recognized to pose significant risks. As such, the product and user populations for these products is typically quite small.

[Slide.]

Restricted access programs, because they, in fact, do restrict access and distribution through pharmacists and prescribers, are perceived as being the most intrusive on prescribing, dispensing, and use.

Because many of the participants in restricted access programs are registered, they are relatively closed systems and, as such, offer more easy opportunities to evaluate their success.

To that end, the data that the Agency has received to date has supported their effectiveness in risk minimization in these specialized populations, but they do also show instances where product uptake has been slow and where there has been substitution of alternative products for products that have risk management programs.

That concludes my remarks. I have a few minutes for questions if you like.

DR. KATZ: Thanks very much. Dr. Wlody.

DR. WLODY: I think one of the things that we could probably agree upon is that although we can't say how large a fraction of the problem it is, that some fraction of the inappropriate use of these opioid drugs may be due to lack of physician knowledge, and with that in mind, I think it is very interesting the case of alosetron where you mentioned that stickers indicating physician expertise have to be attached to the prescription before it is filled by the pharmacist, and I would be interested to know how that physician expertise is demonstrated, is it just the physician attestation of his knowledge?

DR. TRONTELL: I will invite Dr. Raczkowski to add to my comments, but it is based upon physician attestation of the necessary knowledge to diagnose and appropriately treat irritable bowel syndrome, so there is no independent body assessing certification.

There are, in fact, a few programs that do independently require certification. In the case of the drug product dofetilide, that is the case

that a certain competency has to be demonstrated.

DR. RACZKOWSKI: Yes, that is correct. The only thing I would add is that the physician's self-attestation also includes attestation that the physician is familiar with both the risks and manifestations of some of the serious side effects of alosetron and is familiar with how to treat those serious complications.

DR. KATZ: Bob.

DR. DWORKIN: It sounded to me like the two programs you described in a little bit of detail, the alosetron program and the thalidomide program, are ones that don't carry any penalties associated with not following these recommendations.

Is that correct, that these are really structures without a penalty?

Just a follow-on question, if that is true, is the DEA in a position, to the best of your knowledge, to institute similar programs that do have teeth, such that unless the program is adhered to, the individual doesn't have their DEA license maintained?

DR. TRONTELL: The two programs that I described, the penalty, in fact, this probably may

be a difficult term for me to apply, in the case of thalidomide, in fact, product access is not supposed to occur unless every step is done and documented. So, you might presume that the absence of the drug product being dispensed, the inconvenience or going back to, in fact, document the safe-use conditions could be an inconvenience, but no penalty is applied.

In the instance of the alosetron program, there may be instances where individuals are unaware of the program where, in fact, a prescription may be filled without a sticker or a physician may, in fact, write a prescription without a sticker. Those are, in fact, being evaluated at this time to determine to what extent that may be a problem.

Again, I will invite Dr. Raczkowski if there are any specific interventions related to any early signs that this may be having lapses in its application.

DR. RACZKOWSKI: I have no additional comments.

DR. KATZ: Dr. Cush.

DR. CUSH: Could you comment on the utility of a registry system as a restricted

access? I know those could be voluminous in what they collect, and they can also be limited, but nonetheless, have the same sort of effects as far as monitoring and tracking what happens to prescriptions and who they are given to, by whom, how many, and the outcomes of such prescriptions.

DR. TRONTELL: My own perspective on registry systems, it varies in part with our own agency's experience. Registries may, in fact, be put in place for purposes of obtaining information rather than trying to direct use. In the case of pregnancy registries, that may, in fact, allow us to determine if inadvertent pregnancy exposure, so they are more information gathering than restricting, in fact, access to the program.

Registry programs, mandatory registries, such as exist with thalidomide or for dofetilide, in fact, in practice, either because of the product or because of the registry itself, tend to be used on relatively small populations of patients.

To my knowledge, they have not been widely applied to products that have widespread use in the population in that instance where they are being used as a form of gate-keeping in terms of access to the program.

They do offer the opportunity to collect information on a population. It is important, however, that these registry programs be really highly focused on issues of product safety rather than research. There are some human subject concerns in setting up such programs.

DR. KATZ: Final question to Dr. Aronson.

DR. ARONSON: You mentioned education and outreach in the same breath, and I guess I would like to differentiate them at least in my own mind as one being, I suppose, verification of knowledge, not only teaching, but also to verify that the idea was received, whereas, the other is promotion of an idea over concept without necessarily verifying that it was received.

In that light, you have noted that there isn't any data to suggest that it makes a difference, although we all have our sense that it does.

Are you saying that because you are not differentiating those two processes of education and outreach, or because you have and it doesn't matter no matter how you do it?

DR. TRONTELL: I may not be making the same distinction in those two terms that do. The

distinction of some form of education that actually requires some certification that a level of knowledge has been attained. In fact, we might categorize in the guiding systems, which is that a certain level of competency needs to be demonstrated to an external body prior to the ability to prescribe, in contrast to the others which are more passive and dependent on an individual reading and absorbing and applying that information.

DR. KATZ: Thank you, Dr. Trontell.

I realize we are getting to the part of the afternoon where everyone's stamina and energy is probably at its nadir for the day. What we will do is we will take a eight-minute break. We will resume with the final presentation from Dr. Winchell and then we will have a focused and productive discussion until 5:00.

[Break.]

DR. KATZ: It is my pleasure to introduce Dr. Celia Winchell who is Acting Deputy Director of the Division of Anesthetical, Critical Care and Addiction Drug Products, our sponsor, who will be speaking about current opioid risk-management plans.

Current Opioid Risk Management Plan

DR. WINCHELL: To kick off this afternoon's discussion, what is left of it, and tomorrow's discussion, I am going to be describing elements of existing risk-management programs for opioid drugs.

[Slide.]

Before I begin, I will run through the products that I will be mentioning in this presentation to familiarize you with them and their similarities and differences.

I am including OxyContin, Avenza and Palladone which are within the group of modified-release opiates that we are primarily concerned with today and tomorrow. Others, including Actiq, Suboxone, Subutex and Tramadol are not really in the same category but the issues of concern were similar and the programs have many similar features.

OxyContin, as you know, is a modified-release formulation of oxycodone. Avenza is a once-a-day oral morphine. Palladone is a modified-release hydromorphone. Actiq is a high-dose fentanyl product formulated into an oral transmucosal dosage form resembling a lollypop.

For Actiq, the primary concern was the high potency of the product and the potential for accidental overdose, either in patients, themselves, due to improper patient selection or in household contacts of the patients, especially children who might be attracted to the product because of its formulation.

It is sweet, raspberry flavored, could be mistaken for candy. Because of this unique concern related to the formulation, specific aspects of the risk-management program for Actiq were included as conditions of approval under Subpart H.

Tramadol is an analgesic whose abuse potential was somewhat uncertain at the time of its approval. So the important issue at the time that this particular program was put into place was early detection of abuse and misuse.

Finally, Suboxone and Subutex are two bupranorphine formulations for agonist treatment of opioid dependence. All of the issues brought up by the opioid analgesics were relevant to these products as well but there is naturally less emphasis on encouraging doctors and pharmacists to avoid providing the product to patients with drug abuse problems.

Just to keep your interest, because I know everybody is tired, we can make a little game of finding the times that I say Suboxone-Subutex and the times I say Subutex-Suboxone because I know I am inconsistent. Also, you can find the times I left the Capital C out of OxyContin.

[Slide.]

Three themes are prominent in these programs. First, the prevention of accidental overdose or unintended exposure; this refers to possible overdoses in patients, themselves, who lack opioid tolerance and to the possibility of household contacts including children being harmed by accidental exposure to the products.

Second is the encouragement of proper patient selection. This subsumes, basically, two things. On the one hand, providers are urged to ensure the drug isn't given to someone who will be harmed by it.

So, in the case of some high-potency or high-dose products, this would include opioid-naive patients but it also includes patients who don't actually need opiate treatment and would, therefore, have no justification for being exposed to the risks of physical dependence, withdrawal and

overdose

Then the other aspect of proper patient selection refers to making an effort to ensure that the recipient of a prescription is, indeed, a legitimate patient, not a fraudulent patient with criminal intent who is obtaining the prescription from misuse, abuse or sale. Thirdly, the programs address the general topic of preventing and detecting misuse and abuse.

The programs generally employ several different features that have been listed among the possible components of risk management plans, education and outreach to patients, physicians and pharmacists have been incorporated in various ways. Some programs have also incorporated mechanisms to ensure safe and appropriate use along the lines of what was termed guiding systems by Dr. Trontell's presentation.

Some features intentionally restricted distribution to pharmacies early in launch and all included some form of targeted surveillance in addition to the usual passive collection of adverse event reports with the stipulation that some sort of prevention measures would be undertaken in the case of concerning trends.

I will run through some of these components were operationalized across risk management programs, but let me emphasize that the examples I am giving will not be exhaustive, just representative.

[Slide.]

Education has been an important component of virtually all of these programs. Patient package inserts in consumer-friendly language have been made available to alert patients to important information about use of their medications. Each one also emphasizes the risk of overdose and the need to store the product securely away from household contacts who could be harmed by exposure to the products.

A public service campaign about the risks of prescription drug abuse has been a component of one program. Training materials and courses for physicians and pharmacists have also been developed and some companies have established call centers or web sites to provide information about their products.

Some programs have been targeted to particular medical specialties, but a challenge for these education and training programs for these

modified-release opioids is the broad range of prescribers as was mentioned to use in Dr. Rigoni's presentation of prescription usage data.

I will go through in a little more detail what some of these educational programs include.

[Slide.]

The Subutex-Suboxone risk management program includes a brochure for physicians that is separate from the package insert. This brochure is Answers to Frequently Asked Questions. It is about the nuts and bolts of using the product. Because special qualifications and a special notification process involving HHS and DEA are needed before using Subutex and Suboxone to treat opiate dependence, this brochure walks the doctors through that process.

It also gives tips on storage and recordkeeping, so doctors will feel comfortable keeping a supply on hand in order to provide supervised dosing, and it gives some tips on preventing diversion, just simple things like writing prescriptions in a way that makes them less likely to be altered, keeping your prescription pads secure, and so on.

There are many opportunities for in-depth

physician education on these products, some provided by the sponsor, but many provided by the Substance Abuse and Mental Health Service Administration.

These are conveyed through web sites and through professional and through professional organizations and fulfill the legal requirements for training that is part of the notification process.

[Slide.]

For Actiq, the physician education component is aimed at specialists in oncology and pain. In includes a CD-ROM that discusses child safety, proper patient selection, prevention of diversion and abuse, and proper handling of the product, emphasizing safe storage and disposal.

Company made available a speakers' bureau, they trained specialized detail reps to educate the healthcare providers about the product, and in addition, put together a professional information kit and made that available to physicians.

[Slide.]

The program for OxyContin has included physician education materials that address the use of opiates in medical practice. An anti-diversion

brochure gives specific information about how individuals obtain prescription drug from unwitting physicians through theft or alteration of prescriptions or through the fabrication of clinical scenarios that persuade the physician to write a prescription for the desired product.

These brochures alert doctors to these techniques in order to help them guard against them. In addition, materials on pain diagnosis and management were developed, were funded and made available, and, in addition, a CD-ROM-based training program and series of lectures covering both topics was disseminated.

Several program include education directed specifically at pharmacists. I will run through some examples. Prior to the approval of Suboxone and Subutex, pharmacists actually had no role in the agonist treatment of opiate addiction because it was illegal under the Narcotic Addict Treatment Act to prescribe the treatment. It had to be dispensed at specialized clinics.

So, therefore, the entire concept of pharmacist seeing patients coming in to fill prescriptions for this type of treatment was novel, so a pharmacist brochure was developed which, in

addition to the usual pharmacologic information about the product itself, explained the requirements for physicians under the Drug Abuse Treatment Act, described the new role of pharmacists in addiction treatment, gave some helpful information about confidentiality and other things that we thought would be useful to pharmacists.

The seminars at pharmacy professional meetings are also being sponsored to educate pharmacists about various issues in addiction treatment and specifically about the products.

[Slide.]

The Actiq program emphasized enlisting the assistance of pharmacists as gatekeepers. Through Dear Pharmacist Letters and ads, pharmacists were prompted to check that the product was not prescribed off-label, and they were to play a role in ensuring the product did not go to opiate-naive patients.

In addition, the pharmacists were enlisted in giving child safety messages and giving the materials that are intended to prevent accidental exposure.

[Slide.]

A number of programs have employed tools which fall broadly in the category of guiding systems. These have been described as mechanisms or processes that help well-intentioned people to do the right thing.

For example, the OxyContin program featured distribution of tamper-resistant prescription pads to physicians that would help them ensure their prescriptions would be less likely to be altered, and because keeping the product safely away from children in the home is a key message of the Actiq program, the patients are provided with a Welcome Kit that gives them the tools to do just that. The kit contains cabinet locks, a locked bag for storing drug supply, child-resistant disposal container, and, in addition, the Actiq program incorporated prompts in the pharmacy software programs that are used in major chains. It was to encourage pharmacists to verify the patient was opioid-tolerant and to inquire whether there were children present in the home to make sure they got the appropriate child safety messages.

[Slide.]

Although not the type of closed restricted

access system that Dr. Trontell described associated with clozapine or thalidomide, some element of restriction of access is included in several of these programs.

Most obvious is control under the CSA. That is a form of restricted access. Not everyone can write a prescription for a controlled product, only physicians with a DEA license can write prescriptions for controlled products.

In addition, Schedule II control, which prevents phone-in prescriptions, disallows refills, and tends to prompt pharmacist scrutiny is in place for most of these products.

An additional restriction is in place for bupranorphine. Legislation, the Drug Abuse Treatment Act, exists that permits agonist treatment of opiate addiction outside the clinic setting using specific medications. At present, it applies only to bupranorphine.

Under this law, the physicians must meet certain criteria. It must go through a notification process to obtain a special identification number from DEA, and this identification number identifies the physician is qualified to use the product.

Some programs also include mechanisms to limit the distribution of products through retail pharmacies, and they have monitoring to make sure the sales match up with the geographic location of legitimate prescribers and patients.

[Slide.]

One very prominent feature in these programs is the inclusion of surveillance above and beyond the usual approaches to pharmacovigilance that are employed by pharmaceutical companies.

Each program has specific mechanisms or studies to detect early signals that problems are occurring. The Actiq program featured a series of checks and balances. Pharmacists are surveyed to ensure that the drug is being prescribed by physicians on label. Physicians are surveyed to ensure that the pharmaceutical detail reps are delivering the appropriate information, and patients are surveyed to ensure that pharmacists are delivering safety messages.

[Slide.]

Almost every program incorporates monitoring of various publicly available databases, both commercial databases and government-sponsored ones. Sponsors monitor prescription databases,

such as IMS Health, to get the type of drug usage information we saw presented this morning, and in addition, some may include monitoring of the ARCOS database, the DEA-administered program.

Risk management programs also include monitoring of databases, such as DAWN and the Toxic Exposure Surveillance System, to get information about overdoses and other adverse experiences and to keep an eye on how the drug is being discussed in the media and by the general public. Several sponsors have a formal approach to media surveillance, and also monitor internet discussion sites where information about the abuse of their products might be a topic.

[Slide.]

Where street use of the product is a concern, programs have incorporated ways to detect these trends through specific contact with individuals who are in a position to be aware of this use.

Important informants in these programs include entrants into drug treatment. Some programs have tapped into a government-funded system known as DENS, the Drug Evaluation Network System. This program collects information about

recent drug use from entrants into participating treatment programs using a computerized intake interview.

The interview uses the Addiction Severity Index and therefore gives information about the characteristics of patients who report using a particular drug, such as their previous drug use treatment history.

The sample currently includes 115 service delivery units across 79 sites. The initial sample, much smaller, was largely urban, but rural and suburban areas were added in a recent expansion.

For Suboxone and Subutex, an independent system of interviews with entrants into treatment was established, in which a cohort of 60 programs in both urban and rural areas, treating both adults and adolescents, are to administer a product familiarity interview to their treatment entrants.

This interview asks not only what drugs the specific patient has used, but asks what drugs he or she has heard about people using on the street.

Other program features intended to tap into this question include surveys of law

enforcement officials, quarterly surveys of individuals involved in drug abuse treatment and research, who have been termed "key" informants, surveys of physicians who have identified themselves as providing bupranorphine treatment, and semi-structured interviews with people involved in the drug-abusing street culture by trained ethnographers.

[Slide.]

To a greater or lesser extent, the various programs have identified interventions that could be taken if problems were detected through this targeted surveillance. In many cases where the problem might be tracked to improper patient selection or off-label use, the intervention involved retraining pharmaceutical reps and auditing promotional practices basically to ensure that doctors were being given the right information.

The Actiq program went so far as to call for the sponsor to send letters or have pharmaceutical reps go visit doctors who were identified as off-label prescribers. In addition, the OxyContin program has explicitly identified as one possible intervention, the involvement of law

enforcement in the area where diversion is detected.

[Slide.]

In summary, drawing from the risk management programs developed for various opioid products, I have given some examples of education and outreach efforts to physicians, pharmacists, and patients.

I have described some guiding systems that help people remember to do what needs to be done to use the product safely. I have described some way that supply and access to these drugs are constrained, and the various approaches taken to surveillance for abuse, misuse, and diversion.

Today and tomorrow, we will be asking for your input on the pros and cons of different approaches to each of these components of risk management and your insights on how risk management programs for these products can be optimized.

Thank you.

DR. KATZ: We have time for a question or two to Dr. Winchell. Yes.

DR. GARDNER: Dr. Winchell, thanks for that comprehensive list. Can you tell us whether any of these have been evaluated? Do we have any

idea of the effectiveness of any of these methods?

DR. WINCHELL: A lot of these programs are very new and have not been evaluated. We don't have much data collected on some of them. I am going to turn to my colleagues from the division to give you any other information that they have about these programs.

DR. RAPPAPORT: Unfortunately, we don't have any information that we can give you today. There is very limited information on a couple of the programs, and it is somewhat tangential to the discussions today.

The one bit of information that I think will be useful to you will be provided to you tomorrow by the folks from Purdue Pharma on the data that is available from the OxyContin plan.

DR. DWORKIN: I have a related question. After the program is approved and initiated, who is doing the evaluation of two things, the data that are collected by the program, whatever the program is, and the integrity of the program itself, is it simply that this is being done by the pharmaceutical company in-house, or does the Agency somehow provide monitoring and oversight of the collected data and the program?

DR. WINCHELL: All of these programs provide for periodic reporting to the Agency of the data collected, and we evaluate those in contacts with other sources of information that we have, like our AERS database, so we get what they get.

DR. KATZ: Dr. Skipper.

DR. SKIPPER: You didn't mention modifying the drugs, such as with Suboxone, adding naloxone as a risk management mechanism or program. I would like to know how that fits in as a category.

DR. WINCHELL: You could see it that way. Again, that is a strategy that has not had evaluation although it has theoretical appeal. It has been done once before, again without much evaluation.

DR. SKIPPER: It doesn't fit into any of these categories, right, very well. It would be product alteration to reduce risk.

DR. WINCHELL: I am going to let Dr. Rappaport answer that.

DR. RAPPAPORT: I think we have somewhat shied away from that because the efforts that have been made by a number of different sponsors with these types or products to make agonist/antagonist formulations have been thus far unsuccessful,

troublesome, both in the area of manufacturing and in clinical efficacy, and also the work that is being done there in the studies that are being done to evaluate the efficacy and the quality of these products is not completed, so we really don't have any data to present, but it has so far been rather disappointing and we are not as hopeful as we were a couple of years ago that that was going to be an alternative way to deal with this problem.

DR. KATZ: Dr. Maxwell.

DR. MAXWELL: Let me go back and ask again, and I am not quite sure who to ask, but I do want to clarify very specifically. On the targeted surveillance slide, there was comment that one of the things was surveys of interest in some drug treatment and the DENS program.

There was also mentioned the key informant network and the street ethnography network. I really would like to know, has FDA received any reports from either the Suboxone or the OxyContin manufacturers and distributors about any of these three different surveillance methods, have they come back to you and said we have gotten this many people from DENS?

DR. WINCHELL: Bob?

DR. HERTZ: I am not Bob, by the way.

[Laughter.]

DR. HERTZ: Yes, we have some information. Some of it is going to actually be presented tomorrow by the company, so we will hear about some of the information that has been collected so far for programs that are common to the product to be discussed tomorrow, as well as OxyContin. So, we will hear some of that from Purdue.

What was the rest of that?

DR. MAXWELL: Suboxone. Again, this was one of the ones that was mentioned. What data have you gotten back on that one?

DR. RAPPAPORT: You may have more on this, but that is a very new program, so we really don't have anything back yet.

DR. KATZ: Dr. Aronson, then the last question to Dr. Portenoy.

DR. ARONSON: Mine is very quick. You mentioned in your discussions of methodology, the granting of a specialized DEA licensure or privilege. What is that mechanism or what would you propose it to be?

DR. WINCHELL: Was this about the Drug Abuse Treatment Act, the special DEA identification

number associated with bupranorphine treatment, is that the question? Okay.

I am going to hope that my friends from DEA and CSAT will run up here and tackle me if I am very wrong, but the Drug Abuse Treatment Act requires that physicians notify the Department of their intent to use bupranorphine. They have to certify that they have the necessary qualifications and that they have the necessary facility to provide or refer patients for ancillary treatment, that they will restrict themselves to treating a limited number of patients at a time, and this notification goes through the Department of Health and Human Services in the person of CSAT, and to DEA, where if HHS finds the person is qualified, they ask DEA to issue an identification number.

The identification number then can be used on prescriptions or in other venues to indicate that the physician has complied with the requirements for notification.

DR. ARONSON: What is qualified? How do you define that?

DR. WINCHELL: Qualified is defined by law--Nick, do you want to answer this? This is the expert on this law from the Center for Substance

Abuse Treatment, Nick Ruder.

DR. RUDER: The qualifications are established in the statute. The physician must have a license to practice medicine, and it's a physician, it rules out nurse practitioners, physician assistants, and things like that.

The physician must have a valid DEA registration and the physician must be qualified by training and experience, and training and experience in this case means either certification by three or five societies, medical societies, the American Society for Addiction Medicine, the Osteopathic Society, and the American Academy of Addiction Psychiatry, or it could be eight hours of training in addiction treatment.

That is all specified in the statute, and the statute even goes on to say that eight hours of training can be by electronic means, so eight hours of training offered by an electronic web site also qualifies as training and experience under this law.

So, physicians certifies he will treat 30 or fewer patients, they have the capacity to refer patients for other ancillary services, have a DEA registration, license to practice medicine, and the

qualifications and training I talked about.

DR. WINCHELL: To the extent that you might be getting some ideas about how this could be applied in the current situation, it is helpful to know that this law took probably five years to get passed.

DR. KATZ: I am actually going to hold off on further questions for now unless anyone wants to sell one of their children for a question or something like that.

Okay. Go ahead.

DR. PORTENOY: I would actually like to sell three of my children.

DR. KATZ: Oh, no, I already have four, that was a mistake, I take it back.

[Laughter.]

DR. PORTENOY: This is a very, very important question, so my thanks to the Chairman.

From this broad framework of balance, has the Agency given any thought in the evaluation process to looking at the adverse effects of pain control on legitimate patients from any of these interventions? If not, why not?

DR. WINCHELL: Bob.

DR. RAPPAPORT: We have definitely given

it thought. It is a topic we actually brought to you today to ask how to do that, what we should be looking for in those kinds of programs. It is clearly an issue we have been thinking about since you actually brought it up two years ago at the last meeting.

DR. KATZ: I have a very ambitious agenda for the last 18 minutes or so of our session for today. So, hopefully, with the help of the Committee, we will be able to accomplish it, which is to answer Question No. 1 on the list of questions that we have.

Dr. Rappaport, you wanted to intercede with a comment before we do that?

DR. RAPPAPORT: I want to just give a little clarity to my earlier comment about the purpose of the meeting, the discussion that we are about to undertake, and that will probably continue into tomorrow, is a general topic discussion. It is not specific to Palladone. It is followed by a specific question related to Palladone tomorrow, what will probably be tomorrow afternoon by that time, and how we then apply that to other similar products and any recommendations that we glean from your discussion and comments, how we then apply

that to other similar products is still under discussion.

Committee Discussion

DR. KATZ: The last 16 minutes of our agenda. I want to try to answer Question No. 1, so if everybody could go in their packets and look at Question No. 1, which is actually very short.

I think the way that we can actually make some progress on this question in the next 15 minutes is for me to--I will read it to you, but then I will break it up into what I think are more digestible chunks, that I think are relatively non-controversial at this stage, but yet very important to the process of our meeting.

The question reads: Please discuss the role of the potent, modified-release opioids in the management of chronic pain.

What I am going to do is break that up into four pieces. I will read you all those four pieces now and then I will re-read No. 1. I am going to start with No. 1 and see if we can work our way through No. 4, if that makes any sense to anybody.

Here are the four pieces that I would like to break that question up into.

Question No. 1 is are there certain types of patients for whom moderate-release opioids for the treatment of chronic pain are appropriate, or to put it the other way, are there certain types of patients for whom moderate-release opioids are not appropriate, and the dimensions of patient status that we could consider are there is certain types of pain intensities, moderate, severe--you heard that discussion battered about earlier--for whom these opioids should be contraindicated or for whom they are indicated, are there certain diagnoses for which we can say they are or are not indicated, et cetera.

I will go through all of them and then I will go back to No. 1. The next piece is are there certain patients that are at higher risk for complications of opioid therapy that potentially could be identified upfront and perhaps be triaged into a different sort of treatment program or paradigm or clinic or specialist, et cetera.

No. 3 is, is there an appropriate duration of treatment or is there a duration of treatment that we can say a priori is never appropriate.

No. 4 is, is there an appropriate or inappropriate dose of opioids that we can identify.

Those are the four pieces. I know that people didn't take them down, so I will go through them now, one by one.

So, Question No. 1 or Subquestion No. 1 is: Is there any class of patients that we can identify a priori for whom long-term treatment with opioids is not appropriate?

Let me actually prompt the group even further. Is there any level of pain intensity for whom we can say, at the outset, that opioids are not appropriate? People with moderate pain, people with severe pain, mild pain, certain diagnostic types?

Dr. Portenoy.

DR. PORTENOY: It is easiest to go to the populations for which there is a worldwide consensus about the appropriate use of opioids to answer the question, so the populations for which there is very little argument around the world is patients with cancer and advanced medical illness, patients with AIDS who have advanced medical illness, and acute pain patients.

I think, as a general rule, in all those populations, what the guidelines around the world say is that anybody with moderate to severe pain

should at least be considered a candidate for opioid therapy.

So, the population that is not a candidate is the population of patients whose pain is generally mild, otherwise, they are all potentially candidates.

DR. KATZ: Does anybody have anything to add to that or disagree or care to amplify? Yes, Dr. Skipper.

DR. SKIPPER: I am wondering if rather than use the terms "moderate" or "severe," it is better to look at function, you know, pain that inhibits, you know, active function, or is there any question about those terms? They are so relative.

DR. PORTENOY: Could I answer that because I also didn't want to leave the impression that the guidelines or the consensus that has been applied for patients with advanced medical illness are being viewed as being simply transposable to chronic, nonmalignant pain. I didn't mean to say that.

But I think from the perspective of chronic, nonmalignant pain, there is a consensus, at least in the community of pain specialists that

is gradually evolving that patients with chronic, moderate to severe pain, which has impact on quality of life should at least be considered for opioid therapy, but one has to consider what conventional practice is, one has to consider whether other types of therapies exist that might have a better risk-benefit ratio, and one has to consider whether or not those patients have the capacity for responsible drug use.

So, the considerations in the population without advanced medical illness become more complex and require greater assessment, but the bottom line is that as a broad population issue in terms of pain severity, it is moderate to severe from a verbal report perspective, and not requiring them to function poorly.

DR. KATZ: What I am hearing from you, you are telling us that there is more or less a worldwide consensus that patients with terminal illnesses or life-threatening illnesses essentially regardless of pain severity are appropriate candidates for consideration of opioid therapy.

I don't hear anybody disagreeing with that. Somebody can flag me down if they do.

The next category, the much larger

category, as we have learned, is those patients with chronic pain not related to terminal illness, and I am hearing from you that in patients with nonmalignant pain, whether it be moderate or severe in intensity, opioid treatment can be appropriate long term given the other considerations that you had mentioned.

So, in other words, what I am trying to say is that even patients with moderate pain, nonmalignant in nature, should not be excluded from opioid therapy, but should be considered with the other provisos that you mentioned.

DR. PORTENOY: Again, this is from my perspective. If one goes through an assessment of the patient and thinks about what conventional practice is, what the risk-benefit ratio of alternative treatments are, and whether or not the patient has the capacity for responsible drug use, they will end up being a subpopulation of patients whose verbal report is that they have moderate pain for which opioids appear to be the safest and most appropriate therapy, but there will be a large number of patients for whom opioids shouldn't be considered, because either conventional practice is very much against it or because the risk-benefit

ratio falls on the side of trying alternative approaches first.

DR. KATZ: Does anybody disagree with that in the sense that they feel that patients with pain who by verbal report is in the moderate range, should be categorically excluded from long-term opioid therapy? Is there anybody at this table that feels that way? Dr. Leiderman.

DR. LEIDERMAN: Just a question, clarifying for Dr. Portenoy. When you say "opioid therapy," now, are we talking about all opiates, or immediate-release, combination, short-acting, long-acting, and then sort of my corollary to that question is I think it is really important to distinguish because, of course, we are talking, we are differentiating, that is the point of the meeting, a particular class of high dose, high potency, extended-release opiates at this meeting.

Then, I guess another corollary is do you conceive of an algorithm as being appropriate? In other words, should physicians in a best practice sense, either formally or informally, go through a reasonable algorithm that goes from non-opiates, NSAIDs, or whatever, up to immediate-release, combination, and then obviously depending upon

response and failing at one of those levels, be moved on in a sequential way as the WHO guidelines suggest for cancer pain.

DR. PORTENOY: I am glad you mentioned cancer pain at the end because my thinking is that it is always good to start with that population and then to think about how this moving target of what is appropriate opioid prescribing looks today and what has to happen to make it go forward in an appropriate way.

In the cancer population, there has been an ongoing controversy for 10 years about whether or not the latter is necessary, and there have been a couple of studies to show that patients with moderate pain do completely well with long-acting analgesics, with modified-release analgesics if the doses are adjusted appropriately, so they are started at very low doses.

From the pharmacological perspective, there is nothing magical, as you know, about a modified release opioid. If the dose is adjusted appropriate to the level of the patient's prior opioid exposure and pain, the patient should do well with that, and so the latter was developed as a teaching tool, but shouldn't be viewed as dogma,

as the only way you can treat a cancer patient.

So, from that perspective, can you bring that paradigm into the nonmalignant population? I would say yes, you can. I think the first decision to make is whether or not a patient is a candidate for long-term opioid therapy, and if they are a candidate for long-term opioid therapy, then, the question is which drug to be started, at which dose, monitored in an appropriate way over time, so that the therapy remains safe and can have the best chance for effectiveness.

If a patient has mild pain, I think everybody would agree that an opioid is not indicated or it would be perfectly reasonable to try a non-opioid first. If a patient has moderate pain, and they are still functioning well, that might be perfectly appropriate, as well.

Even if a patient presents to the practice and they have severe pain, but they are coping well and functioning well, one might think to try an NSAID first or an alternative non-opioid adjuvant analgesic with other modalities first.

I don't think we should stipulate that a specific therapy should be attached to a certain pain intensity, but if the entire clinical setting

supports the use of opioid drugs, based on an assessment of the patient including a risk assessment, then, the selection of the drug follows, to me, the same guidelines as appropriate for cancer pain.

In some cases, that would be to start with a short-acting and titrate, in some cases, it might be to start with a long-acting. Some of my best cases, parenthetically, have been elderly people that I have started on once-daily drugs at very low dose, because I can be sure adherence to therapy, I find it easy to monitor, and I can adjust the dose to make it safe.

DR. KATZ: Dr. Bril.

DR. BRIL: I guess I have a slightly different viewpoint for chronic, nonmalignant pain. First, pain severity. Someone with mild pain, I don't know that you need to go to an opiate at all.

So, we are talking about moderate and severe, so if you have carcinoma or cancer or terminal HIV or something like that, then, I have no trouble going directly to an opioid. If it's a chronic, nonmalignant situation, I do have a lot of trouble because I haven't yet heard anything that will predict, for me, the patients will have

trouble with the addiction or tolerance.

In all the studies I have seen, the patients who were on opiates for nonmalignant pain have the complications or adverse effects that are typical of the class, so, therefore, they have the potential for tolerance even though I know in diabetic neuropathy, they say that they don't get that with Tramadol, I just don't know about that.

So, I would think that for nonmalignant pain, what appears to be most reasonable for me, with moderate pain, is that you go through alternative therapeutic approaches, and that that will actually be what is advocated.

I just have a real problem in going directly to slow-release or fast-acting or any kind of opiate that has all those potentials for the complications and addiction, and I haven't really heard anything today that can identify for me definitely the patients who will run into trouble with that.

I mean I am really happy to learn more about it if I could, plus I haven't heard that this class of drugs is more effective really in a resounding way, say, as opposed to the tricyclic antidepressants for neuropathic pain or the

anticonvulsants. I mean I haven't heard that one is clearly superior, and they will all have side effects. I mean everything we use will have side effects, so I would think you might start with the least and then build up. That is basically how I would think.

DR. KATZ: Let me try to summarize what you just said, which seems to me that you feel that opioids should not be used until other therapies which have demonstrated safety and efficacy have been tried first and have not been satisfactory. Is that your point?

DR. BRIL: Pretty well, yes, because I have found, I guess for these patients, they do need chronic therapy, so I think the potential for abuse then increases, I would think, but, you know, I am not for sure, but they do need chronic therapy.

I found very few of my patients that can be treated for a few weeks or a few months and then stop treatment. They are on the treatment for years.

DR. KATZ: Certainly, if that recommendation echoes throughout many of the guidelines for use of long-term opioids that are

available, I don't think you would disagree with that, Russ, do you?

DR. PORTENOY: No, I think we are in screaming agreement for the most case, but I think in the absence of good--there aren't good data to show that opioids work in all different kinds of pain syndromes, as you know, and there is a little comparative data as the study that Nat talked about before that compared a tricyclic with morphine in diabetic neuropathy, but we are in a situation where we don't have enough efficacy or safety data for long enough periods of time, in appropriately selected subpopulations to be able to know in a very certain way, so it is in the realm of clinical judgment.

If you have a patient--I am just thinking in terms of case examples--but if you have a patient at the age of 60, who has an evolving painful diabetic polyneuropathy, had no prior history of substance abuse, has no family history of substance abuse, but has some significant risk factors to anticonvulsant and antidepressant therapy, and hasn't responded to NSAIDs over the counter, and that patient is no longer able to function well because the pain is becoming chronic

and debilitating and sleep is interfered with, and the patient is developing a mood disorder, and in your mind, you go through the risk-benefit ratio of thinking shall I start this patient on an opioid, or put this patient at some additional significant risk by trying a tricyclic or an anticonvulsant, I would think that the data at this point in time would support that route.

Again, if you are saying, well, where is the study to show that this 60-year-old diabetic with painful polyneuropathy, predisposed to side effects from anticonvulsants and antidepressants, with no prior history of substance abuse and a negative family history, is going to do well six years later, I don't have that data.

I would say, well, where is the data that they are going to do well with the tricyclic, you don't have those data either. So, I think that is the realm, that is the situation we are in.

DR. KATZ: So, with apologies to people who have questions and are waiting, I am not going to let this point go until it is done since it's two minutes of 5:00. I don't hear anybody saying that patients with pain of moderate intensity should categorically be excluded from opioid

therapy. Everyone is saying that there may be other considerations involved in choosing the therapy, which is the same for any medical treatment for any condition.

This is nothing new for physicians that there might be treatment considerations other than one simplistic one. But I don't hear anybody saying that patients whose pain is of an intensity that is moderate should categorically be excluded from opioid therapy.

Am I missing something here, Dr. Skipper?

DR. SKIPPER: I want to say one thing. It seems like to me that I still think that function needs to be the key element. Even if somebody has mild pain, and they are not able to function, then, that might be a candidate, because I think the problem with these mild, moderate, severe is if somebody wants the drugs, and you say, well, you have to have moderate pain to get it, well, oh, yeah, I have moderate pain. But if we analyze it from the function point of view, which is what we look at to decide if it's working, are they improving their function. If there is no decrease in function to begin with, how do we know?

DR. KATZ: I understand your point. It

doesn't sound like you are disagreeing with me.

DR. SKIPPER: I am disagreeing to use that as a measure, to say that patients with moderate to severe pain would be candidates.

DR. KATZ: You are saying that you would be more inclusive than that and allow patients with even lesser degrees of pain intensity, but functional impairment also--

DR. SKIPPER: Look at it from a whole different perspective, and not use those degrees at all.

DR. KATZ: Fine, that's great.

It's 5 o'clock. I am going to defer to the folks from FDA to see if they have any concluding comments from our session today.

Sorry, one announcement that I have been asked to make about 20 times, and I have forgotten every time.

It is not appropriate for people on the Advisory Committee to speak about Advisory Committee matters between now and 8 o'clock in the morning when you are sitting around the table, and I will see you then.

[Whereupon, at 5:00 p.m., the proceedings were recessed, to resume on Wednesday, September

10, 2003, at 8:00 a.m.]

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