UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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ANESTHETIC AND LIFE SUPPORT DRUGS ADVISORY COMMITTEE

MEETING

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THURSDAY
JANUARY 31, 2002

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The Advisory Committee met at 8:00 a.m. in the Grand Ballroom of the Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland, Dr. Nathaniel P. Katz, Acting Chair, presiding.

PRESENT:

NATHANIEL P. KATZ, M.D. M	Acting Chair
JIM ANTHONY, PhD	Guest
MICHAEL A. ASHBURN, M.D., MPH	Consultant
JANICE BITETTI, M.D.	Member
JEFF BLOOM	Patient Rep.
AMANDA S. CARLISLE, PhD, M.D.	Consultant
HOWARD D. CHILCOAT, M.D.	Guest
MARIA K. CONNOLLY, D.N.Sc	Consumer Rep.
KATHLEEN M. FOLEY, M.D.	Guest
ERIC S. HOLMBOE, M.D.	Consultant
TERESE T. HORLOCKER, M.D.	Consultant
BRUCE ALLEN LEVY, M.D., J.D.	Guest
LYNN A. LLOYD, R.Ph	Consultant
MITCHELL B. MAX, N.D.	Consultant
CHARLES H. McLESKEY, M.D.	Industry Rep.
LAURA F. McNICHOLAS, M.D.	Consultant
WINSTON C.V. PARRIS, M.D., FAcPM	Member
STEVEN PASSIK, M.D.	Guest
RUSSELL PORTENOY, M.D.	Guest
MARCUS M. REIDENBURG, M.D.	Consultant
RICHARD G. ROBERTS, M.D.	Guest

PRESENT: (continued)

MARK SCHREINER, M.D.	Guest
CHARLES SCHUSTER, M.D.	Guest
RICHARD M. SMILEY, M.D., PhD	Member
JOSEPH R. TOBIN, M.D.	Member
KIMBERLY TOPPER	Executive Secretary

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

(8:06 a.m.)

ACTING CHAIRMAN KATZ: Good morning. For those of you who were not here yesterday, my name is Nathaniel Katz. This is the Anesthetic and Life Support Drugs Advisory Committee meeting, Day Number Two. The topic is Opioids, and today we will be focusing primarily on addiction and related matters.

What I'd like to begin with is introductions. Most of the folks from the Advisory Committee introduced themselves yesterday. However, we have some new faces sitting around the table, some of whom are still getting coffee, I suppose. I think those folks were here yesterday.

So if we could perhaps go around the U-shaped table and, if anybody was not here yesterday, if they could briefly introduce themselves for the group. Why don't we start again at that end of the table.

DR. KWEDER: I'm Sandy Kweder from FDA.

DR. RAPPAPORT: Bob Rappaport, the Deputy Division Director for the Division of Anesthetics, Critical Care and Addiction Drug Products at the FDA.

DR. HERTZ: I'm Sharon Hertz, Medical Officer with the Division of Anesthetics, Critical

Care and Addiction Drug Products.

ACTING CHAIRMAN KATZ: Why don't we go ahead and do everyone again, because there are a number of people, I hear, especially from the public who were not here yesterday. So we can do it quickly, I think.

DR. MAX: I'm Mitchell Max. I'm a neurologist at the National Institute of Dental and Craniofacial Research.

DR. LLOYD: And I'm Lynn Lloyd, the Executive Director of the Arizona Board of Pharmacy.

DR. REIDENBURG: I'm Marcus Reidenburg, an internist and pharmacologist at Cornell.

DR. HOLMBOE: I'm Eric Holmboe. I'm a general internist from Yale University.

DR. ASHBURN: Michael Ashburn, an anesthesiologist. I'm the Medical Director of Pain Programs, the University of Utah and at Primary Children's Medical Center.

DR. McNICHOLAS: Laura McNicholas from the University of Pennsylvania and the Philadelphia VA. I am a psychiatrist in substance abuse.

DR. HORLOCKER: I'm Terese Horlocker. I'm an anesthesiologist at the Mayo Clinic.

DR. CONNOLLY: I'm Maria Connolly, and I

am Associate Professor at Loyola University, Chicago, and I am the Consumer Representative to this panel.

DR. SMILEY: Rich Smiley, anesthesiologist at Columbia University in New York.

DR. TOBIN: I'm Joe Tobin, pediatric anesthesia and intensive care, Wake Forest, University.

ACTING CHAIRMAN KATZ: I'm Nathaniel Katz again. I'm a neurologist. I am affiliated with Brigham and Women's Hospital and the Dana Farber Cancer Institute in Boston, Massachusetts.

DR. CARLISLE: I'm Sue Carlisle. I'm an anesthesiologist and intensivist from the University of California, San Francisco, and Chief of Anesthesia at San Francisco General Hospital.

DR. PARRIS: I'm Winston Parris, Tampa Pain Relief Center and Professor of Anesthesiology at University of South Florida in Tampa.

DR. LEVY: I'm Bruce Levy. I'm the former Director at the Texas State Board of Medical Examiners and the former Executive Vice President of the Federation of State Medical Boards.

DR. McLESKEY: Charlie McLeskey, an anesthesiologist. I work for Abbott Labs, and I'm representing industry today.

MR. BLOOM: Hi. I'm Jeff Bloom. I'm a retired AIDS volunteer patient advocate, and I'm from Washington D.C.

DR. PORTENOY: I'm Russ Portenoy. I'm a neurologist and Chairman of the Department of Pain Medicine and Palliative Care at the Beth Israel Medical Center in New York.

DR. ROBERTS: Rich Roberts, family physician, University of Wisconsin.

DR. SCHREINER: Mark Schreiner. I'm a pediatric anesthesiologist at Children's Hospital, Philadelphia.

DR. ANTHONY: Jim Anthony, epidemiologist from Johns Hopkins School of Public Health.

DR. SCHUSTER: Charles Schuster, psychopharmacologist, Professor of Psychiatry and Behavioral Neurosciences and the Director of the Addiction Research Institute at Wayne State University.

DR. FOLEY: I'm Kathy Foley. I'm a neuroncologist and attending neurologist at Memorial Sloan Kettering Cancer Center, and I direct a project called the Project on Death in America to improve the care of the dying which has an international perspective to make drugs available to developing

countries, particularly analgesic drugs for the treatment of pain in patients with cancer and AIDS.

DR. PASSIK: I'm Steve Passik. I'm a psychologist from Community Cancer Care in Indianapolis and the University of Indiana School of Medicine.

DR. CHILCOAT: I'm Howard Chilcoat. I'm an epidemiologist at the Johns Hopkins Bloomberg School of Public Health.

ACTING CHAIRMAN KATZ: I thank everybody for going through that. I want to remind you, the speakers, there is a technical issue with the microphone. So when you speak, you need to hit your button and turn your microphone on, and when you are finished speaking, you need to hit it and turn it off; because it creates some sort of technical problem.

Let me make one more introduction which is not made yet. This is Kimberly Topper sitting to my left. You will hear me whispering back and forth to her during the meeting when she tells me what I'm doing wrong and what I'm doing right. Without her, I can assure you that there would be no meeting today. Nothing would happen correctly, and she will be reading the conflict of interest disclosure.

MS. TOPPER: The following special

government employees have been granted general matters waivers which permits their participation in today's discussion: Michael Ashburn, Janice Bitetti, Richard Gorman, Eric Holmboe, Terese Horlocker, Mitchell Max, Laura McNicholas, Winston Parris, Marcus Reidenburg, Richard Smiley, Joseph Tobin, Nathaniel Katz, Llyn Lloyd, Maria Connolly, Amanda Carlisle.

The Committee will discuss the medical use of opiate analgesics in various patient populations, including pediatric patients and patients with chronic pain of nonmalignant etiology, as well as to the risk and benefit ratio of extending opiate treatment into these populations.

The Committee will also address concerns regarding the abuse potential, diversion and increasing incidence of addiction to opiate analgesics, especially to the modified release opiate analgesics.

The FDA is in the process of amending its policy concerning disclosure of financial interests that give rise to waivers for participation in meetings at which particular products are not at issue. Unlike issues before Committee in which the particular product is discussed, issues of broader applicability such as the topic of today's meeting

involve many industrial sponsors and academic institutions.

The committee members have been screened for their financial interests as they may apply to the general topic at hand. However, because general topics impact on so many institutions, it is not prudent to recite all the potential conflicts as they apply to each member.

FDA acknowledges that there may be potential conflicts of interest but, because of the general nature of the discussion before the Committee, these potential conflicts are mitigated. Should the discussion turn to issues related to a specific party matter, the Chair of the Committee will either terminate the proceedings or redirect the discussion to only matters of general interest.

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

Dr. James Anthony serves as a researcher and has contracts and grants from NIDA, NIMH, NIA, CSAT, CSAP and NIJ. In addition, in the past Dr. Anthony has given a talk for Purdue Pharma and has served as a scientific advisor for Star Scientific.

Dr. Steven Passik is a researcher on contracts and grants from Eli Lilly, Janssen, Ortho Biotech, Organon, and Pfizer. He also consults for Eli Lilly, Janssen and Ortho Biotech. Additionally, he is a scientific advisor to Eli Lilly, Janssen, Adolor, and he receives speaker fees from Eli Lilly, Janssen, Ortho Biotech, Organon, Pfizer, Purdue Pharma, Roxanne and Knoll.

Dr. Richard Roberts is a scientific advisor to Pharmacia's Detrol Global Advisory Board and the Pfizer/ Pharmacia Bextra Primary Care Advisory Board.

Dr. Charles Schuster has consulted for Alza Corporation in the past.

Dr. Neil Schechter serves on Astra-Zeneca's Speaker Bureau.

Dr. Mark Schreiner is a Medical Director of the Children's Clinical Research Institute. As such, he is involved in clinical trials sponsored by Baxter Pharmaceutical, Sanofi Synthelabo, Novartis, Purdue Pharma, L.P., King Pharmaceuticals, Abbott, and GlaxoSmithKline. He receives no direct compensation from the pharmaceutical sponsors.

Dr. Kathleen Foley in the past ten years has consulted with many of the companies that make

analgesic drugs. In the past year she has worked with Purdue Pharma, Janssen, Knoll and Abbott. She is also on the Speakers Bureau for Purdue Pharma, Knoll and Janssen. Additionally, she is a scientific advisor to the American Pain Foundation.

Dr. Russell Portenoy has constituencies with Merck, Ligand, and Akros. He is also on the Speakers Bureau for Purdue Pharma and Janssen. Dr. Portenoy also serves as scientific advisor for Cima Pharmaceuticals, Durect, Chrysalis. Additionally, he reports involvement on contracts and grants with Parke-Davis, Boehringer Ingelheim, Elan, Ortho Bio, Endo, Ametek, Medtronic, Purdue Pharma, Pfizer, Janssen, Abbott, Curatech, Ortho-McNeil, Elan, Pfizer and Searle.

In addition, we would like to disclose that Charles McLeskey is participating in this meeting as an industry representative and acting on behalf of regulated industry. As such, he has not been screened for conflict of interest. Thank you.

ACTING CHAIRMAN KATZ: Thank you, Kimberly. What I'd like to do now is to reintroduce Dr. Bob Rappaport, who is Deputy Division Director of the Division of Anesthetic Critical Care and Addiction Drug Products at the FDA, and he will be giving us

introductory comments this morning.

DR. RAPPAPORT: Dr. Katz, members of the Committee, ladies and gentlemen, I would like to thank you for returning for the second day of this Advisory Committee meeting on opiate analgesic use and abuse.

I would also like to thank the Committee for their discussion and commentary at yesterday's session. I am confident that your input will prove invaluable in our deliberations with our colleagues in industry regarding their development programs for opiate analgesics.

I would also like to thank the many individuals who have taken their time from their busy lives to present at the open public hearings. Your voices, too, will impact on the decisions we make in the future.

Yesterday we addressed the many practical issues related to the interface between clinical practice and clinical trial design. Today we will address the difficult topic of risk management.

Opiate analgesics are a two-edged sword in the medical armamentarium. They provide precious pain relief, relief of discomfort and relief of fear for many patients in pain, and yet their use can also have devastating effects when they are improperly

prescribed, when they are diverted for illicit use or when children are accidentally exposed to these potent drugs.

Our purpose today is to find the right balance between the benefits and risks associated with opiate analgesics. We at the agency are well aware of the concerns of the people who speak passionately for both the enormous value as well as the significant risks associated with these products.

To help us to continue to provide safe and effective opiate analgesics to patients in need while avoiding the inherent risks of these products, we ask that you focus your comments on the discussion points that we have provided to you in your background packages. We also ask that you open your minds to both sides of what is clearly an emotional and complex topic for all of us.

Today you will first hear an industry perspective on the development of opiate analgesics. Following that, Dr. Judy Ball from the Substance Abuse and Mental Health Services Administration will present data on abuse and diversion of these products.

Dr. Deborah Leiderman will inform you about the process by which the FDA assesses the abuse liability of new drug products, and Mr. Howard Davis

will present the DEA's perspective on criminal drug diversion in our communities.

You will also be informed about the epidemiology of prescription drug abuse by Dr. Howard Chilcoat, and about the problems associated with drug abuse in pain patients by Dr. Steven Passik.

Finally, Dr. Sharon Hertz will present to you some of the regulatory approaches that the agency has employed thus far to mitigate the problems associated with the abuse of opioid analgesics.

Armed with this invaluable information, we are asking that you incorporate it into your deliberations on a series of discussion points. First, we are asking you to address the adequacy of the available data to determine the prevalence of addiction among patients treated with opiates for chronic pain.

Second, we want you to address the available methods for assessing and monitoring addiction in the clinical setting and how those methods might be extended to clinical trials.

Finally, we are asking you to comment on what measures we should consider when we are assessing the development of an overall risk management strategy designed to reduce the abuse and diversion of opiate

analgesics while avoiding restriction of access to these drug products by patients in need of treatment.

Once again, as I did yesterday, I would like to read briefly from Dr. McCormick's cover memo. While she has been unable to participate in this meeting due to a medical condition, her words speak eloquently to the conflicting concerns we face when assessing opiate drug development plans.

"This meeting is about the patient suffering from pain who requires opiate therapy for adequate management. It is about the patient who is an addict who also experiences chronic pain. It is about the individual who may have a propensity for substance abuse, who seeks opiate medication under false pretenses.

"It is about the youth who tries prescription drugs for the first time and dies from an overdose. It is about the infant or child suffering from a painful condition who may benefit from what once were adult medications."

Thank you.

ACTING CHAIRMAN KATZ: Thank you, Dr. Rappaport, for introducing some of the difficult challenges that we will be facing today in making some progress on these issues.

What we will do now is proceed to the open public hearing. I see some of our speakers are ready. What I would like to do is just make a few comments to the speakers, which are identical to the ones that I made yesterday.

The purpose of these comments is to make sure that everybody from our rather full list gets a chance to speak their mind. The main theme here is that I am going to be the nasty guy that makes everybody stick to their required time. So you've got three minutes. If you use less than three minutes, there's a special place in heaven reserved for you, I know.

There will be a green light on for two minutes. Then it will turn yellow for your last minute, and then at the very end there will be a red light, and then there will be a horrible buzzer, and then there will be unspeakable punishments.

Everybody should have a list of the order of speakers and, if you see that you are next, you should sit up by one of those "speaker ready" chairs, and the FDA technical people will help you find the right place.

So with that, why don't we have our first speaker, please.

MS. UNDERWOOD: Good morning. It's a pleasure to have this opportunity to speak with you. I'm Catherine Underwood, and I'm the Executive Director of the American Pain Society.

The APS is an interdisciplinary professional society of over 3500 members. The Society is a public, not for profit organization and has received support from pharmaceutical companies in the form of unrestricted educational grants in support of its mission.

Pain is one of the most common reasons people consult a physician. Yet it frequently is inadequately treated, leading to enormous social cost in the form of needless suffering, lost productivity, and excessive health care expenditures.

Patients with chronic pain and related disability are best treated by an interdisciplinary team. Since chronic pain is not a single entity but may have myriad causes and perpetuating factors, treatment strategies and options include behavioral therapies, rehabilitation, interventional therapies, and the sustained use of a number of different medications, including opioids.

Barriers to the use of opioids include often exaggerated concerns about addiction,

respiratory depression and other side effects, including tolerance. In addition, fears of diversion and regulatory scrutiny weigh heavily on the physician's mind when he or she is considering prescribing these medications.

The APS shares society's concerns about addressing the diversion and potent opioids and other controlled substances for illicit use. Substance abuse, including alcohol, tobacco, opioids and other substances, lead to individual, family, and societal harm. However, we must not allow diversion and abuse of opioids by some to deny deserving suffering patients access to medications that relieve their suffering, lessen their disability, and improve their quality of life.

When considering options to address opioid diversion, policy makers should carefully consider the following: Opioids are important in the treatment of chronic pain, and benefits far outweigh risks in carefully selected patients. Opioids should be administered within the context of established patient care guidelines.

Physician and other health care provider education and training regarding the diagnosis and treatment of pain is poor. Patient care and outcomes

could be improved with better education.

Tension exists between efforts to decrease abuse and diversion of opioids versus access to these medications for legitimate use. Policy makers, regulators and those in law enforcement should carefully consider the potential for harm to patients caused by efforts to control abuse and diversion.

Finally, policy makers should also strongly support increased funding for chronic pain research so that we can better understand the role opioids play in the treatment of these complex diseases.

Thank you for your time.

ACTING CHAIRMAN KATZ: Thank you. Next speaker, please. Before you begin, let me just remind all the speakers as well that it is important to begin after you say your name and who you are with your potential disclosure. So who do you work for, if there is anybody that sponsored your trip down here, if you work for an organization that is funded by a pharmaceutical company, please lay all that out right up front. Next speaker, please. Anybody there? Next speaker?

DR. CORK: Good morning. My name is Randall Cork. I'm the Chair of Anesthesiology at

Louisiana State University, and I'm the Director of the Pain Management Clinic there. We serve an area of mainly northern Louisiana, eastern Texas, southern Arkansas.

In terms of disclosures, I've been in academic medicine for about 20 years. I've done a number of research studies in the name of the various institutions, and these institutions include University of Arizona and Louisiana State University, both of which have gotten funds from Merck, Roche, Pfizer, Alza and other companies.

I have also given some talks in northern Louisiana and souther Arkansas that have been funded by some of these companies.

I'm going to briefly comment on the written comments that I have submitted to the Committee, and then kind of take the opportunity of using whatever time might be left to address some of the things that were raised yesterday during the meeting.

In terms of my written comments, they are very brief. They specifically address the issue of opioids compare to nonsteroidal anti-inflammatory agents. It's always impressed me that we spend all of this time and energy attempting to regulate opioids,

but we kill many more patient with nonsteroidals than we do opioids, and yet the regulatory efforts in that direction are minimal. Those drugs are available over-the-counter. We kill 17,000 people a year with nonsteroidals.

With regard to some of the comments that were made yesterday, specifically in my context I was not paid to come here by a drug company. The Department of Anesthesiology funded my trip because of the concern that our patients have expressed that the government is getting ready to help them again.

They were previously helped by the government of Louisiana when they instituted some of the rules that the Texas Board instituted in terms of regulation of physicians. What happened at that time was that suddenly the physicians in Louisiana were afraid to prescribe opioids again, and their patients all suddenly ended up on the doorstep of LSU. We now have about 500 patients on our waiting list.

Some questions for Dr. Levy that I have regarding these board regulations: It seems that the regulations do tend to effectively punish those physicians who prescribe opioids too much, but there has never been an instance as I know where Texas has disciplined a physician for not treating pain

adequately enough, and yet as we found out from previous speakers, that seems to be the main problem.

ACTING CHAIRMAN KATZ: Dr. Cork, I'm afraid I'm going to have to ask you to bring your comments to a close.

DR. CORK: Thank you very much.

ACTING CHAIRMAN KATZ: The next speaker, please.

DR. BATTISTA: Hi. I'm Dr. Ellen Battista. I'm going to read off my paper here. I have over 15 years of experience in chronic pain treatment, both in cancer pain, nonmalignant pain. I have treated also children with pain and have established several programs in this area.

Currently I'm in a chronic pain practice. On the personal side, I am the mother of two, one teenager and a wanna-be teenager. As every parent, I have concerns whether my children will make good choices in life, and I am concerned with whether my children will engage in risky adolescent behavior that provides them with encounters with tobacco, alcohol and illicit drug use.

My multiple roles in life as a pain treatment provider and mother have caused me to look closely at the issues at hand today regarding the

medical use of opiates versus its effect in drug abuse in this country. After close evaluation of the facts and my experience, I have come to today's meeting for the purpose of supporting legitimate medical use of opiates in the treatment of pain.

As you all know, over 100 million North Americans suffer from chronic pain. They are either partially or totally disabled by pain. The toll of unrelieved pain is high.

It leaves the individual with loss of function of daily activities, loss of financial stability, alters the individual's relationship with significant others, causes severe depression where suicide may be contemplated to escape its suffering.

It costs industry over $60 million annually -- billions, excuse me, not millions. There has been much research over the past 35 years, and we have improved our ability to treat pain. It still is not perfect.

More specifically, the advent of opiate drugs that are long lasting, sustained release or controlled release have provided patients an opportunity to experience more continuous relief than their predecessor drugs that afforded only several hours of relief.

Opiate analgesics can be therapeutic in a percentage of patients with pain problems. Their use should depend on intended outcome, and they should be monitored.

The issue at today's meeting is whether legitimate use of these opiates provide a risk to society at large, and we know that the adolescents are at highest risk. But despite this fact that we know that, we have no clearcut guidelines as to why drug abuse is a problem in certain individuals and why moment decisions have long term consequences.

It would appear that addiction behaviors are not only facilitated by environment but may also be influenced by heredity, cognitive development. In short, the addiction issue is complicated and multi-faceted.

Herein may lay the problem with the issues. We are taking a complicated issue of addiction, trying to place responsibility on one category of drug, and superimposing the issue of legitimate medical use for the treatment of pain, when the problems need to be analyzed and dealt with separately.

In a desperate attempt to curtail drug addiction in our society, we have tried to impose a

cause and effect model where it is not appropriate. Simplistic solutions for curtailing or limiting a drug category will not alter appropriate -- not alter abuse for other drugs.

The issue of addition needs to be --

ACTING CHAIRMAN KATZ: I'm sorry. I have to ask you bring your comments to a close.

DR. BATTISTA: I am. Any action that limits or curtails legitimate medical use for opiates will harm millions of Americans who need these medications for the treatment of their pain. These drugs are vital. The use of opiate --

ACTING CHAIRMAN KATZ: I'm sorry. You have to stop speaking. Your time is finished.

DR. BATTISTA: I'm sorry. Okay.

ACTING CHAIRMAN KATZ: Could we have the next speaker, please.

MS. BALUSS: Good morning. My name is Mary Baluss. I am from the Palliative Care Law Project. I have nothing to declare.

I submitted a written statement to the Committee, and I hope that you will review it. In the interest of time and not being repetitive, I'd like to make three major points that were in the brief, but I wanted to highlight them somewhat.

The first is that pain is an epidemic, and it is untreated, as you've heard. I think one of the factors there that doesn't get much talked about is the fact that opioids are the first line of defense against pain in the poor, that there is a great deal of talk about opioids being appropriate only after other modalities have failed. However, in underserved, low economic status populations, it is not possible to refer the patient for extensive MRIs, and they are not available to the anesthesiologies and the procedural efforts to cure pain.

These folks are often limited, because they are on Medicaid. Medicaid often limits the number of prescriptions, and very few specialists will take Medicaid.

So if you restrict Oxycontin to specialists and if the state medical boards continue to harp on -- and I don't mean to be disrespectful -- all other modalities, then the people who work all their lives at jobs that are intensely physical, who have no medical insurance, and who live in a community where the first line of analgesia is alcohol will be seriously disserved.

Secondly, I want to tell you about -- and this is partly in response to Dr. Levy's presentation

yesterday. After I left here yesterday, I got three communications. One was from a man in Missouri whose uncle was dying of massively metastasized cancer, who had had no pain medicine beyond over-the-counters, and his doctor, knowing full well he was in pain, had said to them I am not going to lose my license.

This is a doctor who chose gross malpractice over treating pain, because of fear of losing his license. Dr. Levy was very, I think, appropriately clear yesterday about the number of sanctions by state medical boards. However, that understates the problem very dramatically, because it doesn't take into account letters from state medical boards that quite reasonably scare people off the market. It --

ACTING CHAIRMAN KATZ: Could you wrap up, please?

MS. BALUSS: Yes. So there are -- The other two pieces of news that I got yesterday was that one doctor's DEA license was being pulled. Thank you.

ACTING CHAIRMAN KATZ: Thank you very much for your comments, in particular those about the role of opioids in the poor. You can go ahead and have a seat, please.

I just want to reemphasize the purpose of

the timer for the subsequent speakers. The purpose of the timer is so that today in a very difficult and challenging area where there is a wide diversity of opinions and a wide spectrum of individuals to be represented, we want to make sure that everybody is heard. So I have to be the rude one to enforce the timer, but I hope that you will forgive me in advance and do your best to stick within your allotted time.

Yes, the next speaker, please.

DR. GALLAGHER: Good morning. My name is Rollin Gallagher. I am representing the American Academy of Pain Medicine and its Board of Directors. The American Academy of Pain Medicine does receive funds from a variety of industry sources for continuing education in pain medicine.

The American Academy of Pain Medicine recognizes and is concerned about reports of potential actions by the DEA and the FDA about the -- to restrict the availability of Oxycontin, and the recent media coverage sensationalizing opioid diversion and abuse is causing several states to consider the ban of some opioid preparations.

This action will adversely affect the care and the lives of many millions of patients who legitimately require these medications and opioids in

general for management of their pain disorders in order to function in their lives.

Media publicity, when biased and nonscientifically based, further promotes a believe in the general public that proper treatment of pain disorders with opioids will invariably result in addiction.

Physicians fearing undue discrimination, persecution, investigation and possible prosecution will avoid prescribing opioids to the detriment of their patients, and even when they are the safest and the most effective treatments.

The AAPM, the American Academy of Pain Medicine, and the AMA are on record as strongly opposing medication diversion and abuse and supporting the DEA and state medical boards' efforts to curtail diversion. We support and sponsor continuing education of all physicians on the appropriate use of opioids as part of pain treatment.

We recognize, however, that addiction is an important neurobiological brain disorder affecting many aspects of a person's life, and the root cause of drug abuse is not any one drug but rather untreated addiction and the lack of access to good addiction treatments.

In June the AAPM sponsored a resolution to the AMA which was passed to established policy to (1) support the prevention and treatment of pain disorders, including the continued education of doctors in the use of opioids and other treatments for pain; (2) to support education of all medical students and physicians in pain and addictions; (3) to serve as educational resources to the media by providing objective information regarding the management of pain.

In the interest of time, I will wrap it up for you guys. I support the other statements that have been made about the importance of opioids in pain treatment. The AAMA and the APM remain committed to promoting appropriate pain treatment, and we will be available to you and your distinguished panelists to explore acceptable and available methods to prevent and eliminate diversion and abuse of controlled substances. Thank you very much.

ACTING CHAIRMAN KATZ: Thank you, Dr. Gallagher. May we have the next speaker, please.

MR. LIEB: Good morning. My name is Rick Lieb, and I am here to speak with you not only as a Board member of the National Pain Foundation but also as a person who lives with chronic pain.

Consequently, let me be presumptuous and say that I feel as though I am talking for the millions of people in the U.S. who live daily with pain. I am here because I am concerned at the recent publicity surrounding the misuse and abuse of pain medications, particularly Oxycontin, because of backlash in this country that will set back pain treatment years, if not decades.

Both as a Board member of the NPF and as an individual with chronic pain, I am concerned that this resulting backlash from these tragic incidents will have even more severe repercussions for people like me who rely on these kinds of pain medications to live more normal lives.

I would like to share with you in a very brief manner my personal experience with chronic pain. In 1995 and 1996 I had two low back fusions in an effort to fix degenerative disk disease. As a result, I was left with arachnoiditis which, as you know, is a condition that is progressive and is really disabling and generally leaves people unable to work.

From 1996 to 1998 I lived with this problem. I continued to work, but the pain was clearly beginning to interfere with my personal and professional life.

In my search for pain relief, I visited multiple doctors. Every single -- Every visit was incredibly frustrating. Just five years ago, many physicians viewed pain either as a character flaw or as untreatable because of their own reluctance to prescribe pain medication stronger than nonsteroidals.

In addition, many doctors strongly suggested to me that the use of any medications more potent than nonsteroidals was an admission of character weakness and could lead to addiction. This personal indictment occurred despite any analysis of my own personal background, including a tour in Vietnam as a Marine infantry officer, a flourishing family and demonstrated success in the business world and being on various -- in a publicly held firm and on multiple public and private boards.

In 1998 I met my current pain management doctor. He taught me an entire program, and I manage my pain, including the appropriate use of opioids. He taught me that pain is real and that the appropriate use of narcotic medications will reduce pain, improve an individual's quality of life, and enable someone to continue on with their personal and professional goals.

He taught me that opioid use is not a

result of a character flaw, but an appropriate part of pain management treatment.

I strongly urge the Committee to consider the needs of the many rather than the failings of the few when the time comes to draft public policy for the safe and effective use of these medications.

I speak on behalf of the Board of Directors of the National Pain Foundation to offer our assistance in addressing the serious problem of diversion and access to good medical care and successful pain treatment. Thank you.

ACTING CHAIRMAN KATZ: Thank you, sir. May we have the next speaker.

MR. LIEB: Seven seconds.

MR. CINQUE: I have a brief disclosure. The organization I represent does receive unrestricted educational grants from the pharmaceutical industry.

I'm Michael Cinque, pharmacist, Chief Pharmaceutical Care Officer for Excelerex. Excelerex provides pain management support services for hospice patients across the nation.

I'm here today on behalf of the American Pharmaceutical Association, the national professional society of pharmacists. Prescription medications are safe and effective when used appropriately, but they

can be deadly when used incorrectly.

Pharmacists are the health care providers who work most closely with patients to make the best use of medications. We also work with prescribers and other providers to prevent medication misuse such as diversion and abuse.

We look for such abuse markers to visit -- as visiting multiple prescribers and unusually large quantities. However, it's not always easy to determine if a prescription is fraudulent. No simple algorithm determines appropriate use, and pharmacists cannot view every patient as a potential drug abuser without compromising their responsibilities as a health provider.

The APhA applauds the FDA and DEA efforts to ensure the legitimate users of opiate analgesics maintain the ability to continue using these products. We caution, however, against efforts to restrict distribution or create administrative processes like triplicate prescriptions that limit a provider's ability to prescribe or dispense appropriate therapy.

With every barrier erected to limit diversion, the potential for those barriers to diminish appropriate prescribing increases exponentially. Restrictions in the drug distribution

process will disturb patient care by delaying access to medication therapy and disrupt existing patient/pharmacist/prescriber relationships.

Any additional stigma attached to these drugs will have a chilling effect on a provider's willingness to prescribe and dispense the appropriate pain medication and patients' interest in using it.

APhA believes that measures to curb abuse and addiction should be considered, but discourages using any administrative barriers like triplicate prescriptions as a risk management solution.

A survey conducted by New York State's Public Health Council found 71 percent of physicians surveyed reported that they do not prescribe the most effective pain medication for cancer patients if the prescription requires a special state monitored prescription form for controlled substances, even when the medication is legal and medically indicated for the patient.

We were pleased that during the December House subcommittee hearing on Oxycontin, both DEA Administrator Hutchinson and Subcommittee Chairman Wolf stated that they do not want or intend to restrict legitimate use of Oxycontin. According to Hutchinson, the DEA recognizes that the best means of

preventing the diversion of controlled substances, including Oxycontin, is to increase awareness of the proper use and potential dangers of products. We agree, and not that pharmacists can be an excellent communicator of that information.

In conclusion, it's important that patients do not lose timely access to a valuable class of effective pain medication because of a failure to prevent medication misuse. Again, I emphasize that restricted distribution and administrative barriers are not the answer.

The solution requires the education of health professionals, law enforcement personnel, and the public on the use and abuse of pain medication.

Thank you for your consideration of the views of the nation's pharmacists.

ACTING CHAIRMAN KATZ: Thank you very much. Next, please.

MS. BURKHOLDER: Good morning. I am Rebecca Burkholder with the National Consumers League. I would like to inform the Committee that occasionally the League receives financial support form pharmaceutical companies for specific consumer education projects in which we maintain full editorial control. This amounts to less than one-half of one

percent of our annual operating budget.

The National Consumers League is a national nonprofit consumer organization that has represented consumers and workers in the marketplace for over 100 years. The League provides information and educational materials to consumers so they can make wise health care decisions, including the safe and effective use of pharmaceuticals.

The League commends the FDA for looking at the problem of illegal and inappropriate use of opioid analgesics. A delicate balance must be struck, however, between the prevention of abuse of a powerful opioid and ensuring that individuals suffering from debilitating chronic pain have access to drugs that offer prolonged relief.

NCL believes FDA's decision to strengthen the labeling of Oxycontin is justified. The black box warning prominently reminds physicians, pharmacists and patients that Oxycontin contains a powerful opioid with potential for abuse and addiction.

The more detailed indication and usage section helps limit overprescription by identifying situations in which the drug is not indicated. These warnings should change any faulty prescription practices as well as alert physicians to the potential

for abuse, misuse and diversion.

Although misuse and diversion are and will continue to be potential problems for all opioids, it would be indefensible to deny pain patients a safe and effective therapy. Today there are between 50 and 60 million Americans who suffer from chronic pain.

The under-treatment of pain affects the quality of life for millions of people, from cancer patients to those who suffer from severe osteoarthritis or back pain. Oxycontin is one of the effective treatments for pain, because it provides continuous relief from prolonged or chronic pain.

It is critical that any regulatory measures taken to reduce abuse and diversion of opioid analgesics not interfere with the legitimate use of these drugs. For those patients who find Oxycontin the most effective safe treatment for pain, the drug should continue to be available.

We encourage the FDA to continue to education health professionals and the public on the appropriate use of opioid pain medications. FDA should also continue to monitor reports of abuse, misuse and diversion of opioids and work with other Federal agencies and drug manufacturers to ensure that opioids remain available to the appropriate patients.

We believe that the stronger FDA warnings for Oxycontin will help ensure that the drug is not misused.

Finally, the League hopes the FDA will continue to take into account the entrance of millions of legitimate uses of opioid analgesics when it makes important decisions concerning these drugs. Thank you.

ACTING CHAIRMAN KATZ: Thank you. Next, please.

DR. BUEDE: Good morning, members of the Committee and audience. My name is Dennis Buede. I have a PhD in Engineering and no conflicts of any kind with pharmaceutical companies to report.

I am here today as the spouse of someone who suffers from perimenopausal exacerbated severe hormonal migraines, often three days of duration and duration disabling pain. For approximately 12 months my wife has been under the care of Dr. Statkis of the Dulles Pain Management Center.

Not only has her condition greatly improved, but the improvement in her wellbeing and ability to function has made it possible for me to accept a position at Stevens Institute of Technology. This position requires greater time away from home.

As a Professor of Systems Engineering and with a specialization in decision analysis, the description of your announcement indicating that you were undertaking the risk to benefit ratio of extending opioid treatment into the populations of pediatric patients and patients with nonmalignant etiology intrigued me.

This is very relevant to our family situation, especially since the DEA has mounted a campaign against doctors and pharmacists responsible for the Oxycontin abuse.

I would like to address some key issues involving both values and uncertainties for viewing the risk to benefit analysis that you are considering.

First, let us address uncertainties. Uncertainties exist for many reasons. Three of the most important for the opioid treatment of pain are the variation among humans -- none of us is the same, and no solution fits us all; the unknowns in medicine that are still left for us to fathom; and the relative ratio of people using opioids for pain relief versus abusing the opioids for an addiction.

The first example of uncertainty presents itself to us on a daily basis. Yet we are constantly finding educators and health care providers trying to

fit us all in the same pair of shoes. When one of us visits a doctor and receives any kind of medicine, there exists uncertainty about whether our body will respond the way others have.

As an example of the second reason, a limited knowledge in medicine, it was not too long ago that we discovered that infants feel pain, changing the medical recommendations of family decisions associated with such practices as circumcision.

I would like to also address the fact that -- the issue of patient complaining of pain. It is not difficult to use opioids responsibly. I know it is indeed a difficult issue faced by prescribing doctors.

I would like to offer an analogy for viewing this problem. In this nation and many others, there are a certain number of bad police persons. As a society, we do not disband the police force, because most police persons are honest, and we need them, just as we need pain relievers.

A police chief cannot tell a bad potential hiree from a good potential hiree with perfect accuracy during the interview process, just as a doctor does not have the ability to perfectly discern a new patient is a person in pain from an addict.

Just as we let the police chief hire the individuals that he/she believes are the best candidates, we should let the doctor prescribe the appropriate pain medication.

ACTING CHAIRMAN KATZ: Dr. Buede, I'll have to ask you to wrap up your comments.

DR. BUEDE; Okay. I'd like to wrap up with this statement from Albert Schweitzer in 1953: "We must all die, but that I can save a person from days of torture, that is my great and ever new privilege. Pain is a more terrible lord of mankind than even death itself."

I would suggest that this privilege be considered at the FDA as well. Thank you.

ACTING CHAIRMAN KATZ: Thank you very much. Next speaker, please.

DR. CRANMER: Yes. I'm Kerry Cranmer from Oklahoma City. I have been a geriatrician, have been involved in Speaker's Bureau for Abbott, Lilly, Falding, Janssen, Purdue, Ortho-McNeil and Novartis. We have done Phase III and IV studies for Omnicare Clinical Research involving several companies.

As a geriatrician, I have limited my practice to long term care and the treatment of the frail elderly. Our concern is to be able to provide

the comfort and dignity that they do deserve.

I want to kind of spend a little bit of time discussing what some of the research has shown as far as the prevalence, the results and the treatment of pain in the frail elderly population.

First of all, in 1996 Winnie Stein showed that 45 to 80 percent of all the patients in long term care facilities had chronic daily pain, depending, of course, on the facility. In 1998 we are all aware of Joanne Lynn's support study showing that 50 percent of the patients dying in the hospitals were in moderate to severe pain in the last few days of life.

In 1998 Bernibye basically showed that cancer patients going into long term care were not treated in their daily pain, and that 40 percent of them showed chronic daily pain, and approximately 25 percent of those were not on any analgesics whatsoever.

The next year provided another study based on a chart review. The MDS, minimum data set, is required on every patient admitted to nursing homes. Based on those assessment forms, we found out that -- and reviewing 50,000 of those patients -- that the same figures were found. Thirty-three percent were in daily pain, and 25 percent of those were on no

analgesics whatsoever.

We found out by that that we had to increase physical therapy. We had increased depression. We had increased loss of activities of daily living.

Even last year, Joan Tino at Brown University showed us in 110,000 charts that were viewed and MDS data that was reviewed, we found out that similar findings, and I'll just surmise to say that we had 40 percent of those that were in severe pain, were still in severe pain 60 to 180 days later.

We have a tremendous prevalence of pain in these areas. The results of that chronic pain have basically shown us that we have physical as well as psychological consequences. The depression, the increased activities of daily living are major issues that we have to be concerned about.

Opioids are the most geriatric friendly medications that we can use. Nonsteroidal anti-inflammatories can provide renal impairment in their chronic use. I think proproxyphene has been on the inappropriate list for over 20 years now for geriatric patients.

Opioids remain the preferred treatment for the elderly. Diversion is always a concern for every

conscientious physician, and yet we have yet to find in the nursing home increased stolen televisions and selling of sex for increased drugs. We just haven't seen it.

I just want to surmise to say that we feel like we have to address the needs of the frail elderly in America and provide the comfort and dignity that they deserve. Thank you.

ACTING CHAIRMAN KATZ: Thank you very much. Next, please.

MR. MONAHAN: Thank you for the opportunity to be here this morning. My name is Jim Monahan. I'm the Program Administrator of Houston Hospice in Houston, Texas. I've been doing hospice work for the last 16 1/2 years.

This morning I am speaking on behalf of Houston Hospice and the Texas and New Mexico Hospice Organization on whose Board I serve as Vice President. Neither I nor Houston Hospice has been reimbursed or given any consideration by pharmaceutical companies to be here today, although both the hospice and the hospice organization have received educational grants from pharmaceutical companies to put on educational offerings to the professional community.

I'm speaking on behalf of the 14 to 1500

patients also who will be treated by Houston Hospice in this next year and by the many thousands of other patients treated by the hospices in Texas, New Mexico and the rest of the country, with the goals of eliminating pain and other symptoms and finding meaning in the last days and weeks of life.

Let me tell you about one of these families. Last summer I went to visit a patient in one of the better hospitals in Houston. He was in his mid-seventies. When I arrived at the hospital, his granddaughter was holding his hand and saying, "Grandpa, I love you."

He was moaning in pain. That was his response. His family was there, adult children and his wife of many years. After some conversation about hospice and hospice goals, they said we know he's dying; if he could die without pain, we'll be happy. The man was in extreme pain. He had been in the hospital for ten days at that point.

His son and daughters were medical personnel. They were nurses, paramedics and helicopter pilots who did emergency medicine. The son came to me and said that his father's physician had suggested morphine for his dad, but it was up to the son. It was up to the son to make that decision.

There were fears that the son expressed of addiction, of ceiling limits that we know about with patients afraid that if they start now, it won't be available later, and just stoic ideas of a very practical family about using narcotics at the end of life.

I think this is wrong. It shouldn't be left to the family. It shouldn't be left to the person. It should be up to the health care providers to make these decisions with the input of the family, and every obstacle that we put into place that limits the good pain control is a disservice.

Obstacles include physical obstacles such as limits on the manufacturing or distribution, psychological obstacles such as fear and other factors involved, and educational obstacles. We need to teach our health care providers more. We need to do less to increase and enhance the fear of distribution of medications.

Two days ago in the local paper I saw an article about the theft of Oxycontin from a pharmacy. I did not see in today's paper anything about the wonderful testimony yesterday about people's pain, people's lives being given back from eight years of pain, and others.

These are the stories that are overlooked by our media. It's up to us to get the word out about good pain control, good symptom control to the American public and to our health care providers. Thank you.

ACTING CHAIRMAN KATZ: Thank you, Mr. Monahan. Next, please.

DR. GLOTH: I'm Dr. Michael Gloth. I'm on your list for yesterday actually, and there was apparently a mix-up, and I got today as being my day.

I'm Associate Professor of Medicine at Johns Hopkins. I'm the Chief of Geriatrics at Union Memorial Hospital. I serve as President of Victory Springs Senior Health Associates, one of the few private practices in the country that consists of physicians all fellowship trained in geriatrics.

I serve on the American Geriatric Society Board that is currently revising the chronic pain guidelines for the older adult, and I also serve on the panel that is revising the Behrs criteria. I'm the immediate past President of the Hospital Network of Maryland.

Eastern Cooperative Oncology Group study, a study of cancer patients looking at pain, demonstrated that the number one risk factor in that

study for inadequate pain management was simply being over the age of 70.

We often get sidetracked with side effects, and thus do not provide effective pain management. It would be unfortunate if additional regulation and restrictions on opioids were instituted and, by doing so, we limited the availability of these opioids to those folks that need them.

It is important for us to make sure that we recognize that such singling out of opioids will lead to a limited use of these opioids by prescribers.

Recognize that the Behrs criteria will not list Oxycontin as a drug to be avoided in the elderly. IT is one of the opioids that reaches its steady state in the most timely fashion of all oral opioids available.

In the interest of maintaining my special place in heaven, I am going to close, but I hope that you all will maintain your special place in heaven by allowing us to continue our efforts to relieve suffering for seniors. Thank you.

ACTING CHAIRMAN KATZ: You forgot your disclosures, Dr. Gloth.

DR. GLOTH: I'm sorry. I am affiliated with just about every pharmaceutical organization that

is associated with oral analgesics. I'm either serving as a speaker on their speaker's bureau, a consultant, or else I have received grants from those organizations. Thank you.

ACTING CHAIRMAN KATZ: Thank you very much. You still get your place in heaven. Let me remind the subsequent speakers to begin with their disclosures. Thanks.

MR. COLEMAN: Good morning. My name is John Coleman, and I am a former Assistant Administrator of the Drug Enforcement Administration who for several years was in charge of law enforcement operations for the agency, including those carried out by the DEA Office of Diversion Control.

In 1998 I retired from the DEA after 32 years of service. Although I appear here today as a private citizen, in the interest of full disclosure, I must state that I am member of the Speaker's Bureau for Janssen Pharmaceutica. I have also been the recipient of an unrestricted educational grant from Janssen to support my academic work.

I would like to spend the next few minutes talking about something I believe is directly related to the questions posed by the Committee regarding prescription drug abuse.

Given my background, I am concerned about the quality of data being collected and published by the government on prescription drug abuse in America. Prescription drug abuse is a function of many things, including price, availability, accessibility, rate of onset and duration of effects, the effects themselves and the route and ease of administration.

Subjective factors also play an important role, but they are far more difficult to isolate and assess on a global basis. Knowing some of the key factors that influence prescription drug abuse should intuitively lead us to design survey instruments that distinguish and measure these specific characteristics.

Of all the national drug abuse surveys conducted by the Federal government, none provides enough specificity to measure these factors. Ironically, field collection procedures often harvest the data, only to have them discarded when they are aggregated and assigned to broad categories or generic chemical names for publication.

Let me give you an example of what I mean. According to figures released by the Drug Abuse Warning Network, our most important survey for estimating drug abuse, in the year 2000 hydrocodone

was the nation's most frequently abused prescription opioid. This information is surely useful, but consider how much more useful it would be if we knew the specific formulations of hydrocodone that were most often abused.

This limitation in data becomes even more critical in the case of C_2 opioids that are available in injectable, solid doses, sustained release and/or transdermal forms. Research shows that the form of an opioid may be an important determinant of its overall abuse potential.

As a former DEA official, I am familiar with some forensic databases that do provide product specificity for prescription drug abuse, and exhibits that are submitted to laboratories for analysis. These data provide very useful information but cannot be used as a prognostic system or one that estimates drug abuse in the general population.

I urge this Committee to support the efforts of the Substance Abuse and Mental Health Services Administration as it redesigns its survey methodologies that I believe can be improved significantly with some very reasonable and modest adjustments. What I propose is almost something unheard of in government, a no or low cost solution.

As for the potential economic consequences for those products identified as most frequently abused, I would offer that the interests of both the public and industry will be best served by more, not less, information. Indeed, it seems like an imminently proper use of government regulatory authority to encourage the development of abuse resistant drugs and/or innovative delivery systems that inhibit abuse. I believe that over time --

ACTING CHAIRMAN KATZ: Mr. Coleman --

MR. COLEMAN: -- providing product specific abuse information will have immediate benefits for the groups I have cited. Thank you very much.

ACTING CHAIRMAN KATZ: Thank you. And I'll point out for the group that Judy Ball from SAMHSA will be addressing some of these issues later on in her discussion. Next speaker, please. No next speaker?

Why don't we do this then. Are there any other speakers who are on the speaker's list for yesterday who, for some reason, could not make it and are available today? Okay.

Next then, we will go -- We have a very short waiting list of other speakers who wanted to

share some comments with us. The ones that I am aware of -- Is Myron Yaster here? Okay. Dennis Fisher?

DR. FISHER: Thank you, Dr. Katz. I'm Dennis Fisher. I am a Vice President for Medical Affairs of the Durect Corporation in California. Until about two years ago, I was a professor of anesthesia at the University of California, a pediatric anesthesiologist and very involved in pharmacokinetic and pharmacodynamic studies of opioids and other anesthetic drugs.

The issue I would like to address regards some comments that were made yesterday regarding the conduct of studies in pediatric patients. The Committee could readily have come away from the meeting yesterday thinking that it's very easy to conduct chronic studies in pediatric patients.

Dr. Katz, I think, tried to elicit some comments about the difficulty of that, but unfortunately the various members of the Committee, I think, directed that it really was not difficult to conduct those studies.

I'd like to cite an example that indicates some of the difficulties of doing these chronic studies. Recently, I spoke to the Medical Director of a large pharmaceutical company that is presently

evaluating a pediatric formulation of their new opioid.

This company had so far been able to conduct studies in a little over 100 patients, but it had taken 18 months to enroll these 100 patients, and they had over 100 sites that they had used to enroll these 100 patients. These 100 sites were in something like 15 countries on four continents.

One can readily imagine the quality of data from a study conducted with 50 different case report forms in different languages, etcetera, etcetera. I think the reality is that doing these chronic studies, the true chronic studies, not the acute perioperative studies, is very difficult.

I would be very concerned if the Committee would leave here with the wrong impression of that. I welcome comments from Dr. Robin and Dr. Schreiner regarding this issue. Thank you very much.

ACTING CHAIRMAN KATZ: Thank you, Dr. Fisher. I think that it would be fine to take one or two minutes while we are on the subject, if anybody from the Committee or invited guests wanted to respond to Dr. Fisher or comment about whether it is easy or difficult to do trials in pediatric populations. It would be a good time to do that. Dr. Foley?

DR. FOLEY: I want to support what Dr. Fisher said. This is exactly what we from the National Cancer Policy Board heard repeatedly, at least looking at chronic pain studies in children with cancer.

ACTING CHAIRMAN KATZ: Did anybody else want to comment about that? Dr. Schreiner, did you want to talk about that?

DR. SCHREINER: I think if you are looking at the true chronic pain population such as cancer, it is going to be very difficult to do studies that go beyond seven days. The majority of pediatric use for opioids is for much shorter periods of time.

I think that the other thing is, if the studies can be focused on the information that we really need to know and eliminate the unnecessary parts of the studies that create barriers for patients' willingness to participate, then it would be easier to do the trials.

I personally as a pediatrician want as much information as possible, but I want it to be focused on the information that we need to use the drugs.

ACTING CHAIRMAN KATZ: Thank you all for your comments on that important issue. Now is there

anybody else here who did not pre-register to speak in the open forum who would like to come up to the podium and have three minutes to share comments? I can't guaranty that everybody will get time, but we can certainly start. Yes, please, name, disclosures and your thoughts.

MS. STEFFLER: Good morning. Thank you. My name is Dorothy Steffler. I have nothing to disclose. I am here in twofold purpose. I am the mother of the young gentleman aged 42 who went through the crisis.

Everyone is talking about the euphoria that comes with use of Oxycontin or opioids. The euphoria that he displays is the new life that he now has, and it's more of a happiness and a socialization return rather than the deep depression and antisocial life that he had. So that could be misleading, that term.

I am also here because I am a state inspector for the Department of Health in the state of Pennsylvania. I have been there for 11 years. I've been in health care since 1951.

I am one of the persons who, on a daily basis, visits the nursing care facilities with the elderly, and I have seen hands on the difference since

pain management has been addressed by the HCFA, now CMS.

It is my responsibility in my position to write deficiencies for physicians who have not managed pain. We see -- I have seen in this year since HCFA has addressed it as the fifth vital sign -- and I do a lot of this in-servicing, too, not only the nursing staff and the professionals but the housekeepers and the nurse aides who are there to see the nonverbal pain behaviors that are exhibited.

We see a decline in dietary, in their weights, sudden, unexpected, and physicians usually immediately go to Megase or supplements. No one asks them if they are hurting, and we have been on this promotion.

So I am twofold in the use of opioid therapy. I have seen it. They are giving Darvoset n100, Tylenol 325 times two, 650, q4. I can read it in every single record that I audit, but I have seen the difference in this year of the rise in the activities of daily living when in the plan of care we are addressing pain management for the elderly and the nonverbal we have taught -- are in the process of teaching. However, it's the physicians that we need to reinvent the wheel, because they are fearful of

writing anything.

As the physician before had mentioned, it is in the MDS. We scrutinize the MDS. That's the pain -- or the money, financial part, and we have residents who have nonverbal pain, and it is less than daily or excruciating, mild to moderate. But we have strictly one medication. That is Tylenol, again 325. They are fearful.

I do see the difference when they do order. Some of them are doing Duragesic patches. I do Oxycontin, not only for hospice but the other one. Thank you so much.

ACTING CHAIRMAN KATZ: Thank you. Is there anybody else from the public who would like to have three minutes to share thoughts with us about these issues?

DR. MERRICK: Mr. Chairman, Dr. Merrick from yesterday, if you would allow me to speak again. I just have -- I want to echo a few comments from some eloquent speakers this morning.

One of the factors a family physician -- I have no disclosures, self-funded. As a family physician, one of the greatest barriers I've seen to the treatment of chronic pain in the poor in my area of rural Virginia is going to be access to how to pay

for all the ancillary services and complementary services that you can give patients in treatment of chronic pain. They are simply not available. Opioids are the keystone for treating rural poor as far as chronic pain.

The second issue, to address the gentleman from the pharmaceutical industry, from the pharmacist industry rather: One of the key obstacles that I have as a family doctor treating chronic pain now is the fact that pharmacists in my area will not fill my prescriptions because even I have communicated with them before as far as the patient is legitimate. They have gotten a copy of the patient-doctor contract. I've done everything I can possibly do to contact the pharmacist.

One of the problems I see is the pharmacists of this country have not been brought along with all of the physicians in the education with chronic pain, and I think that that is a major issue that we are going to have to address if we are going to really have a comprehensive national approach to chronic pain, is bringing the pharmacists with us. Thank you.

The last comment was basically, in yesterday's discussion I noticed that function was

left out as a major keystone to see the effectiveness of opioid treatment. That, to me, is one of the major issues, is function is the key to whether or not successful therapy is being administered. Thank you.

ACTING CHAIRMAN KATZ: Thank you, Dr. Merrick, and we'll hear more about that from Dr. Passik today as well.

What I'd like to do now, since we still have a few extra minutes, is if there were any of the public speakers from today whom I had to rudely cut off at three minutes, if you would like an extra three minutes -- but I would just ask you to bear in mind what's already been said and, if you've got something new to add to the conversation, we would look forward to hearing it. So three minutes each, please.

DR. CORK: Well, thank you very much.

ACTING CHAIRMAN KATZ: You're welcome.

DR. CORK: Again, I'm Dr. Randall Cork from Louisiana State University.

There were some issues regarding the specific questions that I know the FDA wants answered that I wanted to take an opportunity to respond to those, the two questions from yesterday, the target population and the second question about clinical trials.

In terms of target population, I really think that it's important to have a multi-level target. I think that the FDA should be concerned that -- We know about opioids. They have been around for so many thousands of years. There is really no reason to focus on efficacy so much with opioids. You need to focus on safety with opioids, and I think Dr. Portenoy's three points on safety should be adhered to in terms of FDA plans for certification of new drugs.

In terms of clinical trials, the issue of chronic efficacy, I think if you dwell on that, it will only serve to delay the introduction of new drugs into the system and will increase the cost of those drugs.

So in terms of today's questions, the adequacy of available data in terms of the prevalence of addiction, I believe the FDA can help with that by indicating on the package insert, as Dr. Portenoy recommended, the risk of addiction for the drugs. I think physicians need to be educated that short acting narcotics have a higher risk of addiction than longer acting narcotics such as Oxycontin.

The methods for assessment and monitoring of addiction, I think, are a good idea. Those things should be introduced into the protocols and addressed

in the package insert.

In terms of reduction of addiction or the risk of addiction, I really believe that that is more of a police issue rather than an FDA issue. I think that rehabilitation, forced rehabilitation has been shown to be effective in terms of reduction of addiction.

In terms of another comment that was made yesterday from Dr. Zedd or Zetma from Virginia -- I forget what -- it had to do with criticizing the drug company for providing education to physicians. I think that was misplaced. I think Purdue Pharmaceuticals should be commended. They have provided us with a lot of educational materials to involve the Family Practice Department and to provide education to our medical students about treatment of chronic pain.

Thank you very much for this additional three minutes.

ACTING CHAIRMAN KATZ: Thank you. May we have the next speaker, please? Mr. Coleman.

MR. COLEMAN: Thank you very much, Doctor, for this opportunity to resume.

As I was talking about the specificity of the data that I believe is seriously needed, I would

like to add that, in my view, we will not be very effective in addressing prescription drug abuse until we can identify with a reasonable degree of specificity the frequency of drugs by product names and formulations that are being abused.

Presently, we do not have this information available in the field of drug abuse research, although something similar does exist in another very similar or somewhat related field. For example, the FDA is justifiably proud of its adverse event reporting system that is used to collect and disseminate post-marketing drug and therapeutic biological product safety reports.

In addition to other pertinent information, the AERS data format requests that the contributors enter a, quote, "valid trade name" for the product being reported. I am sure that every member on this Committee is familiar with the value of the AERS.

Now I ask you, how valuable would that information be for you or your patients if the, quote, "valid trade name" were dropped somewhere in the process and replaced by simply a generic chemical name?

I hope this helps you to understand my

concerns about the need for better drug abuse data. by not providing what the AERS refers to as valid trade name for the most frequently abused drugs, usefulness of surveys is limited. As a result, anecdotal information often takes over and, as someone on the Committee yesterday wisely pointed out, anecdotal information may regrettably become the basis at times for public policy.

Thank you very much. That's the conclusion of my statement.

ACTING CHAIRMAN KATZ: Thank you, Mr. Coleman. Next, please.

DR. DESJARDINS: Thank you, Dr. Katz. I'm Dr. Paul Desjardins, Senior Vice President for Clinical Site Operations for a research organization named SCIREX Corporation. I am also a member of the American Society of Clinical Pharmacology and Therapeutics and I am speaking on behalf of the investigators and individuals who are actually trying to perform the clinical research to develop better drugs and better strategy for dealing with patients who have both acute and chronic pain.

I would like to suggest to the Advisory Board and to our colleagues from the Food and Drug Administration that we are in a very similar position

to those of us who were investigators 30 years ago who were facing many of the same questions in terms of how best to deal with patients with moderate and severe acute pain.

The analgesic guidelines which were developed by the scientific community with the concurrence of the Food and Drug Administration and sponsors was an enormously successful project. The current guidelines which exist deal in explicit detail for drugs with acute pain, but deal very superficially on drug development issues for patients with chronic pain, and in particular developing the standards for what will be considered appropriate and well controlled clinical trials.

I would strongly urge that the Advisory Committee work with and advise the Food and Drug Administration to continue that process, to update either those guidelines or develop separate guidelines which will address the scientific issue to the satisfaction of the clinicians, the scientists and the regulators who have to make very difficult decisions. Thank you.

ACTING CHAIRMAN KATZ: Thank you. Did anybody want to address the issue of whether there are any plans in place for reexamining the analgesic

guidelines or shall we leave those discussions for later?

DR. RAPPAPORT: I just want to clarify that at this time the guidelines that are out there are outdated, as far as we are concerned, and we are in the process of developing new guidelines. I can't give you an exact time course for when those will be ready, but we are working toward those coming out as soon as possible, and we are working with the other analgesic division to see that they are consistent across the agency.

ACTING CHAIRMAN KATZ: Thank you, Dr. Rappaport. Next speaker, please.

MS. BALUSS: Thank you.

ACTING CHAIRMAN KATZ: We will have time for one more after this.

MS. BALUSS: It's unusual for a lawyer to be talking about facts, but I do have to prove them.

I wanted to talk with you about how little we know that is very relevant to some of the law enforcement and diversion questions that come up.

We don't really know who the chronic pain patients are or where they are or what has failed them and what has worked. We don't know a whole lot about long term outcomes for them.

Where that becomes important to me is that I see someone testifying that a doctor has acted improperly because he has continued to prescribe opioids for someone whose function may or may not have improved enough. Well, what's enough, and how long should someone -- Is there a temporal limit on opioid therapy?

I don't think we know this, and it works as a severe detriment, because some of these little markers get translated into kind of unstructured evidence where it really isn't evidence.

I think that we need to know a whole lot more about outcomes. We have no idea -- We are requiring doctors and penalizing doctors for not having a good command and control system, but we don't know whether the patient contracts affect the diversion rate at all, and there are a lot of other things we don't know about that kind of medicine. Thank you.

ACTING CHAIRMAN KATZ: Thank you. Next, please.

DR. BUEDE: My name is Dennis Buede again. I want to address one issue I hadn't quite gotten to. That has just been raised by the last two speakers, our intrinsic failure as humans to think that we know

a lot more than we do.

Oh, I see this in engineering, and I have also seen it in visiting many doctors that we've gone to over the years. My wife and I were talking to a prospective primary care physician just a few weeks ago, and he was telling my wife that he really does not prefer to treat the pain. He prefers to treat the underlying cause.

Yet in most cases today, as many of you know, the doctor has no hope of finding an underlying cause. There has been some recent research. It may or may not prove to be true, but it indicates that by treating the pain, the patient has a much better chance of recovering from whatever is ailing them if you are also able to treat the other aspects.

So while we are stuck in this situation, and I probably think that we probably know less than half of what there is to know about medicine and taking care of people, we still have to make decisions with the best information that we have and recognize this amount of uncertainty. Thank you.

ACTING CHAIRMAN KATZ: Thank you. Dr. Max, one comment.

DR. MAX: Yes. I just want to comment in regard to Paul Desjardins' call for more academic FDA

consultation. Ray Dionne at the National Institute of Dental Research and Jim Witter of the Anti-Inflammatory Allergies Division of CDER are holding a symposium on the NIH campus on some issues in acute and chronic pain drug development on March 13th and 14th, and they want -- It's an open meeting, and you can contact either of them for an agenda.

It seems like it's still open for shaping. That's all I know about it.

ACTING CHAIRMAN KATZ: Thank you. That will be the end of our open public hearing for today. Thank you very much, everyone, for coming, in particular the patients and their families for taking the trouble to come visit us today.

What I would like to do now -- We do have an industry presentation that we have scheduled for 9:30. What I would like to do in the five or so minutes before we start that is to make a few introductory comments of my own for today's session, and then also to attempt to summarize for the folks who were not here yesterday what seemed to me to be the salient themes in our conversation from yesterday that, hopefully, will inform our discussion today.

Of course, it's always a risky business to summarize everything, because nobody ever really

agrees on what exactly it was they heard, but I'll do my best. If I get anything completely backwards, then, hopefully, somebody will raise their hand and briefly point that out, without necessarily reopening the discussion in just the few minutes that we have before our scheduled presentation.

Let me begin by thanking the rest of the Committee and invited guests for what I think was a very productive and professional discussion yesterday. This is a very difficult topic, the issue of opioids, and people tend to get very dogmatic and excited about it, and I think that our discussion yesterday was very fruitful.

Today we have even greater challenges, I think, in our discussion. I don't know that there is any medical issue that I deal with that gets people as excited or dogmatic as the issue of addiction and opioids, and it's been that way for a long time.

Medical professionals are coming at this from very much different angles. Historically, there's been fairly little communication among different subspecialties of medicine in terms of how one can understand these problems.

There are different languages that we use to describe the same phenomena, and we will often have

difficulties in communication, not necessarily because of disagreement about underlying principles, but because we are using different words for the same thing. That will be a challenge for us today.

So I look forward to the -- What I want to do is reiterate what I said yesterday in my introductory comments, which is that the goal of today's meeting is not necessarily to solve the problem of addiction and opioids, which we certainly aren't going to be able to do.

It's not even to come to consensus on all these issues, which also, I think, is unrealistic, I've heard today. We will definitely end up disagreeing on some of these issues, but what I hope that we can do for the FDA today is to at least lay the issues on the table, help to define what the problems are that we are dealing with, present all the relevant points of view, even though they may be opposing, and try to understand them, and discuss what the implications are of those perspectives for development and marketing of opioid analgesics.

I think, if we can do that, that will be a tremendous accomplishment. I would ask the members of the Committee today, when they do make their comments, to try to move forward from what have been the

historical problems of the past in communicating about these issues.

One problem has been that we all have biases because we tend to see very select populations and then come to conclusions about what is true about the whole world. So as you do make your comments about what you think is true, please bear in mind whether your convictions may result from seeing selected populations, and present your views to the Committee with that in mind.

Secondly, as you present your convictions and thoughts to the group, I would ask you to try to also communicate what you feel the level of evidence is for your assertions.

Is it an anecdote or a collection of anecdotes? We heard yesterday what that amounts to. Is it research? What kind of research is it? Is it randomized controlled trials? Is it long term follow-up? That way we will be able to evaluate your comments more thoughtfully in terms of what the strength is underlying them.

So that's my charge for the group for this morning.

To quickly try to summarize some of the salient themes that I heard discussed yesterday which

will, hopefully, provide a platform for our discussion today before we begin our industry presentation, this is what I heard yesterday. Again, if I get anything completely wrong, without necessarily opening up the discussion right this second, I hope somebody corrects me.

Number one, it seems like we all agree or we certainly heard many times that opioids are essential for relieving pain. There has been a great -- That's point number one.

There has been a great deal of progress made over the last few decades by increasing the availability of opioids to physicians who need to prescribe them appropriately, and a great deal of progress made with demonstrations in the literature of safety and efficacy of opioids for both acute and chronic pain.

My point number three is that any restrictions on the availability of opioids to patients or prescribers have substantial potential risks of harming patients and reversing some of the progress that's been made. So there clearly is risk involved in any restrictions.

Therefore, the theme that I heard was that it's important that we all take a balanced approach in

our recommendations about opioids where we simultaneously try to balance maximal availability to patients that need them, at the same time trying to stem the problems of addiction, diversion and related processes without trying to impede patient access. I heard that many times yesterday.

I also heard that taking care of patients with chronic pain, including the prescription of opioids, is appropriately within the province of the primary care physician, although there may be a need for education and further efforts to optimize therapy in that setting and any other setting. I heard that expressed many times, and the specific issue of the need for more education I heard expressed many times as well.

I also heard expressed that broad labeling for mu agonist opioids is in general something that should be strived for, and that we heard clearly from Jeff Bloomer, patient representative, that broad labeling is better for patients, and we heard from Dr. McLeskey that that is also more attractive to industry.

We heard a number of times, most especially from Dr. Foley, that in terms of the patient populations that are potentially appropriate

for opioid analgesics, we don't have enough data to exclude a priori any patient population for consideration of opioids for long term therapy. There's just not enough data at this point in time. More data is needed.

Therefore, we shouldn't a priori exclude any patients from consideration for both clinical treatment and clinical trials. However, we also heard that different subpopulations may have rather different considerations in terms of understanding the risk/benefit ratio.

For example, patients with a history of substance abuse, elderly as we heard today, pediatrics -- there may be a number of subpopulations where we need more specific information to really understand the risk/benefit analysis. That's what I heard yesterday.

I heard that, quote/unquote, "traditional" efficacy programs may be sufficient to define a drug as an opioid analgesic and that that may be sufficient to work toward this broad labeling, and it seemed to me that I heard that one did not need to demonstrate efficacy in every last type of pain in order to understand that an analgesic was behaving like an opioid analgesic.

I also heard that there was, however, other very important types of information that was critical to the understanding of the risk/benefit ratio of opioids, particularly for chronic pain. In particular, we need to understand safety issues to understand the risk/benefit ratio of opioids, and safety includes the risk of addiction.

It includes neuropsychological side effects. It may include, as some folks mentioned, potential endocrine side effects. These are important issues in terms of understanding the risk/benefit ratio of opioids.

We need to understand the durability of response, and perhaps we will get a chance to talk more about tolerance today. Dr. Portenoy addressed that a bit yesterday. Again, we need to understand risk/benefit for certain specific subpopulations.

We heard some creative discussions yesterday about how some of these studies might be done. Since some of these issues are not necessarily product specific but are germane to the whole class of opioid analgesics, there was some discussion about whether there could be collaboration between industry and NIH to study these risk/benefit issues across the class of opioids.

There was discussion about whether there could be a possibility of acquiring some of these studies as part of a Phase IV program, and also I heard discussion about whether these would be more appropriately part of a traditional Phase III program, and we certainly didn't resolve the issue yesterday about how these studies are most appropriately conducted.

So that's what I heard yesterday. For now, right before a presentation, if anybody thinks that I got something completely wrong or neglected to say something that was absolutely critical from yesterday on these points, please point it out now. There will certainly be ample time later to delve into the details of everything that I've said now, including the topic for today, which is addiction.

Dr. Roberts, please.

DR. ROBERTS: The only thing I would add, Dr. Katz -- that was an excellent summary. You were awake the whole day. The only thing I might add is that we discussed at several junctures the value of going to the practice setting to do the kinds of research that needs to be done, because it's really where the rubber hits the road, and the issues of diversion contrasted against effectiveness, safety --

I mean, that's really where you're going to see what's happening out there.

ACTING CHAIRMAN KATZ: Thanks. Dr. Haddox, then why don't we -- Thank you very much -- go to your presentation then, and perhaps, Dr. Haddox, you could give a more complete introduction to yourself before you begin the presentation.

DR. HADDOX: Thank you very much. I appreciate the opportunity to be here to address the Committee. I thank the PhRMA and thank the FDA for giving me this opportunity.

By way of disclosure, I am a relative newbie to the industry, and in the past five years I have either consulted for or spoken on behalf of Astra, Merck, Pfizer, Janssen, Purdue, Ortho-McNeil Pharmaceuticals, Roxanne, and I had some research funded at Emory by Wyeth-Ayerst.

For those of you who don't know me, I started out life as a dentist. I then went to medical school, and I did a residency in anesthesiology and psychiatry following that. Following the dual residency, I then went into a pain medicine fellowship.

I am certified in pain medicine, in psychiatry. I have a subspecialty certification in

addiction psychiatry pain management, and I was a practicing clinician/educator up until two years ago when I joined Purdue Pharma.

I am the past President of the American Academy of Pain Medicine, the American Board of Pain Medicine, and a former Director of the American Pain society.

If we can get the slides going today, what I would like to do is share with you an industry perspective on how we can ensure the proper use and curb abuse of opioids.

One of my main functions, I forgot to admit, is to make sure that Dr. Portenoy is not alone as the only graybeard in the field of pain.

I would like to talk with you briefly about the disease burden of pain. I know there's been a lot of comments about that, but I'd like to report some data. I want to talk briefly, recap the treatment of chronic pain in particular, since that is an issue that's come up quite a bit.

I would like to talk and share with you what we have learned about -- in the past two years about prescription drug abuse, and I'm sure it's no surprise to the Committee that we've learned a lot about this in the past two years.

I would like to close with an analysis of risk management plans and where the industry sits on this and where we should sit on this.

When we talk about the disease burden from chronic pain, we are somewhat hampered, because we don't have overall national statistics. The Centers for Disease Control and Prevention, for instance, does not assay chronic pain in its annual disease and health survey.

So we really don't know from a full demographic study what is going on, but there are three surveys that I would like to highlight for you. Now these surveys are done by reputable survey organizations, typical polling organizations with demographically representative studies that can be extrapolated to represent the entire United States, and they span five years.

The first occurred in the state of Michigan. The second was about midway between, and the last was one that we paid for and had done actually just a few days ago in preparation for this presentation.

In 1997 a survey was done in the state of Michigan called "The State of Pain," and it showed that 1.2 potentially out of their 9.8 or about 12

percent of their population had a pain problem that had lasted for more than six months, either continually or intermittently.

Seventy-seven percent of the sample had experienced pain for over a year. Thirty-five percent had missed more than 20 days of work, a tremendous economic and social burden to the society and to the individual and family.

In a heavily managed care penetration state, 13 percent had been denied medications, devices or referral to a specialist. Now this can be extremely demoralizing for a patient with chronic pain. The types of patients that I saw in my clinical academic practice often had to go through enormous hoops to even get into the door.

This can be so demoralizing that, in fact, ten percent of the survey had contemplated the idea of suicide as a way of relieving their pain.

I have personal experience with this in a patient that I'd like to share with you. I was treating a woman who, fortunately, with our integrated treatment plan at Emory had done very, very well. She was very pleased with our care and, while she was not perfect, she was much better. She was sleeping better. Her quality of life had returned and, most

importantly, she was able to enjoy things again.

She was doing very well. I was seeing her about every month, along with our psychologist and a physical therapist. She came in one day, and she was very distraught. I, treating chronic pain, know that we have flare-ups and things go, but I asked her what was going on.

She immediately broke down into tears, and she told me that her 26-year-old daughter who was a worker's compensation patient, who had chronic low back pain from a work related injury, and she had -- because the mother had come to a pain center and had found out that there were, in fact, pain physicians and multi-disciplinary teams, and her quality of life had improved so much, she was entreating her daughter to get the primary assigned doctor at worker's comp to refer her to a pain program, mine or someone else's.

The daughter had a lot of hope for this, and she pursued this actively with her adjuster, and what they did was denied it, and they sent her to yet another type of specialist.

This person diagnosed depression, not terribly surprising, given the fact that this woman's life was coming undone, prescribed an antidepressant, and after a few weeks she took her own life, 26-years-

old, low back pain, noncancer pain. Took her own life, and she left in her suicide note to her mother that all hope had been dashed when her referral was denied, because she had seen how well her mother had done, and she was hoping she would be in that category.

I submit to you that this is an absolute travesty in a country that has the best available health care system, ostensibly, in the world.

In 1999 the American Academy of Pain Medicine and the American Pain Society did a survey funded by Janssen looking at moderate to severe, chronic, noncancer pain.

The extrapolated figure was again about ten percent of U.S. adults, but this is a slightly smaller scale, because we are not looking at any chronic pain. We are looking at moderate to severe, and you had to have a five or above on a numerical rating scale to actually get into the survey.

I have the seven and the eight through ten highlighted as 57 percent of people that had severe pain in this survey. Fifty-one percent, consistent with the things we heard yesterday, are in fact seeing a primary care physician. Another chunk were seeing some other specialist, and a very small percentage

were seeing a pain specialist.

Two-thirds of the sample had lived with pain for more than five years. Seventy-eight percent reported daily pain, and ten percent reported turning to alcohol as an analgesic, which we all know is a very dangerous pastime.

I was interested in how the public felt about treatment with opioids in preparation for this presentation. So we contracted with Harris Interactive and surveyed 1439 patients who had chronic pain and who had been taking an opioid for at least four months.

Most commonly reported: Arthritis, low back pain, migraine, cancer, not terribly surprising, and some patients reported more than one pain causing condition.

The analgesics spread: About what you would expect. 638 were taking Schedule II opioids. Schedule III through V were 1125, NSAIDs about the same, and acetaminophen about 800, and many were taking more than one. In fact, the average, if you look at chemicals, it was about three to four chemicals per person, including combination analgesics.

The numerical pain rating estimates on a

one to ten scale: You can see here that 22 percent were in the severe range. Now remember, these are people taking opioids. That's how you would get qualified for the study -- or for the survey.

We asked if pain was controlled. Twenty percent said no, not surprisingly. In those whose pain was well controlled, 39 percent had had to go to more than three physicians and pursue care for more than six months to get some kind of care that resulted in decent pain control, and in the ones whose pain was not controlled, 65 percent, two-thirds, had seen more than three physicians, had been trying for -- Almost all had been trying for more than nine months, and still their pain was not well controlled.

We asked some statements: Do you agree or disagree with the following statement? Patients do not have trouble obtaining needed pain medications. Fifty-four percent of the sample disagreed. These are people taking pain medications.

We asked: I have not experienced any problems getting treatment for my pain. Thirty-five percent disagreed.

As you've heard yesterday and today, a significant barrier to treatment is the fear of addiction, and in clinical practice, and many

clinicians here on the panel know this quite well, there is a great deal of confusion between the entity physical dependence, which most of us recognize as a known effect of certain classes of medications, and addiction, which is a disease.

So we asked this case. We said, imagine that a patient was taking a pain medication for six months and suddenly stopped taking it. As a result of not taking the medication, they experienced nausea, sweats, had difficulty sleeping, and felt tense and jittery. Based on this information, can you conclusively state that the patient is addicted, physically dependent, both, neither, or not sure?

Now people on this panel know that the correct answer, based on this limited case information, is (b). That's the only thing that you can conclusively state. There might be other things, but that's what you can state based on what was presented.

When we looked at how the patients did, 37 percent, little over a third, got it right. Unfortunately, 16 percent said this was addiction. Thirty-five percent said it was both. Two percent said neither, and ten percent were not sure. So a little over 50 percent of the patients are confusing

this on a regular basis.

When we asked the question a slightly different way: If you are taking a pain medication and you stop it and you have withdrawal, does that mean you are addicted? -- 53 percent said yes.

The Liaison Committee on Pain and Addiction composed of the American Academy of Pain Medicine, the American Pain Society, and the American Society for Addiction Medicine got together, and it promulgated definitions that they hope will become standard that will span all specialties, not just addiction or not just pain.

They stated that addiction is a primary chronic neurobiologic disease. It is a disease with genetic, psychosocial, and environmental factors influencing its development and manifestations, and it is characterized, as Dr. Portenoy said yesterday, by behaviors that include one or more of the following: impaired control over drug use; compulsive use; continued use despite harm; and craving.

Contrast this with physical dependence, which is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or the

administration of an antagonist or a neutralizing or reversal drug.

Physical dependence is a known effect of certain drugs, including opioids. Addiction is a disease that sometimes involves opioids and sometimes involves other substances.

So as we go to treat chronic pain, we must integrate therapies. I found this very interesting, because this is very similar to what Dr. Portenoy showed you yesterday, and yet we developed these quite independently, I assure you.

Physical therapy can certainly have many things to offer people with chronic pain. Therapy for the comorbidities, the sleep disturbance, the anxiety disorders, etcetera. The cognitive therapies have been shown to be extremely useful, particularly in helping people cope with pain as severe as rheumatoid arthritis. Behavioral therapies are a mainstay of many programs, involving the lifestyle changes you've heard mentioned several times yesterday.

The interventions, the things that I did as an anesthesiologist, spinal cord stimulators, pumps, nerve blocks, have a role in helping certain patients. Surgery may be of use in some other patients.

The spectrum of rehabilitation services ranging from orthotics and splints and specific occupational therapy all the way to comprehensive rehabilitation programs such as run at many -- like that are run at many universities.

Of course, pharmacotherapy is going to be a part of this. What the physician does is to take each individual patient sitting before them and integrate a plan of care, drawing from each of these various spokes on the wheel to optimize the function and comfort of that individual patient.

When you talk about pharmacotherapy, of course, you are going to talk about prescription medicine. In this discussion that we've been having yesterday and will continue to have today, it's important to emphasize there are two distinct populations at the very least that we are discussing, patients with legitimate need who are appropriately using these very valuable medications and inappropriate use, the abusers, the diverters, the people suffering with addiction.

Prescription drug abuse is a longstanding, serious problem in this country. It predates the Food, Drug and Cosmetic Act. This is not new. I think what is new, and quite frankly I'm very happy

that it's new, is the heightened awareness of the problem.

Clearly, that has happened, and Purdue takes this very seriously, and we are devoting enormous energy to reduce the inappropriate use of these medications. But what is the real scope?

As you've heard today from Mr. Coleman and others yesterday, and you will hear more today, there are issues with our national data sources. The surveys that are commonly used to show trend information about abuse were not designed to assess abuse of prescription medications and, therefore, they have some areas that could be improved.

In fact, this was pointed out at a NIDA press conference in April of last year, that prescription drug abuse is a largely unrecognized problem in this country and is a significant component of the overall drug abuse picture and, unfortunately, not much has happened since that press conference in heightening the understanding.

Now we've learned a lot about diversion in the past few years. We are very actively engaged with law enforcement as well as regulators and clinicians. Doctor shoppers are clearly one source of diverted drug. These may be organized rings.

I've actually heard of people conducting classes in how to dupe doctors, how to forge medical records, how to feign signs, or how to feign symptoms and create signs to lead a doctor down the wrong path, or it might be the sole proprietor, the individuals who are doing it for money or to support an abuse interest, or both.

Prescription fraud comes in many varieties: Altered prescriptions, simply changing the number or the information; forged prescriptions, stealing prescription pads from the doctor's office; or counterfeiting, just manufacturing prescription pads, fairly simple to do these days with scanners. Theft from patients and from pharmacists, and then prescribers.

The AMA has described the classic four D's: The outdated physician; the duped physician; the dishonest, criminal physician; and the physician who he or she himself is impaired and is engaged in prescription drug diversion to support their own habit.

The public health ramifications of this are substantial. There is the problem of experimentation in naive persons, and by naive I mean in both contexts here, people who are opioid naive.

That is, they have had little exposure to opioids and, therefore, have not induced respiratory depression tolerance; or the naive person who is taking something they know nothing about.

There is a new wave sweeping the country where people put a bunch of pills, prescription pills, in a candy dish and pass them around, and you take one or two or a handful at a party. This is called pharming, p-h-a-r-m-i-n-g. It's a very distressing trend, and as a parent of two young daughters, that just scares me to death.

Then we have found, as has the DEA in their autopsy studies have found, that quite frequently prescription drug abuse is not abusing a single drug. It is abusing multiple drugs in combination, often with alcohol, a very deadly cocktail.

There are the problems of substance abuse which you've heard about and will hear more about today, the cost to society, the cost to the individuals and, most importantly, the cost to patients, how this is impacting access and appropriate care.

If we look then at an integrated approach to ensuring proper use and curbing abuse, as some of

the questions the FDA has posed to you today, certainly statutes and regulation have a role here.

The Controlled Substances Act is designed to ensure an adequate supply for legitimate medical and scientific needs of controlled substances, while at the same time preventing diversion.

Regulation such as -- and statutes such as prescription monitoring programs, as was referenced yesterday by Dr. Levy: Electronic data capture programs can be very, very effective in curbing abuse and making sure legitimate patients have the medication available to them.

Surveillance systems and interventions: Again, going to Dr. Levy's talk yesterday. The medical board gets the prescription monitoring plan data, and then can make appropriate educational or, rarely, disciplinary interventions as needed.

Law enforcement: There are many, many jurisdictions in this country where there is not a single officer doing drug diversion work. There are many doing vice and street narcotics, but there's relatively few who are focusing on this very important problem.

Access to addiction treatment: We know the statistics are very clear that addiction treatment

is more effective, resulting in fewer relapses, and is far more economical than incarceration.

Education and prevention: If we can educate our young people, give them the smarts to say no to prescription drug abuse, to not start to dabble in that area and go down this road, we will find that this is also more effective and cheaper than even treatment.

New chemical entities and new formulations: Purdue is actively pursuing these kinds of things to try to find medications or create formulations that will not be desirable to abusers and yet will still provide full benefit to patients.

Well designed, articulated, multi-pronged, living risk management programs that can adapt to new situations as information is brought forth is a very important part to this approach.

Finally, improved practice at the clinical level: Better knowledge and skills and better application of those knowledge and skills.

All of these facets together working in harmony can result in optimal public health.

The risk management plans have been talked about by the FDA for sometime, and they are to be commended for pursuing this, because it is time that

we look at this in a different perspective.

As we get more and more sophisticated medications on the market, we are going to find new risks that we didn't even see before, and we have to be able to communicate those risks and manage them appropriately for optimal public health.

Scheduling, of course, when you are talking about controlled substances, is the linchpin of a risk management program. Scheduling, by its very nature, implies that the drug has abuse potential, and yet, if it's a Schedule II or lower, has legitimate medical need.

Labeling is the dominant communication, the thought from which all subsequent communication from a manufacturer to the end prescriber or dispenser derives. Labeling has to be accurate. It has to be clear, and going to the scheduling issue again, if labeling -- if the box warning you heard about today is the strongest form of labeling that the FDA can use, and scheduled drugs by their very nature have abuse liability, we support the use of box warnings appropriate to the schedule for every scheduled drug.

In fact, we in conjunction with the FDA worked on the box warning for Oxycontin's package insert, and we submitted without any prompting or

discussion a similar box warning for our MS Contin product.

The education of health care professionals is an imperative part of risk management. These are the people who are making the clinical decisions. This should be an industrywide commitment. Purdue, for our part, has been doing a great deal of education and prevention of diversion, stopping abuse, detecting and assessing addiction.

In the last two years, we have touched over 250,000 health care professionals with those messages. In places where Oxycontin abuse and diversion were problematic in some of the rural areas where it was difficult for people to travel long distances, we did long distance learning education through Webcasting and through teleconferences. We took the information to them, made it accessible in their backyard.

We have put together CD ROMs of important links on the Webs of diversion related and addiction related materials, monographs, and in documentation kits which we have distributed, about a quarter million kits to guide a doctor through the documentation process that the medical boards require.

Education of patients and caregivers:

When we started getting into trying to understand the abuse and diversion problem of prescription drugs, we ran up on a sobering fact. All of the educational programs that currently exist to try to dissuade our young people from drug abuse mentioned nothing about prescription drugs. They tell you about street drugs, but they don't tell you what's in your medicine chest or your kitchen at home.

So we created a program called "Painfully Obvious" that is designed specifically to market the message to youth in a way that youth will get, which would be quite different than marketing to you, I assure you, that prescription drug abuse is drug abuse.

We also have created what I believe to be -- and it's been approved by the agency -- the first patient package insert for a scheduled opioid.

Surveillance activities I referred to earlier, and there is a number of different types of activities, including the post-market experience, the MedWatch program, and other types of programs which I'll highlight in a moment.

Stepped interventions: When you do surveillance and you gather experience, you must make interventions that are appropriate to the information

that you find. You must continuously assess the outcome of those interventions in a constant cycle of reassessment, reemphasizing different parts of the risk management plan, and revision as situations dictate.

In balancing the need to treat chronic pain, I'd like to give you some examples of what the various players can do.

Government, clearly, can encourage education about pain care and addiction. In California there is now a legislative mandate that, as a condition of licensure, you must have pain medicine and palliative care education in medical school. West Virginia has now invoked required CME for pain for renewal of licensure.

Class labeling: The broad labeling we've talked about is appropriate, but also there is information that is appropriate to the class. We have enough knowledge now about opioids that we can put in reasonable statements in all opioid labels to talk about things that are common. Also the long term studies that are proposed would provide more information in this area.

In law enforcement: In some states, for instance, the trafficking in Schedule III opioids is a

misdemeanor. It's not a felony, and busy prosecutors often will not waste time with misdemeanors.

Industry can certainly encourage, facilitate and provide education. We have distributed, for instance, the Federation of State Medical Board guidelines. Purdue has distributed well over 100,000 copies of those to physicians around the country. The APS Analgesic Guides, thousands of copies. Lawful prescribing slide kits, addiction assessment slide kits, and we have also been very actively involved in educating law enforcement.

Risk communication: Clearly communicating the risks such as the box warning.

Here's an example of some of the diversion information we put out, and we have samples that I will leave with Ms. Topper for the Advisory Committee. You can see with a simple four strokes of the pen, I was able to alter the prescription on the left to now get something that is four times as strong as the physician intended and to walk home with 60 more than the physician intended.

If, however, we get physicians to carefully write this out with the word "ten" behind the strength and the quantity, as they would write their own checks, this would be much harder to do.

There's a phenomenon called rinsing whereby someone uses a solvent to try to take away the ink that I've written and then write in what they wish. Tamper resistant prescription pads, not pre-printing your DEA registration number on prescription can help with this.

The tamper-resistant pads I mentioned, we are now distributing. These pads have six different security features included. A couple that I'll point out: You can see the word "void" appearing here when it is scanned or photocopied. In the actual sample, it's much more prominent. It doesn't project well.

It says right here "valid for controlled substances only" so that the pharmacist knows, if they get a controlled substance from a prescription pad in my office and it's not on one of these, they should be suspicious.

This background bleeds very easily if you try the rinsing or alteration technology. On the back there is a watermark, and there is also a disappearing thermochromic ink that, when you rub it, the heat from the friction of your finger makes it disappear; and while you can emulate that with a scanner, you can't duplicate that with a scanner.

We are now distributing these on a state

by state basis, starting with areas where prescription abuse and diversion have been most prominent.

Government can also, as you heard today, assist with data collection and interpretation on pain, addiction, abuse and diversion, and we welcome partnerships with NIH for these long term studies that were talked about yesterday.

Government can promulgate state statutes, model state statutes for well designed, nonintrusive, privacy protected electronic prescription monitoring programs.

Industry can continue to develop and administer product specific risk management plans that are unique to the individual attributes of a particular product, and progressively work on developing lines of progressively more and more abuse resistant formulations that, while are harder to abuse or undesirable to abuse, provide the full pharmacologic benefit to patients with legitimate need.

Of course, discovery research: If we can find the compounds that are excellent analgesics that have no abuse potential, that will be a great boon to society.

One type of surveillance system I'd like

to take just one second to talk about that complements the government and other surveillance systems is one that we have created called the RADARS system. Our objective here is to develop a more robust and reliable indicator of diversion and abuse than currently publicly accessible databases.

In order to look at abuse and diversion of a legitimate pharmaceutical, it's a very different issue than looking at street drugs. We have to have rate information to make intelligent decisions. That is, for every 100,000 people exposed in a year to Drug X, what percent was abused? How much was diverted?

Only by rate information can we make intelligent choices, and we hope this will provide earlier signal detection through an active data gathering rather than a passive or spontaneous reporting system.

Health practitioners, of course, if we are offering education, must avail themselves of it. They should support model state statutes. In fact, it's interesting. When I talk about this notion to physician colleagues in states that don't have prescription monitoring programs, they immediately dig in their heels until I point out that in Nevada and Kentucky, which tracks this information, that the

queries of the system from health care practitioners out number the queries from law enforcement by 15 to one. That is, it's a very useful tool for me to protect myself and make sure that my practice is protected.

Of course, prescribing conscientiously and thoughtfully, taking the few extra seconds to write out the quantity and strength, writing on tamper resistant pads.

Academia also has to get education about pain care and addiction, two of the most common things we are likely to see as physicians, into the primary curriculum. Of course, they can research the best educational practices, looking at what is the most effective way to change physician behavior and other health care practitioner behavior, as well as researching the best care practices.

So in summary, there is a significant burden of unnecessary suffering from chronic pain in the United States. Opioids have a significant role, and will continue to have a significant role in this therapy.

All opioids, however, have a recognized abuse potential. The product specific risk management plans can reduce the abuse.

Improvements can and should be made in both the assessment and the treatment of pain and substance abuse. We need better data. There is no question about it.

The most cogent approach to protecting patient access to opioids is a multilateral, integrated strategy based on data, and we welcome collaboration with our industry, our government, and our academic partners in trying to get our arms around these issues.

In conclusion, there is really a few things that, I think, everyone in this room wants to do. We want to ensure access to effective and appropriate care for patients with pain. We want to curb abuse. We want to diagnose and treat addiction. We want to prevent diversion.

In order to do that, the regulators, the health care professionals, the law enforcement officials, industry, educators, legislators, and the general public must engage in an active dialogue, respecting the different viewpoints you've heard expressed in the past two days and our varying experiences, but trying to talk in a rational dialogue so that we can come to consensus on ways to optimize the health of the citizens of this country.

An example of this is the DEA statement where 21 organizations joined with the DEA to come out to say that, while we must be aggressive in preventing diversion of controlled substances, we must ensure that those efforts do not adversely impact patient care.

I would like to thank the FDA, in particular Dr. McCormick who, I know, really wanted to be here today, for assembling this forum where we can begin this kind of dialogue and mutually share things to our benefit.

Purdue believes that if all the assembled parties work together here as described, we can collect and disseminate accurate information. We can improve accountability, and we can ensure access to pain medicines for patients with legitimate medical need. Thank you, Mr. Chairman.

ACTING CHAIRMAN KATZ: Thank you, Dr. Haddox. Why don't you stay up there for one minute. Does anybody around the table have any questions for Dr. Haddox? Dr. Portenoy, please.

DR. PORTENOY: David, thank you for your comments. They were terrific.

Can you just summarize what we do have in the way of outcome data to suggest that a risk

management strategy of the type you outlined works, and to what extent it works?

DR. HADDOX: I am not sure that we have a lot of outcome data in that regard, Russ. I think that there are pieces where we have some data, and we have been able to show, for instance, in some of the areas where we have been very actively involved in diversion prevention education that we have gotten feedback from local law enforcement that it seems to be making a difference in the prescription drug abuse problem.

So I think right now it's more of a piecemeal thing. I believe that that is part of the whole of idea, is developing appropriate outcomes measures -- the RADARS system, for one, would be one outcome -- and then taking that outcome and putting it back into the system to recycle it, to keep fine tuning and, as I said, make this a living plan, not something static that's on a shelf somewhere.

ACTING CHAIRMAN KATZ: Dr. Horlocker, followed by Mr. Bloom.

DR. HORLOCKER: You gave some specific examples of things that the FDA and we as health care providers can do to decrease diversion and addiction among patients, and also went into some detail that

Purdue and other industries have done for education.

Have you considered different formulations, such as adding naloxone to some of these long acting preparations to decrease the likelihood that, if it's crushed up and mainlined, the person would go through withdrawal or would not have the same opioid high?

DR. HADDOX: Yes, we have. We have an entire line of thinking along this point. We have -- It's really our number one research priority presently.

There are two things that we are working on presently that we think are further along in development. One is the addition of naloxone. Now while that sometimes is said to be very simple, it's actually fairly challenging, because one of the things we don't want to do is to harm a patient.

There are issues about giving patients who are not abusing medicines a medication they don't need in order to prevent someone else from abusing the same formulation, and there's the issues of what is the right dose. But we are exploring that very aggressively right now.

A second way of doing this is using a sequestration methodology, to sequester an oral

bioavailable drug such as naltrexone, such that when a person takes a tablet intact, they would not experience or be exposed to the naltrexone. If they tried to alter the formulation, they would release it, and then accomplish the goal that you mentioned of either no euphoria or perhaps induction and withdrawal if they are physically dependent.

These are very challenging technical issues, however.

ACTING CHAIRMAN KATZ: Thank you. Mr. Bloom?

MR. BLOOM: Thank you very much. Just a couple of technical clarifications of some terms in the handout. In the "Attitudes and Beliefs 2002" thing, there is a slight typo that's rather important. In the VPE ranges of the 8 to 10, the number is 22 percent. It's 2 with a space with 2, which makes it look like it's two percent. So that should be corrected to make sure it reflects accurately that it was 22 percent.

DR. HADDOX: Thank you. That's an artifact of Bill Gates.

MR. BLOOM: No problem. A second thing is in the "Attitudes and Beliefs 2002" the answer 37 percent, number 2, you suggested, was the only right

answer. The handout does not indicate that. It would be helpful if it would indicate that.

I also believe that I am correct that you did say that in the survey the patients were asked that, if they experienced withdrawal symptoms even though they were physically dependent on a medication, that they said they were addicted.

DR. HADDOX: What we asked was: If you are taking a pain medicine yourself, and you stop it and had withdrawal, does that mean you are addicted? Fifty-three percent said yes.

MR. BLOOM: Right. That's not reflected in your handout anywhere, and also I think that would be an important thing to highlight.

DR. HADDOX: So noted. Thank you, sir.

ACTING CHAIRMAN KATZ: Llyn Lloyd, followed by Doctors Schuster, Foley and Portenoy.

DR. LLOYD: Thank you. Doctor, you mentioned about tamper resistant prescription pads being made available. I'd like to know, are there any states that have so far required those?

DR. HADDOX: Yes, there are. As a matter of fact, Kentucky when they instituted their electronic prescription monitoring program in 1997, part of that bill also required the use of a security

paper technology like this.

What they do in Kentucky is they mandate the criterion, and then you can purchase those from whichever printer has the state seal of approval. So you can get your best deal on the market.

There are some other states that do require that you purchase them from the state, New York state, for instance, for Schedule IIs and the benzodiazepines, Texas for Schedule IIs in their triplicate form, California the triplicates.

So there's lots of variations around this. What we are doing with our program is in states where there is not a state mandated or a state purchased form, we are going to the Board of Pharmacy and saying here's what we want to do, do you have any objections, how would you like the face of the prescription to look, because there are statutory and regulatory requirements that differ from state to state as to where you sign for generic and where you sign for brand necessary and what those words say, brand necessary versus dispense as written.

So it's a process, but we have been going very rapidly, I think, with this. Right now we have about 8,000 physicians who are taking us up on this offer. We are providing these free of charge, and

there is no commercial attribution to the forms.

ACTING CHAIRMAN KATZ: Dr. Schuster.

DR. SCHUSTER: Yes. I was interested in the use of formulations that would be effective in preventing parenteral abuse of these products, such as the addition of naloxone. But if I understand the data coming from the Drug Enforcement Agency of the 177 deaths attributed or most likely attributed to Oxycontin, only seven of those were associated with anything other than oral administration.

Do you care to comment about that?

DR. HADDOX: Yes. I think that the -- I have some issues with the analysis of that supposed study, number one. We can talk about it later, if you wish, in the discussion section.

That's why the oral sequestered Naltrexone, we think, is another potential option, because -- and there's actually some other options we are pursuing as well that would prevent oral abuse of just by taking a handful of pills. But as I said, we have about five different things that we are pursuing right now, and they do involve a number of sort of variations on that theme.

ACTING CHAIRMAN KATZ: Dr. Foley.

DR. FOLEY; Yes. I think I have a

statement and then a question.

The statement is that Dave Joranson from the University of Wisconsin has reported data to show that looking at the degree of drug diversion with a drug such as a controlled release product such as the long acting morphine preparations showed, when you increased availability in this country or in India, that you didn't see much in the way of diversion.

I think that that hasn't been sort of here included in all of the discussions, and I think it's important to recognize that there is a sort of uniqueness to Oxycodone and Oxycontin that is causing the sort of spurt in epidemic perspective, and it may not be consistent with many of the other products that are on the market. So I think that that should be considered.

I think the second issue to Dr. Haddox is: Clearly, there is under-treatment of pain and profound under-education of physicians in the country. Now we are asking you to divert your funds to teach the country about substance abuse, not about pain management.

How does a company or how should we be asking the pharmaceutical industry who is trying to advance pian management to now take on a national

epidemic that we have without the government or other groups playing a major role in this kind of educational force? How do we think of the risk/benefit there? How do we look at the burdens to company? What should be the role of companies?

I think I'd like to hear that from Dr. Haddox.

DR. HADDOX: I think that industry does have a very important role in educating people about these issues. Clearly, we don't want to back away from the important mission of getting pain better treated in this country, and yet we realize that in doing so and using controlled substances that have abuse liability, there is an obligation there.

I do agree with you that this should be a multi-lateral effort involving government, involving academia, and it should be an industry-wide commitment. I don't think it is fair to put the burden on one single company.

ACTING CHAIRMAN KATZ: Dr. Portenoy?

DR. PORTENOY: David, I'd just like to hear you comment on one last issue. That is, how do we assess outcomes in relation to medical practice?

I struggle with this all the time when you are trying to educate physicians about how to

prescribe in a way that involves appropriate patient selection and monitoring of abuse behaviors.

We have an indication that using sort of public relations marketing technology in primary care can influence prescribing -- increase prescribing, at least in the setting of huge unmet need. Obviously, Purdue Pharma has been under a lot of criticism for that. And now we are saying that it's out there, it's being done. Good outcomes are being seen, but there are also some problematic outcomes. So we want to pull back a little bit. We want those primary care providers to gain some different kinds of skills and to exercise some different kinds of judgments.

What's the perspective of industry in terms of monitoring that or in terms of providing that kind of education, monitoring those kind of outcomes, and are you aware of any data that really allows us to know whether or not any of those efforts work?

DR. HADDOX: Well, the last question is the easiest one to answer, because it's a simple no. The other issues: I think that industry would clearly welcome partnership with academic and medical societies to try to look at these issues.

I suppose the mantra that I go by, and I fall back on my anesthesiology training, is the motto

of the American Society of Anesthesiologists: "Vigilance." I think that that is something that is incumbent upon doctors, to be vigilant, to see what's happening with their patients.

I have seen very few instances where physicians who were paying attention to what was going on with the overall treatment course got themselves or their patients into significant trouble. The key is to know what your comfort level is, to hopefully increase that comfort level with new skills and knowledge over time, and to know when to call for some assistance.

Just like you mentioned yesterday about hypertension, I had a very low threshold for calling for help for treatment with diabetes when I was doing chronic pain, particularly if I was considering invasive technology. I'd get an endocrinologist to help me out here to make sure that I wasn't going to make the person worse rather than better.

So I think it's just part of -- One of the things that I find frustrating personally is that people, physicians particularly, seem to think of opioid therapy as something different, and it seems to me, if you just be a good doctor, just do the stuff you do every day with opioids like you do with insulin

and ACE inhibitors, you know, the odds are you are going to help a lot of folks.

ACTING CHAIRMAN KATZ: Dr. Parris.

DR. PARRIS: David, nice presentation. My observation and my question has to do with the education of health care professionals. You have been on the inside in academia, and you are now proposing that the education of the health care professional is important.

I continue to be amazed at the ignorance of our graduating young physicians as far as their education on pain in general and opioids in particular. Do you have any specific recommendations to make, given the fact that you have been at Emory and now you are in industry? Do you have any specific recommendations as to how we can correct this ignorance that exists in our young graduating medical and nursing personnel?

DR. HADDOX: As was mentioned yesterday by Dr. Levy, I believe, integrating new information into a medical school curriculum is a remarkable challenge. As you know from your work at Vanderbilt, everyone wants a piece of the pie, and the pie is only four years long, and there's only so many hours in the day.

I think, however, that when you think

about what a physician, regardless of what they wind up doing, is likely to encounter, there is a disconnect between what we are taught and what we see. Every physician is going to see pain. It might be acute pain. It might be procedural pain, might be traumatic pain. It might be the type of pain that you and I have treated.

Every physician is going to see substance abuse, although they may not recognize it. I think these should be basic, fundamental things. The American Academy of Pain Medicine, as you are aware, is working on a curriculum to try to present to the Association of American Medical Colleges that will make it easier for curriculum committees to put this throughout the curriculum.

I think it's going to take a real commitment, and the Chairman-elect of the Board of Trustees of the American Medical Association, Ed Hill, has called for -- and I think it bears some thought -- Flexner II.

It's been 100 years almost since Abraham Flexner delivered his report on the state of medical education. Maybe it's time to take another look at it.

ACTING CHAIRMAN KATZ: Even though we are

running a couple of minutes behind schedule, I'm going to take one final question myself, Dr. Haddox.

DR. HADDOX: Certainly.

ACTING CHAIRMAN KATZ: In reviewing your slides and listening to your very thoughtful presentation, it struck me that, despite the fact that we know so little about some of the syndromes that we are concerned about here today, addiction, tolerance, diversion, and the fact that there's been almost no clinical research in those areas, I didn't see clinical research mentioned on any of your slides about how we are going to move forward here to better understand what it is exactly that we are dealing with.

I'm sure that wasn't a deliberate omission. I wonder if you could describe in more detail what industry's perspective is on pursuing an aggressive program of clinical research to better understand what is it exactly that we are talking about here?

DR. HADDOX: Well, I think that in terms of the pharmaceuticals and the labeling issues we talked about, I believe that these efficacy trials that were discussed yesterday and a little bit this morning make a lot of sense.

We are dealing with compounds that are not exactly new. Oxycodone, for instance, has been synthesized since 1917, has been continuously marketed in the world since then, morphine, of course, in the 1800s isolated. So I don't think we're talking about new issues.

The question that I think it begs is what is the pharmaceutical industry's obligation to fund studies to understand addiction? I think that's an issue that, I think, bears some discussion, and I'm not going to tell you that I can stand here and tell you that I have industry consensus on that.

I think that, clearly, in our post-marketing surveillance we should be actively looking for this, as we have longer experiences with patient registries, for instance, as we do with Oxycontin where we are constantly culling this data and looking for things much like we talked about yesterday, the real world.

Now we have the drug out there in the real world, let's follow these people closely and find out what's going on. That is one way of doing this, but I think the key here is active rather than passive reporting.

The RADARS surveillance system that I

mentioned to you -- we think that this is going to be -- Well, we know it will be a series of studies that we hope will put together a much clearer picture of this issue of diversion. We are looking, for instance, at -- We've added items to the DENS, the Drug Evaluation Network System, the ONDCP-funded online, real time intake system for treatment centers, about prescription drugs. That will probably be up to about 250 reporting centers by the end of this year.

We have established a key informant network of NIDA grantees, pain clinicians, dentists doing facial pain, people doing substance abuse, to feed us information on a regular basis about what they are seeing.

So I think there's lots of things industry can do. I don't think industry can do it along, however. That's why I wanted to put forth this notion of an active partnership with academia and government.

ACTING CHAIRMAN KATZ: Thank you very much. It's very helpful. I appreciate -- We all appreciate your time.

Let me then bring Dr. Rappaport up to introduce our upcoming session on prescription drug abuse.

DR. RAPPAPORT: I think we all understand

what we are here to talk about today. So I just want to take a minute to remind the Committee members about one particular regulatory issue that you need to keep in mind in your discussions today.

We believe that there are ways in which various aspects of drug development may use the labeling process to prevent problems like abuse and addiction. You need to understand that what ends up in the label may end up in the sponsor's advertising.

Now that's fine. That's the way the system works. However, while these materials are subject to a number of regulations that ensure that they provide a fair and balanced presentation, lack of adequate data on the risks of a drug to inform the label may result in potentially dangerous information being disseminated.

Another way in which it is very important what goes into the label, as Dr. Haddox was talking about with the black box warning -- I mean, that's not just there to inform physicians about the dangers of the drug. It also then becomes a requirement that go into all the advertising materials.

There are ways that we can manipulate the label into being more informative for you as prescribers and for the public, but there are a lot of

regulatory twists to this. So you need to keep that in mind in terms of what you ask for in clinical studies of safety concerns such as addiction and abuse and diversion issues.

ACTING CHAIRMAN KATZ: May I just ask you to -- Doug Rappaport, for a quick clarification. So is what you are saying then that, if a label states that a drug is safe and efficacious for a particular consideration, that it is important for the Committee to bear in mind that safety encompasses all the aspects of safety for the intended population? That's what I'm hearing, from what you're saying? Is that fair take home message?

DR. RAPPAPORT: Essentially, yes.

ACTING CHAIRMAN KATZ: Anybody else from FDA want to add any comments to that -- to Dr. Rappaport's introduction? Mitchell, question?

DR. MAX: Bob, I have no idea what you just said we should keep in mind. I'm trying to help. Could you try it again? Maybe give an example of what we shouldn't do. What would be a terrible mistake?

DR. RAPPAPORT: I'm sorry. Okay.

DR. KWEDER: Bob, can I help you?

DR. RAPPAPORT: No. I mean, I've got --

Only information from an adequate and well controlled study can go into the clinical trial section of the study -- of the label. However, if you have safety information, that can be put into the label at anytime and can be fit in appropriately.

So I'm just trying to tell you to be aware that, if we don't ask for certain information, we won't get certain information in the label, and then in terms of the marketing and advertising materials, we cannot require -- The agency cannot require that sponsors put that information into their materials. Dr. Kweder?

DR. MAX: Yes. I hear that you just want us to underline like Nat did the key areas of ignorance that we must know more about if we are to responsibly expand the prescription of some of these drugs.

DR. RAPPAPORT: That's correct. Dr. Kweder, did you want to make a comment?

DR. KWEDER: Yes. I think the reason Dr. Rappaport brought this up is because the term "labeling of drugs" has come up many times over the day and half we've been here, and the label -- but we haven't had a real discussion about it.

I think a couple of the highlights are

that the labeling is designed for prescribers to be informative and help prescribe a product appropriately. We also know that most prescribers don't read them.

Another reason -- but there are things that we do to try and ensure that key information about a product gets out. Now yesterday, for example, there was discussion about people on the Committee -- by way of example, that you like the idea of a very broad indication for opioids, because that allows you to use them as you see fit, particularly in a specialty setting, very understandable.

The downside to that is that the label is a legally binding document for the company. The company can only promote a product based on what's in the label. If a broad indication is in the label, despite the fact that some clinicians in practice think that certain uses of a product might not be appropriate, it's perfectly appropriate for a company to market the product for very broad indications with specifics.

It's not unique to this area of medicine, not at all. So it is just something to keep in mind.

Secondly, on the black box issue, one of the reasons that the black box is often a useful tool

is, while warnings must be reflected in promotional materials of any product, they must be particularly prominent on all promotional materials when there is a black box.

So often in order to get the word out about a unique safety problem or something particularly troubling, the agency will utilize the black box tool, because it ensures that that two-page spread in the journal you get has the information from that black box prominently figured.

I think that's part of Bob's point, is trying to keep in mind that there are a lot of ways to deal with this, to deal with some of these issues and try to balance appropriate prescribing information with warning information. We have some tools that work better than others.

Does that help you, Mitch?

DR. MAX: Yes. Well, if we were to say as a committee that we do not have data at this moment about the overall benefit/risk at one year, and we really can endorse that only on an anecdotal basis, would that get -- would that make payers not pay for this? Would we be damaging a lot of patients?

I mean, there's one way to do it right like I think the arthritis -- There are these

rheumatoid arthritis guidelines where they set up tiers of evidence requiring longer and longer studies. You relieve pain first tier. You relieve -- you increase function, and eventually erosions, and it's like the Olympics. All the companies are spending more and more money to go to bigger and longer studies, because they really want it, and it seems to be working marvelously.

Is there some scheme where we could do that without doing something really bad to cut off patients?

DR. KWEDER: I think that's a much longer discussion.

ACTING CHAIRMAN KATZ: It doesn't sound like we're going to get --

DR. RAPPAPORT: No, I don't --

ACTING CHAIRMAN KATZ: Does anyone have an answer for that?

DR. RAPPAPORT: I don't have an answer for that at this time.

ACTING CHAIRMAN KATZ: Let's go to -- Sorry, no answer. Let's go to Dr. Tobin, who has a question. Oh, I'm sorry, Dr. Smiley.

DR. SMILEY: That's all right. I'm very flattered to be mistaken for Dr. Tobin.

Dr. Rappaport, one thought, and it's obvious to you, painfully obvious, that we are not regulators and don't understand the process particularly well. But it seems to me that, if we are pushing the idea of broad labeling, whatever that actually means in the regulatory process, does that give you or give the FDA some more leeway to require safety information on a broad basis also?

Maybe I'm not phrasing the question in a regulator's way, but seems to me, if we are saying that we agree that opioids could be labeled broadly because we know that opioids are opioids and, you know, pain relief is a result of all of them, then can't the problems with one opioid be at least in some way mandated or encouraged or whatever the proper word is for a new product, even if you don't have information on that product about the safety issue?

DR. RAPPAPORT: We do include information about classes of pharmacological products in safety information in the labeling, but primarily what we put in the labeling is what we see from the clinical experience, from the trial experience, and the data that we get out of that.

In a sense, saying that something is part of a group of products such as the opiates

automatically has its own set of information that comes with it. So, yes. In a sense, yes, but primarily our information in the label is coming out of clinical trials.

ACTING CHAIRMAN KATZ: I'll take one more question from Mr. Bloom, and then we'll go on to the presentation.

MR. BLOOM: Thank you. This is a question for the FDA, and I don't know if this is under your mandate or not. Do you decide the yellow warning labels that are on the prescription bottles from the pharmacy or is that individual pharmacies that decide the wording on them?

DR. RAPPAPORT: We don't decide those in particular. We can work with a pharmaceutical company when we approve a product to request special warning markers on labeling and product packaging. It's a process of working with the sponsor to develop that, if it's felt to be necessary.

MR. BLOOM: The point being that I have thought for years now -- and this has been a joke during my college years, and I've noticed this for the last 20 years, and I have a bottle right here. I think the fact that all of the benzodiazepines and opioids all say "Alcohol may intensive this effect" is

hardly a warning label telling you the consequences of it, and intends to be an encouragement label to say that, if you mix alcohol with it, you're going to get a better boost out of the medicine.

I would suggest that there's probably a better warning label to put on it than the current wording.

DR. KWEDER: Jeff, we actually. He's right. Those little stickers are put on by pharmacists, and those are not specifically regulated by FDA. That's really sort of the practice of pharmacy.

There have been specific situations where, particularly for products that are distributed in unit of dose use -- you can only get them in a package of 30, for example -- where we work with companies to have a specific warning imprinted on the bottle that doesn't rely on a pharmacist to apply it.

We recently did it for an antiretroviral drug, for example, that has a very potent and worrisome toxicity.

MR. BLOOM: Let me say that probably is a good idea. You know, I think it's -- In college this was a big joke to people, and I mean, I've never seen -- From any pharmacy at least in the Washington area,

everyone has that same label that says alcohol may intensify this effect. You can imagine what that translates to. So --

ACTING CHAIRMAN KATZ: A final, very quick comment, and then the presentation.

DR. CARLISLE: You would be interested to know at a major university in the midwest a recent study has shown that young women reported that they used benzodiazepines for weight control. Not being able to understand this, we did focus groups and established the fact that they would take a benzodiazepine prior to the time they go to a party so that they would drink less alcohol which, of course, contained the calories.

ACTING CHAIRMAN KATZ: With that, let me introduce Judy Ball from the Substance Abuse and Mental Health Services Administration, who will be speaking to us on current data on abuse and diversion, with apologies for being behind schedule.

DR. BALL: I want to thank my colleagues at the FDA for inviting me to come and present data from DAWN. In the interest of full disclosure, I should also tell you that I did not pay Mr. Coleman to say good things about the Drug Abuse Warning Network this morning.

DAWN is one of those data systems that collects data both on the illegal and legal drugs. We collect a lot of data on prescription drugs. In fact, SAMHSA is required by law to collect information on drug abuse related emergency department visits and drug related deaths that are reviewed by medical examiners and coroners. The Drug Abuse Warning Network is, in fact, the vehicle by which SAMHSA meets this requirement.

On the emergency department side, DAWN relies on a stratified probability sample of hospitals, short term, general, non-Federal hospitals in this country, that operate 24-7 emergency departments.

Based on the way the sample is structured, we are able to produce representative estimates for the coterminous U.S. -- Alaska and Hawaii will be joining the union shortly -- but also for 21 major metropolitan areas. What I'm going to show you mostly today are national estimates.

Cases that are reported to DAWN have to meet very specific criteria. The patient must be between the ages of six and 97 and was actually treated in the emergency department. Patients that get triaged out without treatment aren't included.

The emergency department visit has to have been related to drug abuse, and that means the use of an illicit drug or the non-medical use of a prescription or over-the-counter medication. The motive for the drug use actually has to be documented in the record as being dependence, psychic effects, or suicide attempt or gesture.

So while you might want to think about every drug abuse case that shows up in the emergency room being reported to DAWN, in fact, there are probably some cases missing, and we are making some changes in the case definition shortly. But in the meantime, this is what we have to work with.

The drug detail in DAWN is important for you also to understand, because it varies based on the detail that's in the source record. We do not collect any information directly from patients. We only abstract information from medial records.

So the medical record may contain the brand name, the trade name. It may contain the chemical name. It may give us only the generic or it may only give us nonspecific information. If nonspecific tests for opiates are performed, for example, that might be the only information we are able to derive.

For both legal and illegal drugs, street names may also be documented in the record. The result of this is that we do not publish estimates for particular brands. That doesn't mean that we don't have data on brand level information, but the data are sufficiently incomplete that we think publishing estimates by brands would be unreliable and misleading.

From the emergency department sample in DAWN, we estimate that for the total country, there were about 96 million emergency department visits for any reason in 2000, and out of those about 600,000 were related to drug abuse.

Each case of drug abuse can have up to four drugs reported, and we refer to that instance of a drug report as a drug mention. The drug may be mentioned on the record. So for the 600,000 visits, we had nearly 1.8 million drug mentions or 1.8 drugs per episode. This is based on a responding sample of 466 hospitals.

As you can see from this chart, about 80 percent of the 1.1 million mentions are made up by just eight categories of drugs. The cocaine, heroin and marijuana plus alcohol in combination make up about 50 percent of mentions, but then the

benzodiazepenes, the antidepressants and the analgesics make up another about 30 percent, and it's the narcotic analgesics that I will focus on today.

About six different substances make up about 85 percent of the mentions of narcotic analgesics. What we see here is, if you think of morphine of sort of the base for comparison, for every one mention of morphine we find ten mentions of a nonspecific narcotic, eight mentions of hydrocodone, four mentions of oxycodone, and then about two mentions of propoxyphene or codeine, again relative to the number of mentions of morphine.

Take a look at our recent trends. What we have found, the middle column there shows you estimates for the year 2000. From 1998 until 2000 we had a 40 percent increase in the mentions of unspecified narcotics, nearly a 50 percent increase in hydrocodone mentions, and a doubling of oxycodone mentions.

From 1999 to 2000, the only statistically significant increases occur for hydrocodone, which rose 30 percent, 32 percent, and oxycodone which rose 68 percent.

To look at the longer term trends, this shows just the most frequent, the oxycodone,

hydrocodone and narcotics unspecified. You can see that hydrocodone and narcotic analgesics unspecified sort of started at the same point in 1994. Since then, the unspecified mentions have risen three times. Hydrocodone has a bit more than doubled, and oxycodone has risen 166 percent, so doubling plus another two-thirds.

For the lower frequency narcotics, we actually see that codeine from 1994 to 2000 dropped 44 percent. Propoxyphene has sort of been jiggering along there. There's no real trend about it, and morphine rose 126 percent from '94 to 2000, but in fact that increase sort of happened by 1998, and the trend has been flat since then.

So that's, in summary, what DAWN shows us about emergency department visits associated with the abuse of narcotic analgesics. Now the other kind of sentinel event that DAWN tracks is cases that are reviewed by medical examiners and coroners.

Unfortunately, we do not have a probability sample of drug related deaths in any way, and we are not able to produce national estimates. But we do collect data from about 140 medical examiners in the country. This is both drug induced deaths, when there were overdoses and when there were

-- and when the death was drug related.

We only have partial participation in some of 40 metropolitan areas. We have full participation in others. What I'm going to show you now is some data from the medical examiner component from seven metropolitan areas where we have complete participation, and these happen to be seven metropolitan areas that we also can produce estimates on the emergency department side.

So we can get a sense of both morbidity and mortality associated with these particular drugs. To make sure that we control for population size across these cities, I have expressed all of the numbers you are going to see from here on out in terms of rates per 100,000 population.

So let's start with the narcotics not otherwise specified. You can see from the emergency department visits that Baltimore has a far higher rate of reporting of these mentions than these other cities, but even among the other cities here there is quite a bit of variability in the rate of these mentions.

The deaths, on the other hand, medical examiners usually report fairly specifically. So we don't have a lot of reports of unspecified narcotics

on mortality cases, but we do see a few, and the numbers here go from a low in San Francisco of .2 deaths per 100,000 population up to .8 deaths per 100,000 population in Boston.

For oxycodone, you should notice here that the scale on this chart is not the same as the scale on the previous one. This only goes up to 20 per 100,000. Again, we do see a lot of variability across the cities, and the deaths actually range from a low of .3 per 100,000 population in Denver and San Francisco up to a high of one death per 100,000 population in Miami and 1.1 deaths per 100,000 population in Baltimore.

Oxycodone is not necessarily the only drug that was involved in these deaths. Just as on the emergency department side, multiple drugs are typically involved, and the average number on the medical examiner side is 2.5, I believe.

So again, we see variation both on the emergency department side and on the medical examiner side, and the pattern is not consistent necessarily across the cities. As you can see here, looking at hydrocodone rates, again the cities that have the highest rates are not necessarily those that have the highest rates for oxycodone.

On the deaths, we have rates ranging from .2 deaths per 100,000 population in Baltimore, going up to .9 deaths per 100,000 population in San Diego and Los Angeles.

As we expand the DAWN sample to include more medical examiners, we will be able to produce more information like this that can be put together with the emergency department side.

To give just an overview of the limitations of DAWN, because there are some that are important to understanding these numbers: The first is that the intent to abuse the drug has to be documented in the medical record. Currently, we will miss cases if such documentation is lacking.

Second, we cannot distinguish diversion versus the abuse of prescription drugs consumed by the person for whom they were prescribed. That's simply not possible, based on medical record information.

There is variable reporting of nonspecific terms over which we have limited control. Finally, right now we do not have any good information on health status or the presenting complaint or the diagnosis for the patient coming into the emergency department. For DAWN to speak to health consequences, certainly some of that information is necessary.

The strengths of DAWN, however, have to do with the extensive drug detail, that there is no other systematic drug abuse data collection system that collects as much or as specific detail on illicit, prescription, and over-the-counter drugs.

We get drugs regardless of the frequency. We get new and old drugs. We start seeing new drugs coming into DAWN as soon as they start appearing in emergency departments, and we are able to produce statistically valid estimates on the emergency department side and trends over the long run.

DAWN is also one of the more timely of the substance abuse data collection systems, and as I intimated earlier, we are actually -- we have some major changes planned for the next five years that we hope will make DAWN even more useful for a variety of users.

Our sister agency, FDA, is one of our principal users, and we work with FDA all the time to provide them with information out of DAWN that will help them do their jobs. Thank you.

ACTING CHAIRMAN KATZ: Thank you, Dr. Ball. Are there any questions from the table to Dr. Ball, specifically about the content of her presentation? Dr. Carlisle, you are first.

DR. CARLISLE: I would like to know a little bit more about how your cases are defined. You said in, I believe, your second or third slide that you had drug related ED visits. Does that include other things such as soft tissue infections, accidents that are all drug related but are not specifically an overdose?

DR. BALL: Yes. Yes, DAWN includes any kind of case that is treated in emergency departments that is related to drug abuse. It doesn't mean that the drug had to be the particular cause of the visit. The kinds of examples you give for skin infections and for accidents are certainly reportable to DAWN.

The kinds of cases that we miss are things like drug rape, when a woman is given a drug without her knowledge. That would not be currently reportable to DAWN. And if the visit is totally unrelated to drug abuse but drugs were on board, the case would probably not be reported.

DR. CARLISLE: And then the second part of my question is do you have any way of capturing those patients that have drug related problems but do not come to the emergency room per se?

The reason I ask that is that in San Francisco at my hospital we have now taken

approximately 1,000 cases a year of soft tissue infections and put them in a special clinic. So those patients are never seen in the emergency department. Do you have any way of capturing those patients in your database?

DR. BALL: Right now, we collect data only from emergency departments, and there may be -- Some hospitals have multiple emergency departments for treatment of different populations.

Especially with the increase in managed care over the past decade, there has been an increasing concern that drug abuse cases, because of insurance or other reasons, may be being diverted outside of emergency departments, being treated in these alternative settings.

We were very concerned about why the leakage of these cases out of emergency departments was making the DAWN -- the information in DAWN less valid. We actually awarded a contract two years ago to take a look at this and many other design issues having to do with DAWN, and we looked at the necessity and the feasibility of trying to capture patients in other settings of care.

On the managed care issue, what we found was that there was no consistent pattern, and much of

the research that has been published recently and is ongoing suggests that, in fact, managed care is not reducing the caseloads in emergency departments. In some cases, it may actually be increasing caseloads.

Alternative care settings such as -- I don't know what they are called officially -- urgent care centers and doc-in-the-boxes, we found very considerably across time and place, and they are simply not a source of care that is sufficiently stable to be able to do a sample and collect data from on a regular basis.

The kind of clinic that you have at San Francisco General, if the patients are not seen in the emergency department and treated in the emergency department, they would be lost to DAWN. But if they have other issues that cause them to be treated in your emergency care facility, we certainly would pick them up.

ACTING CHAIRMAN KATZ: Dr. Reidenburg is next, and there about five people before you, Mitchell.

DR. REIDENBURG: Yes. Two questions on the medical examiner's data. Firstly, if somebody successfully commits intentional suicide where a drug is detected, would that appear in the medical

examiner's data?

My second question is: As you showed your slides, it seems as if the death rate per 100,000 city by city isn't nearly as variable as the choice of drug from one city to another. So in Baltimore hydrocodone doesn't kill nearly as many as oxycodone; whereas, in San Francisco, it's the opposite. Have you looked at your data from this standpoint, and is my superficial review close to correct?

DR. BALL: The answer to your first question about suicides is yes. On the emergency department side we pick up attempted suicides. On the medical examiner case, we have the potential to pick up completed suicides.

Having to do with the variability and the death rates across the cities, I think you are probably right. It does look as though we have more variability sort of between drugs and across cities, but I would also urge you to exercise some caution.

The numbers for those death rates are so low that even very small things look to be big. The fact is none of the rates that I pulled for these cities out of the DAWN data are very large at all. One death per 100,000 population was the largest, and I think occurred only in two cities for one drug.

ACTING CHAIRMAN KATZ: Dr. Anthony.

DR. ANTHONY: Dr. Ball, congratulations. That was a very wonderful overview. First, I'd like to say that criticizing DAWN, I've been working with DAWN since 1972, DAWN data since 1972, and criticizing it is like shooting fish in a barrel. It's about as easy as one can do.

So my comments aren't intended so much to criticize DAWN as to draw attention to what may be important points of interpretation of the DAWN data. Before I had mentioned -- three points. I should add that DAWN around the world among people who study drug dependence and the epidemiology of drug dependence, it's considered -- it's an envy. It's considered a gem surveillance system. So anything that I say should be taken in that light.

A surveillance system -- this is true for DAWN or the National Household Survey on Drug Abuse which Dr. Chilcoat will talk about a little later -- is designed to be practical, to provide relatively rapid information and to reveal outbreaks that need to be investigated in more detail, and is almost never -- A surveillance system is almost never designed with validity or accuracy paramount in mind, and completeness of data.

One of the interpretative points that is important here concerns this category of nonspecified narcotic antagonists -- narcotic analgesics. A question I have particularly is whether heroin is excluded from that category or whether heroin might be included here.

DR. BALL: If heroin is identified in the record, it's not included there.

DR. ANTHONY: But if it were identified as a narcotics overdose, but heroin was not specifically mentioned, would it show up in the NOS category?

DR. BALL: I suppose that's possible.

DR. ANTHONY; It think this is a fairly crucial detail, and the relative magnitude of the number and rate of nonspecified narcotics events or mentions in DAWN to those that are specific to the generic or chemical names of the drug is important to pay attention here to.

So when we are comparing city by city, looking at the specific ratios of, say, oxycodone versus hydromorphone, we have to wonder what is lurking behind in that not otherwise specified category of narcotics. It could be that the specific drug ratios are giving us a somewhat misleading picture in the story.

DR. BALL: So you are thinking that heroin rates are high in Baltimore. Therefore, the narcotic analgesic rates in Baltimore that are unspecified probably reflect the heroin rate?

DR. ANTHONY: Well, I do know the heroin rates are high in Baltimore, but I'm more -- In terms of answering the question raised earlier about the ratios of hydromorphone versus oxycodone mentions, for example, for two different cities, I'm more worried about that very large category of not otherwise specified.

In epidemiology generally -- and I know you know this -- whether we are studying anthrax or heroin overdose, having a very large not otherwise specified category makes the interpretation rather difficult.

DR. BALL: Yes.

DR. REIDENBURG: But this is why I specifically focused on the medical examiners cases where they were specified.

DR. ANTHONY: I believe the medical examiners include quite a few not otherwise specified narcotics as well, because bioassays aren't always done. Toxicological tests and evidence is not always available for those records.

DR. BALL: Actually, the number of deaths that were reported to DAWN in these cities with narcotics analgesics unspecified was three in San Francisco, seven in Miami, 11 in Denver, and 29 in Boston.

DR. ANTHONY: Ah, thank you. That helps, not so much for the emergency room episodes but for the medical examiners.

The second point is that these are mentions. These are drug mentions as opposed to episodes or patients -- let me straighten that out. These are mentions as opposed to episodes, and so more than one drug can be mentioned at the same time.

If someone empties the medicine cabinet, happens to die of an overdose of aspirin, but in the medicine cabinet there is some residual narcotic analgesic, that will get counted in the DAWN numbers.

This is important because, as we look at newly marketed products, the number of daily doses circulating in the population is increasing over time, and an old product that is being retired it will be declining in time. So our trends are going to be reflecting, to a certain extent, the number of daily doses circulating in the population.

So when we see these, for example, for

oxycodone increasing, what we may be seeing is simply the increasing availability of oxycodone in the population, and that's another interpretive point. I'm not certain that it undercuts the importance or value of the DAWN data, but it's one of the reasons why we have to think about this as a surveillance mechanism that then leads us to guide us toward more probing investigations, as opposed to standing on its own two feet, interpreted as more than the surveillance data.

Then the final point that I think may be worth mentioning is that the inclusion of suicide and suicide attempt in the analysis of the DAWN data makes for problems of the type I mentioned before where a person might actually not be a casualty that should be attributed to a specific product or even to the chemical class, but simply it's a casualty that's related more to the mode of suicide that a person or suicide attempt that a person tried to make.

So those are just three points about DAWN that I think are important when we consider the investigation of DAWN data as part of the regulatory evaluation. Again, with a surveillance system, whether it's DAWN or the National Household Survey on Drug Abuse, the goal would be to detect something

happening, and then to use more probing and rigorous methods to sort out what is actually happening. I guess that would be what I would leave the Committee with.

ACTING CHAIRMAN KATZ: Dr. Ball, are you available to stay here for another -- If we take a break now, will you be available to answer more questions after that break?

DR. BALL: Certainly. I plan to be here the rest of the day.

ACTING CHAIRMAN KATZ: Why don't we do this. Why don't we take a break right now for ten minutes. We'll regroup here -- My watch says ten minutes after eleven -- and then we can address any remaining questions.

(Whereupon, the foregoing matter went off the record at 11:05 a.m. and went back on the record at 11:15 a.m.)

ACTING CHAIRMAN KATZ: Why don't we go ahead then and address other questions to Dr. Ball based on her presentation, if everybody could bring their conversations to a close and have a seat, so we can free ourselves of any unnecessary distractions.

I did have a number of people on our list to ask questions. If anybody feels that, in the

interest of time, their questions have already been adequately addressed, please feel free to pass your time on to the next person. Dr. Portenoy, you were first.

DR. PORTENOY: Just very quick: You know, we are concerned about the definitions applied to abuse and diversion -- abuse and addiction, when patients with pain receive opioids for legitimate medical purposes. I notice that the data are abstracted based on a diagnosis of dependence or psychic effects.

In common clinical experience, dependence is often used in a way that doesn't seem really linked to the diagnosis of addiction in chronic pain patients. So the question is who is doing the abstraction? Is there any sort of training in the abstraction of the DAWN data that relates to this definitional issue when controlled prescription drugs are given for legitimate medical purposes? Is that one of the things that's going to happen in the next five years?

DR. BALL: The people who abstract information from DAWN are sometimes health care professionals, sometimes health care paraprofessionals in hospitals.

There is training currently done, and there has been for a long time, but with the redesign of DAWN, we'll be changing the case definition. There will be much more intensive training of reporters than we currently have.

Taking away this requirement to find evidence of abuse in the record is actually one of the changes we have planned for the case definition, because we don't know what we are missing that simply doesn't have that kind of documentation.

ACTING CHAIRMAN KATZ: Dr. Max, you had an opportunity to ask a question.

DR. MAX: Yes. Have you tried correcting the increases in Oxycodone or hydrocodone over the pat couple of years for the number of doses dispensed from a country?

DR. BALL: I have not. I don't have access to the dose information, but I think that is probably something that FDA not only has access to but can do and probably does.

ACTING CHAIRMAN KATZ: Dr. Parris was next.

DR. PARRIS: Since DAWN is supposed to be a surveillance tool, and given the fact that managed care practices, as you alluded to, is changed, do you

think it would enhance the quality of your sample if you were to include data received form walk-in clinics, from clinics at schools, and from clinics in factories and other large places where workers seek health care assistance?

DR. BALL: There are certainly many different sites where drug abuse cases might be picked up, and there are many different surveys that try to capture data from many of those. School surveys come to mind, for example, as a way of getting information about drug abuse among students.

Our field studies told us -- or the study of design alternatives told us that going into other settings of care and trying to collect data on similar patients was not a proposition that was going to pay off very well.

It's something, as the health care system changes, that we will continue to monitor. There's no intent in our redesign that the new DAWN is going to be the same way for the next 30 years. As health care changes, we will continue to try to make sure that we are finding the patients in the places that they are being treated.

The walk-in clinics and such are -- We did case studies in four metropolitan areas, in addition

to reviewing the literature on this, and basically, what we learned from those areas was that there are these other settings, but they vary so much across time and across place that trying to use them as a stable source of data collection simply isn't feasible at this time.

ACTING CHAIRMAN KATZ: Dr. Passik, you were next.

DR. PASSIK: One of the, I think, important pieces of data that it would be nice to have would be whether or not, when a person shows up in an emergency department with a prescription medication that's led to that episode, whether or not that drug was actually prescribed for that person and/or the relationship of that person to the person to whom it was prescribed.

I think a lot of times decisions and statements get made about hydrocodone is the most abused prescription opioid in the country, but it's perhaps not by people to whom it's prescribed. When you are concerned -- If you have concerns about getting some information on the epidemiology of prescription drug abuse by, for example, pain patients, it would be important, I think, to try to get that information, and not only about the patients

but also by the children, for example, of the patient. So that, you know, what's the risk to everyone in the household, for example, of someone who is being described a drug for pain.

I think we have very little that we can tell from these data about that particular aspect of it.

DR. BALL: Source of the substance and where legal prescription is one of the sources is currently a data element in the DAWN system, and it's a data element that we plan to be dropping, because we mostly get missing data.

It's not the sort of information that's well documented in medical records.

ACTING CHAIRMAN KATZ: Dr. McNicholas, you have the last question for Dr. Ball.

DR. McNICHOLAS: Actually, I've got two short questions. One of them is a follow-up on that question, and that is: If a person has a legitimate prescription for, for instance, hydromorphone, and then abuses another drug, either antidepressants or whatever, is there any distinguishing attribute in the record or are both drugs simply mentioned as part of the emergency room visit or the associated death?

DR. BALL: That's a really good question.

Right now it is possible that co-occurring substances will be reported. So if somebody comes to the emergency room for cocaine and they took three aspirin, the aspirin might be reported as well.

It's one of the changes that we are planning to make to DAWN, is to try to either eliminate or at least differentiate substances that were taken for therapeutic purposes versus those that were not, because it is a limitation.

ACTING CHAIRMAN KATZ: Thank you, Dr. Ball, for your presentation and for coming up after you were done to answer a few extra questions.

What I would like to do now is to introduce Dr. Deborah Leiderman. Are you around, Dr. Leiderman? Yes, there you are -- who is the Director of the Controlled Substance Staff at the FDA. Dr. Leiderman will be speaking with us about FDA assessment of abuse liability.

DR. LEIDERMAN: Good morning, Dr. Katz, members of the Committee, members of the public. I have the task of trying to keep you awake, because this can seem to be a somewhat tedious and less maybe intrinsically interesting topic.

This was brought to my attention when I was reviewing my slides early this morning in the

kitchen, and my nine-year-old daughter decided to go back to bed. So anyway, what I am going to do today is to provide you, I hope, with a regulatory background, regulatory context in which we actually do our work, mostly prior to the drug approval process, but sometimes afterwards.

The abuse potential assessment process is actually mandated by two distinct acts or laws, both the Federal Food, Drug and Cosmetic Act of 1938 and the Controlled Substances Act of 1970. The FD&C Act actually mandates that abuse liability be determined during the new drug -- the drug development process and actually addressed in the New Drug Application.

Then, of course, a crucial part of the labeling process, if it is pertinent, is to describe abuse and dependence potential.

Then, of course, the Controlled Substances Act mandates, if appropriate, that a drug be placed into a schedule.

In the NDA requirement, the clinical section, actually delineates what must be included in the submission. Probably members of the industry who are here are quite familiar with this. It specifies that all data pertinent to the abuse of a drug must be included, as well as data relevant to overdose, and

then a proposal for scheduling under the Controlled Substances Act at the time the New Drug Application is submitted.

The Controlled Substances Act is mostly the authorizing act for the Drug Enforcement Administration, and you will be hearing from the DEA a little later today. But it also provides a small but, hopefully, we think, important role for the Department of Health and Human Services.

It actually specifies Health and Human Services. In fact, this responsibility has been further delegated to the FDA and to specifically our group.

This requires that we perform a scientific review of data on a new drug or substance. It basically establishes the legal procedures on which the DEA does everything, but again specifically for how HHS, our group, interacts with the DEA.

It also specifies the five classes of control, which most of you are familiar with. It's schedules, Class I substances, for example, heroin, LSD, marijuana. Class I substances are most restrictive -- is the most restrictive class, and those are the substances that have no medical use.

Examples of Class II include substances --

include the substances cocaine, morphine, opium, oxycodone. These are substances that have the highest potential for abuse, but have medically approved use.

The CSA addresses several classes of drugs. Very specifically, I know the concern today, the focus of this meeting, is primarily the opioids, but in fact the Controlled Substances Act does schedule central nervous system depressants, other central nervous system depressants, CNS stimulants, hallucinogens, cannabinoids and then, most recently, anabolic steroids as well.

The Controlled Substances mandate for the Health and Human Services Department reads as follows, and you can all read this, but it basically requires that the Secretary for Health and Human Services notify the Drug Enforcement Administration if a drug having a stimulant, depressant or hallucinogenic effect on the central nervous system, has abuse potential and is being reviewed in a New Drug Application. The Attorney General must be notified.

Again, that responsibility is delegated to the Food and Drug Administration.

So how actually do we go about scheduling drugs? At the FDA we perform the scientific assessment and recommend an initial schedule or a

scheduling change to the DEA. All scheduling is done by the Drug Enforcement Administration.

They schedule drugs through a rulemaking process, again complex, and they can describe it in more detail for those of you who are interested. Schedule changes can be initiated by the DEA itself, by the FDA, by Congress, and by any citizen or sponsor through a petition process.

I'd just like to mention that there are international treaties that address this, and we must comply with those as signatories, but again that is a whole separate topic. But it is something that we must bear in mind.

Again, the levels of drug control that are specified under the Controlled Substances Act, just to go into this in somewhat more detail for those of you who may not be familiar with it: Schedule I substances are not approved for medical use in the United States. They may be in other countries.

They have the highest abuse potential. So this is the most restrictive class. Special DEA licenses are required for any research.

Schedules II through V: All drugs placed into these schedules have some medical -- approved medical use in the United States, and they have

diminishing but present physical or psychological dependence liability.

The abuse liability assessment that we do and that we ask sponsors of New Drug Applications to do is really something that should be interwoven through the drug development process, and really begins in the pre-IND stage, at least ideally, and hopefully, continues throughout the IND, New Drug Application as well as the post-approval phase.

All data must be evaluated. We look at and we anticipate that sponsors will provide and analyze all potentially relevant data, including the chemistry, animal and human pharmacology, pharmacokinetics, pharmacodynamics, as well as the adverse events reported in clinical trials or subsequent to approval.

If appropriate, a new drug should be compared to a pharmacologically similar substance.

In evaluating abuse potential, obviously, chemical structure may be very critical. Pharmaceutical characteristics, including such things as ease of synthesis, extractability, solubility, are also critical elements; and, of course, the central nervous system pharmacology, receptor binding characteristics, behavioral effects.

Again, the FD&C Act requires that an actual abuse liability package, if relevant, be submitted. This package should include all these elements and address the pharmacology, preclinical and human, clinical trial data, and again make a proposal for scheduling under the Controlled Substances Act.

To expand a little bit on what we mean in the pharmacological arena, in the preclinical phase we look at full neuropharmacological characterization, binding studies, animal behavioral studies that are at least, hopefully, sometimes valuable models for predicting human behavior: Reinforcing effects, self-administration kinds of models; discriminative effectives; and of course, we look as well at any physical dependence evidence in animals, and tolerance.

Then, similarly, in the human arena we can actually ask humans about their subjective effects, drug liking measures. We can look at toxicity and performance impairment, and again tolerance and physical dependence data.

The Controlled Substances Act actually specifies a so called eight-factor analysis. These are delineated here, but basically again it requires all the scientific data that I have described, as well

as pertinent history, data from other countries, public health risks, psychic or physiological dependence liability, and then some clinical data if a new drug is a precursor of a substance that may already be controlled.

These eight factors are then relied upon in determining the appropriate schedule. Scheduling criteria that the Act delineates for Class II through V drugs are, of course, the approved medical use, then relative potential for abuse, and dependence liability.

FDA and DEA both have roles under the Controlled Substances Act. To recap, the Food and Drug Administration's role is limited to the assessment of abuse potential, which we really regard as another kind of risk assessment, in many ways not that different from other kinds of drug risks, whether it is hepatotoxicity, cardiotoxicity.

These risks need to be labeled, just as other risks do. Abuse and dependence risks are required to be in the label. FDA does not have any role for control at the level of the prescriber, dispenser or patient under the Controlled Substances Act, under the scheduling process.

The Drug Enforcement Administration, whose

Act this primarily is, licenses manufacturers, sets quotas, licenses prescribers, and of course, does the law enforcement.

Kind of to sum up, I think what we want to convey today is that abuse liability assessment is a very complex composite. It's based upon a lot of different kinds of data: Chemistry, pharmacology, clinical data, public health risks, both in a target and in a general population.

Abuse or dependence potential is another risk that needs to be managed. Labeling and drug scheduling alone have limited impact on these risks. Thank you very much.

ACTING CHAIRMAN KATZ: Thank you, Dr. Leiderman. I hope you can stay up there for a couple of questions. Dr. Schuster, please.

DR. SCHUSTER: Dr. Leiderman, we have had a lot of discussion in the past couple of days about the issue of iatrogenic dependence. I think it's of some relevance to note that in abuse liability testing, we generally choose active drug abusers or individuals who are highly vulnerable to abuse to assess the abuse liability of a new compound, as opposed to the patient population for which this medication is indicated. Am I not correct about that?

I think it's important for this Committee to understand that.

DR. LEIDERMAN: Dr. Schuster, I think you can better address that as an active researcher in the field, but yes, that is what is typically done.

DR. SCHUSTER: I simply point out that many times when we do studies of abuse liability, we use what we call polydrug abusers, not individuals who are dependent, and the answer that we get there where all of them say they like this drug and they are going to actively -- if it was available, they would actively abuse it, does not necessarily mean that the patient population for which it is going to be prescribed is at the same level of risk. That's all I wanted to point out.

DR. LEIDERMAN: Yes. I think Dr. Schuster is highlighting one of the very important issues in this whole field in trying to tease this out. But, of course, patients who have any disease, whether it's diabetes or chronic pain, may in fact have potentially the same risk for the, you know, neurobiological disease of substance dependence as any of the rest of us. Knowing that in advance can be complex.

ACTING CHAIRMAN KATZ: Dr. Reidenburg.

DR. REIDENBURG: I'm unaware of any

practical difference between something in Schedule III or Schedule IV for the drugs I prescribe. I don't even know which level they are.

Is there a practical difference or why do we keep these many different schedule numbers?

DR. LEIDERMAN: Well, again I probably should defer to my DEA colleagues, but I would agree with you for the practicing physician there is very little -- and the patient -- there is very little distinction between a III and a IV drug.

For example, you can have refills under a Schedule III or IV drug. There are no refills permitted for Class II drugs. Again, a whole 'nother area, but states also regulate these substances, and may regulate them more restrictively than the Federal regs do. So that again state laws may distinguish more between Class III and IV drugs practically than does Federal law.

ACTING CHAIRMAN KATZ: I have a question myself, since nobody else seems to be in line right now.

It seems to me, on reviewing the wealth of data that the FDA requires to make its abuse liability risk management assessment, that all of the data that are required or requested are all surrogate measures

for what we are all interested in, which is to what degree is the drug actually abused in the target population to whom it's prescribed or in individuals to whom it is diverted.

So it didn't seem to me, in reviewing the data that's requested or required, that data from the actual individuals to whom it is prescribed to look at the degree to which the drug is abused appears there.

So if that's correct, and we are all really looking just at surrogate measures, it seems like there are two obvious consequences of that, the first one being that we never really know, based on the information that you listed, what we are really interested in.

Secondly, we never have any information about what the validity is of any of those surrogate measures for predicting abuse or addiction or what have you in the real life setting.

So to me, I have that reaction, and I wonder if you could respond to that.

DR. LEIDERMAN: Well, in fact, perhaps I didn't make this clear enough. Clinical trial data are relied upon as well, but you are quite right that they don't usually set out to assess misuse of drugs. But in fact, this should be looked for, when

appropriate, and we do ask that that be done.

Of course, what you are highlighting is that clinical trial populations are by definition fairly narrow and homogeneous, and do not represent the population as a whole. That's why again for many adverse events we really don't see problems until they are in a more heterogeneous population. So that includes all kinds of concomitant, you know, diseases and drug interactions and again not restricted to the abuse and dependence arena.

ACTING CHAIRMAN KATZ: Thank you very much. Dr. Parris?

DR. PARRIS: Dr. Leiderman, this may not necessarily be your purview. It may be more a question for the DEA, but I will still go ahead and ask it.

Since you have international treaties, I guess, with other countries, do you have a handle on whether the diversion or the abuse problem -- to what extent it exists in other countries?

DR. LEIDERMAN: I really can't comment on that very specifically. I can say generally that reliable data are very hard to come by, and that the United States is regarded as having sort of one of the better and sort of most systematic systems for

acquiring these kinds of data and, obviously, ours is not optimal.

ACTING CHAIRMAN KATZ: Did anybody around the table want to address Dr. Parris' question about relative rates of prescription opioid abuse in different countries in terms of what's known about that? Dr. Foley?

DR. FOLEY: The International Narcotics Control Board has been working with the World Health Organization to try to address those issues, and obviously has a high rate of concern related to it. But one of the best studies, at least looking at opioids, comes out of India recently where, with the change in the opiate laws within the country and with really detailed studies, they have been able to show the availability of oral morphine in a large both rural and urban population, and demonstrate that there was no further diversion of that into a public perspective. That is now being looked at as a model.

Uganda, in the setting of an AIDS epidemic, is now embarked on looking at that, and at least preliminary data suggests that there is no diversion into a general population.

Not to suggest that this is not a very important issue, but at least the WHO and the

International Narcotics Control Board are trying to advance the availability of analgesics and study this at the same time.

ACTING CHAIRMAN KATZ: Great. Thank you. Dr. Passik, a question?

DR. PASSIK: I just wanted to highlight what I think, you know, is a disconnect, just like what you were saying before, Nat, that when you don't look at the population to whom the drug is intended -- I mean, I think, especially when you start looking at things like drug likability, I mean, amongst people who are perhaps genetically or otherwise predisposed to like a drug in a different way than the rest of the population, but also to highlight the limits of the conclusions you can draw from that.

My reading of the literature on whether opioid abusers can tell mu agonists apart is that they basically can't. So, you know, all the drugs -- all mu agonists, for the most part, are sort of the same from that point of view, and yet we know that drug abuse and the kinds of behaviors that we're really interested in in the target populations -- that is, people that are going to be prescribed these things -- has very little to do with that, really.

I think what we really need, you know, is

longer term looks at this in the populations to whom the drugs are prescribed, and actually look at their behavior with these agents, which I think is going to be vastly different.

ACTING CHAIRMAN KATZ: Dr. Foley?

DR. FOLEY: In the studies that Ray Hoode did over a period of about 30 or 40 years at Memorial in both acute cancer pain patients and in chronic pain patients, what became very apparent in their data was that up to 85 percent of patients were dysphoric on their first dose of their opioid, and in the chronic studies remained dysphoric for a period of time.

So I think that there is clear clinical studies that have addressed that, which is different than those that have looked at the abuse liability issue. And I think there's a need for further studies there.

DR. LEIDERMAN; Dr. Katz, can I make a comment? Thank you. Just a couple of points.

I want to emphasize that it is the FDA's mandate, however, to consider the public health. So that it is not only the target patient populations who must be considered. That's very clear under the Controlled Substances Act but also under other FDA -- under FDA regulations.

As we know, again leaving the whole drug abuse arena to quote from many comments by our Center Director, Dr. Woodcock, most of the problems we've seen, serious adverse events with drugs that have resulted in severe restrictions and in drug withdrawals have mostly been seen when there is inappropriate prescribing, labels in fact are not regarded and complied with, and the reality is again that all drugs, not just CNS active drugs, will in fact be used in broader groups than just the narrowly defined targeted clinical population described in the label. That is the public health reality that we all have to grapple with.

ACTING CHAIRMAN KATZ: Thank you. Dr. Schuster.

DR. SCHUSTER: In recent years some pharmaceutical companies have approached the Food and Drug Administration with a notion that perhaps if they were willing to do post-marketing surveillance studies, that they might be able to either have the level of scheduling changed for their compound if it were found to be not actually abused when it is dispensed into the general population.

So there are at least the beginnings of some post-marketing surveillance studies that I

personally think we should be emphasizing, because it will allow us to determine whether or not our preclinical predictors are in fact really predictive.

That's my interest in it and why I've gotten involved in post-marketing surveillance studies, because for 35 years I've been doing abuse liability studies in animals and humans, and I don't want to wait 20 years until we happen to find it out by some of the other means.

It is far more, I think, efficient if we do post-marketing surveillance studies, and I know that Dr. Leiderman is aware of these.

DR. LEIDERMAN: Well, more than that, we absolutely support them and, in fact, as will be discussed later on, sometimes mandate them in approval agreements. So --

ACTING CHAIRMAN KATZ: Dr. Parris, the last question for Dr. Leiderman.

DR. PARRIS: Following up on a comment Dr. Passik made about patients being aware of individual new receptors. I bring this up with some humility because there is an unofficial perception that, if a patient would have come to the clinic and would state I cannot take morphine, I cannot take codeine, I can only take Demerol, then that patient has a problem.

Do they have a problem? I do not know, but I would be inclined to believe. I ask this with specific reference to the point that 20 years ago, if a patient with RSD, so called diagnosed RSD of the arm, would say, hey, it spread to the other arm or to the leg, I'd say that's nonsense. But we know that's not correct today. But at that time that was the state of our knowledge.

So I'm asking that question, which I don't know if you would answer, but in the light of what is the state of our knowledge regarding those opiate receptors in the patient's presentation or expression of a preference for a particular drug?

ACTING CHAIRMAN KATZ: Steve, did you want to address that?

DR. PASSIK: Yes. I just wanted to say, I was talking specifically about being able to tell the drugs apart for abuse, and I certainly would be inclined to believe the patient in most of those instances -- many of those instances, at least, give them the benefit of the doubt when they say that they really do differentially respond.

I think we are just, as you know, now beginning to have some basic science, Gave Pasternak's work, where we're finally starting to get a little bit

of a handle on what has seemed to be a kind of random thing out there, the way people idiosyncratically respond to the drugs for pain control.

I was talking about specifically being able to tell the mu agonists apart from the point of view of euphoria and likability, and I agree with what Kathy said, although I am aware of some recent data that really does need to be replicated by Jim Zacny from the University of Chicago which actually showed for the first time the only mu agonist that you can give to a healthy population where the majority of the patients will report a euphoric feeling in the beginning as opposed to the dysphoria is oxycodone, but it's not been replicated.

ACTING CHAIRMAN KATZ: Thank you. Dr. Leiderman, thank you very much for your presentation.

I would like to now introduce Howard Davis. Are you here, Howard Davis? Yes, thanks. He is the Chief of the Domestic Drug Unit at the Office of Diversion and Control of the DEA.

MR. DAVIS: Good morning, and thank you for the opportunity to be here to speak before your prestigious -- Can you hear me now? Is that better? Good morning. I hear myself now, but okay.

Let me start over. Good morning, and

thank you for the opportunity to be speak before your prestigious Committee this morning. I'm quite honored to be here and spend a few minutes with you.

I am Howard Davis, as Dr. Katz said. I'm the Chief of the Domestic Drug Unit, Drug Operations Section, Office of Diversion and Control, and the first question that you might have, well, that's real nice, but what does it mean?

So let me just say very quickly to set some kind of a boundary that DEA -- this is a bit of an oversimplification, but DEA basically has two investigative entities, the agents that deal with the criminal investigations of illicit drugs -- talking about heroin, crack cocaine, methamphetamine, that kind of thing -- and the investigators, diversion investigators, of which I am one, that deal exclusively with the diversion of pharmaceutical controlled substances that are diverted into the illicit marketplace.

With that, I also need to put a disclaimer out first thing, that I am in -- As my job title suggests, I'm involved with diversion investigations, enforcement activities of pharmaceutical controlled substances, and across the board conversations that I've heard this morning from the other distinguished

speakers and public officials.

I may not have specific expertise over some of the questions that you may be interested as far as registration issues and policy and liaison issues, drug and chemical evaluation issues, those kind of things. I mean, I was invited to speak about diversion criminal investigations where my expertise lies, and I'm pleased to share some of these things with you today.

So with that, let me start off in saying opiate -- opioid analgesics generally fall into six broad categories. As Dr. Haddox's presentation indicated in his introduction this morning, I'll first talk about doctor shopping.

It's an individual or a group of individuals that go to several doctors until they get the drugs that they are seeking. Now it's very important to differentiate that I'm not talking about doctor shopping being a situation where an individual would go to several doctors looking for a specific treatment, and they have to go to another doctor and they have to go to another doctor to receive that treatment. That's not doctor shopping in the context that I refer.

I'm talking about individuals that in a

short period of time receive controlled substances from many different practitioners without the other practitioners knowing the same individual is going to the other practitioners, receive controlled substances to satisfy their personal addiction and/or for the purpose of diversion, to make the controlled substances available to others on the street.

There was one specific example that I thought was rather interesting where the head of a criminal organization recruited people, other individuals on the street, to go to various physicians, told them who to see, what to say, and to obtain the drugs of choice. In this particular case, the drugs of choice happened to be various Schedule II and III opioid analgesics.

This prescription -- This doctor shopping ring consisted of approximately two dozen individuals. There was quite a bit of activity on a daily basis. We launched an investigation -- The DEA diversion investigations, with the special agents launched a diversion investigation which led to the disruption of the doctor shopping ring, and the end of a large money making operation and, as many of you may have heard at one time or another, significant seizures as a result which were obtained through drug proceeds.

Another source of diversion activity is prescription drug rings, similar to doctor shoppers, but they often bypass doctors and go directly to pharmacies. A recent investigation involved a forgery scheme where prescriptions which appeared to be legitimate -- they were produced with a computer on a scanner -- were manufactured and bore the false name and address of a physician. It was just made up.

The phone number referenced on the prescription was actually connected to a cellular telephone answered by a member of the prescription drug ring. They would answer the phone like a medical receptionist in a doctor's office and verify the prescription in question to be legitimate, and then the other -- another individual would go into the pharmacy and obtain the controlled substances of choice.

Again, the ring recruited people. They exchanged for pills, cash and other services, and before being caught, this particular ring obtained approximately 3,000 opiate analgesics per month. So it can be very profitable, if that's the intended motive of the target.

Employee thefts can happen anywhere that controlled substances are maintained. Registrants at

the wholesale and retail level, for example, manufacturers, distributors, pharmacies, doctors' offices, which is basically why, as Dr. Leiderman just indicated in another context -- why Federal laws and regulations are in place, to protect controlled substances, restrict record keeping and security provisions.

Institutional settings, hospitals, nursing homes are other primary examples where employee thefts routinely occur.

Thefts, in general: Cases have been reported where -- again, a broad range -- where there have been many individual instances. Cases have been reported where real estate agents -- real estate customers go into people's houses under the guise of -- you know, you've seen the thing, want to buy the property, and steal controlled substances out of the homes of people's medicines cabinets, unbeknownst to anyone.

In a recent case we had a wife of a man who was dying with cancer convicted for diverting her husband's pain medication. Even more straightforward, kind of interesting case, I think, an armed individual with his face masked entered a pharmacy with a shotgun, fired the shotgun into the ceiling to

announce his intent, and demanded the opiate analgesic controlled substances maintained by the pharmacy. He happened to be caught, because the pharmacist recognized the voice of the robber as a recent previous customer, and it was a very quickly resolved case that ended in his arrest and conviction.

In-transit thefts is growing in popularity as a means to obtain a large amount of controlled substances without going to a DEA registrant at all. It typically involves the transfer of controlled -- It's typically done through the transfer of controlled substances from the wholesale level to the retail. You know, for example, hospitals, for example, who are large purchasers.

A recent conspiracy case where every time a certain substitute driver was called from this particular trucking company, the substitute driver was called in by the dispatcher at the trucking company who worked in concert with each other.

The dispatcher had inside knowledge of this particular shipment contained a large amount of controlled substances. The dispatcher called in the substitute driver, and unfortunately, situations like this take a certain period of time before we recognize a trend, before we have inside information that this

is the scheme.

In 20-20 hindsight, you look at an example like this perhaps and say, well, why would that be so difficult to investigate and conclude. But long term investigations of this type typically take a certain period of time to gather all the information and come up with a reasonable conclusion.

Other standard routine forms of diversion include illegal sales. A typical example is a pharmacy that sells out the back door for high mark-up profit. Can be as much as ten times or more retail value.

We had a pharmacy recently who sold twice the combination of other all other pharmacies in the same area combined of a particular product, which led to an in depth investigation, and in the end the target of the investigation justified his own action in his own mind by saying, if he didn't make the sale of controlled substances, someone else would, and he might as well make the money. These are the kind of people that we are dealing with on a daily basis.

Then finally, as a major source but to a lesser extent than the other ones that I just mentioned is inappropriate prescribing by a medical professional. In all fairness, I have to tell you up

front that it's a very small number of cases overall.

The DEA registrant population of practitioners is approximately today approximately 925,000 individuals. One-one hundredth of one percent of these practitioners are arrested as a result of drug related charges through a DEA investigation. In fact, in the year 2001, I believe, the number was 79.

One representative example: An individual would call this doctor at his -- He didn't have an office, but he had a phone number. The doctor would meet the, quote "patient" unquote in his car in a parking lot and ask what do you need.

The patient would name the drug, and the doctor wrote the prescription for $100. If you wanted a second prescription, that would be another $100, and if you wanted a prescription in someone else's name for yet another drug, it would be another $100. So it just continued, and it was also a fairly straightforward case.

Also, an inappropriate prescribing, we had a patient who would ask for prescriptions by standing in line, waiting in line for literally hours. It could be up to ten and 12 hours you wait in line to see this doctor who would see 300-500 patients a day and work until he had seen everyone. So it could be

two, three, four o'clock in the morning before he would be finished, and a similar situation.

You would name the drug of choice you want. The doctor wrote the prescription for $50 cash. There would be no medical history, no physical examination, no treatment of any kind. Said here's my money; here's what I want. The prescription was issued. In and out of the door -- or in and out of the room with the doctor in just a matter of seconds.

After a case is closed and action taken against the target, they all sound pretty straightforward, as some of the representative examples I just described. That's not often the case during the course of the investigation as we are dealing with people that have a lot to lose. When a fair amount of income is coming in, they have a lot to lose when it all stops.

As far as investigative leads, where do we get our information, and how does the information translate into an investigation? Referrals to and from state and local law enforcement and regulatory agencies occur on a daily basis formally and informally.

As such, statistics are not always maintained on every conversation that occurs between

investigators, either at the Federal and/or state and/or local level.

To that end, some states have state run diversion investigation units. The Drug Enforcement Administration has tactical diversion squads where diversion investigators team up with state and local law enforcement officers to conduct diversion investigations of retail level diversion, the doctor shoppers, the prescription ring people, typically non-registrant type investigations that would otherwise go unnoticed, if you will.

Intelligence information is also received from complaints form the public. Someone in a subdivision may notice activity in their neighborhood that they find suspicious. They report it to the DEA or local law enforcement authority.

Another source: Patients and individuals themselves that are perhaps disgruntled because they didn't like the way they were treated by a pharmacy or by a physician, and they want to get even.

Relatives, unhappy that their loved ones are getting controlled substances that they receive on a regular basis and are questioning why this person is always in a less than coherent state.

Medical professionals themselves often

provide us invaluable information. For instance, suspecting approach by a doctor shopper or prescription ring, a pharmacist or a physician calls the DEA on a regular basis somewhere around the country with information that starts us to suspect a specific problem.

Other registrants: Pharmacists, hospitals needing help finding a suspect to a problem that they are having in their particular setting, whether it's again a prescription ring, a doctor shopper, employee theft, whatever the situation may be.

We also use excess purchase reports. DEA registrants, especially at the wholesale level, are required to notify the DEA of suspicious or excessive purchases. That is, whether large orders are being placed all of a sudden that are uncommon by that particular registrant or orders are placed more and more frequently in a shorter period of time can raise a red flat that something out of the usual is occurring.

Registrants are also required to report thefts and significant losses of controlled substances at anytime that they may occur.

We also have an automated system, automated computer system called ARCOS, A-R-C-O-S.

It's the Automation of Records and Consolidated Orders Systems. What this does is tracks the distribution of all transactions involving Schedule II controlled substances and of all opiate analgesics in Schedule III.

It's a great intelligence tool for trend analysis. If we have a -- receiving a lot of information on one specific individual or area based on the examples that I just gave, you go into this ARCOS computer system that we maintain internally and find that this particular target is the number one purchaser of a certain drug in a certain area in a certain time period, which is yet another reason why we should initiate a Federal investigation, a criminal investigation or an administrative investigation against this particular person or business.

DEA order forms: Basically, it's a three-part form that any DEA registrant is required to use to order a Schedule II pharmaceutical controlled substance, and DEA receives a copy of one of the three parts of that form. That's also a good intelligence tool.

It's important to point out also as a caveat that none of the individual items I referenced as intelligence tools are, in and of themselves,

uniquely authoritative. They are just indicators.

If a registrant -- for instance, a pharmacy -- is close to an oncologist or a major clinic, then obviously they are going to have higher transactions with a particular opiate analgesic, for example, than a pharmacist that is located in a rural setting.

So all those things have to be taken into consideration. We just don't take one piece of information and say, oh, that looks good, and rush out and try to see if there is inappropriate activity. We don't have the resources for that. We take a combination of all these factors and, once it appears to be apparent that we have a problem, we will initiate an investigation.

Last year approximately 850 investigations were initiated by DEA diversion investigators. Of that figure, only three-quarters resulted in some type of action being taken. Some kind of action can be as simple as a letter of admonition where DEA notifies the registrant that a recordkeeping -- something of the recordkeeping provisions may be lacking, and ask for voluntary cooperation in resolving that issue, and that ends the whole matter, and the case is closed.

Administrative hearings can also be held.

In the most egregious situations the facts of the case may be referred to a prosecutor who takes the case from there and decides if it's worthy of additional judicial action. At that time, it's out of DEA's hands other than we are the fact gatherers. The judicial process would take over as the lead in the ultimate outcome of that particular investigation.

Ultimately, DEA and other law enforcement and regulatory agencies rely on invaluable communication from other agencies, departments, registrants, and the general public for indications of a problem in a particular area. Like I said, one complaint does not -- is not the basis for an investigation.

Finally, as Dr. Haddox mentioned himself earlier this morning, it's extremely important to point out, I believe, based on the comments I heard from the public first thing this morning, that on October 23, 2001 DEA's Administrator Asa Hutchinson joined 21 of the nation's leading pain and health organizations to call for a balance to protect the appropriate use of opiate analgesics while preventing abuse and diversion of the drugs.

At the DEA, no attempts are now or have ever been made to prevent practitioners acting in the

usual course of professional practice from prescribing medications, including opiate analgesics, for patients with legitimate medical needs.

Federal law and regulation, as a footnote, do not attempt to define legitimate medical need, nor do they set standards as to what constitutes the usual course of professional practice. The DEA relies on the medical community to make these determinations.

For information that -- For more specific information on this specific topic that you might have, DEA has an Internet website. It's 222.deadiversion.usdoj.gov which contains a broad -- a potpourri of all types of information that may satisfy most of the questions that you may have this morning.

Thank you for your attention. I'd be glad -- look forward to any comments or questions that you might have.

ACTING CHAIRMAN KATZ: Thank you, Mr. Davis, for a very interesting presentation. In view of the fact that we are substantially behind schedule, I'll just limit this to one question, if anybody wants to be the one. Oh, sorry, Dr. Reidenburg already volunteered. Go ahead, please.

DR. REIDENBURG: It's clear from your

presentation and from Dr. Levy's yesterday that our perception of risk of having our practice interfered with is grossly exaggerated compared to the realities of the regulatory agencies.

Has the DEA thought about ways to help bring the perceptions of us doctors more into line with the reality of the kind of people you are really prosecuting or going after?

MR. DAVIS: Indeed. That's the reason that we look forward to opportunities like this to present this information in person and the reason that we created the Internet website that contains even more information, that anyone that is interested can go to that site for more up to date information on a broad range of topics.

ACTING CHAIRMAN KATZ: Thank you very much.

MR. DAVIS: Thank you, sir.

ACTING CHAIRMAN KATZ: We'll move right along into Dr. Chilcoat's presentation. Dr. Howard Chilcoat from Johns Hopkins University will be speaking with us about the epidemiology of prescription drug abuse and implications for the clinical setting.

DR. CHILCOAT: It's a great pleasure to be

here today, and I want to give basically an epidemiologic overview of prescription drug misuse, focusing on analgesics basically. I had given a talk at the NIDA press conference when they announced their initiative on prescription drug abuse research, and I have to say that this is a relatively new area for me. Most of my work has been in the area of illicit drug use and dependence.

So when I was asked to give a talk for NIDA, I basically went to my usual sources of epidemiologic data, and I think, as has been pointed out today, there's a lot of -- there's, obviously going to a lot of limitations to the data that I'll be presenting, I think. Hopefully, it can provide some clues for where we need to go, and provide some basic information about the use of analgesics drugs and the -- or the misuse of analgesic drugs and extra-medical use, as well as the problems developing related to that use in the population.

Now one of the things that I want to do is try to give a population base perspective. A lot of what we've talked about -- obviously, you hear a lot about anecdotal reports of the misuse of certain drugs, and that there's also, obviously, press reports, and certain data surveillance systems such

as DAWN are certainly useful as picking up kind of new trends in drugs and emerging drugs, but there are certain limitations that we've talked about earlier today in terms of that.

Those cases may just sort of be the tip of the iceberg and don't really pick up what's going on in the population. So I hope to point out some of the advantages of epidemiologic studies, population based studies, but there are some tradeoffs in terms of some limitations, and we have to think about the data in the context of that.

Now one of the things I want to make clear, that what I'm going to be talking about throughout my talk today is extra-medical use. The way it's asked about in the National Household survey on Drug Abuse and other surveys is basically that -- it's when you use the drug when it was not prescribed for you or that you took only for the experience or feeling that it caused.

So I mean, this is a specific type of drug with people using the drug on their own or could be using more than prescribed, and all the examples that I'll be talking about throughout this talk deal with this particular type of drug use. So it's not necessarily someone who uses the drug as prescribed

and develops withdrawal or tolerance.

Obviously, there's a variety of classes of drugs. I'm going to focus on analgesics today, but have some comparisons to some other classes, just for reference.

The data that I'll be using: There's two main sources. I'm using data from the National Household Survey on Drug Abuse. At the time when I originally did this talk, data from '85 to '98 were available. Now the -- As I was actually getting ready to send this talk off to the meeting last week, we just got our hands on the 1999 data, and so I was able to incorporate some of those results in today's talk.

The National Household Survey is a representative sample of the U.S. household population, and now includes all 50 states . It picks up people that are 12 years of age or older, and the sample size has grown over the years. Originally it was about 5,000 people. Up through '98 it was in the 20-30,000, and starting in '99 there was a much larger sample with about 55,000 people interviewed.

Another dataset that I'll be talking about is the National Comorbidity Study. Now this data -- These data were collected about ten years ago. So

there's some problems in terms of it being current. However, it is one of the sort of major sources when we talk about drug dependence as a diagnostic entity, and we want to look at other psychiatric disorders that may co-occur or be comorbid with the drug dependence.

Then we have to use a study such as the National Comorbidity study that had these kinds of measures available. There are very few studies -- population based studies that have these measures.

The National Comorbidity Study was carried out in the early Nineties with about -- a sample of about 8,000 people age 15 to 54.

Just talking about some of the drugs from the National Household Survey, just to give you an idea of the prevalence of drugs, the National Household Survey asks -- and SAMHSA has done a lot of work, I think, in trying to improve the methodology of collecting information about individual drugs. So they ask about tobacco, alcohol and then marijuana, cocaine, inhalants.

Then they ask questions about drugs that are typically prescribed, with using the language in terms of capturing extra-medical use, to start off, and the respondents are also given pill cards which

are pictures of specific drugs that could help them in answering the questions about the drug.

So they are asked about the use of specific drugs within each category. So for analgesics, it would ask about certain specific drugs, and there are some open-ended questions, too, where people can respond.

There was some concerns in some of the discussion earlier about whether or not, you know, certain specific drugs within classes aren't mentioned. As you will see, there is a problem with that.

I mean, it's probably good for public health but bad for statistics, that there's very few numbers that come up when we look -- When we start breaking down by specific drugs, it's really hard to work with statistically, because the numbers really get small.

So this gives you an idea of the -- for various prescription drugs -- the prevalence lifetime, which is sort of the cumulative occurrence of drug use among the people that are still around to be interviewed at the age that they are interviewed, and then past year where we ask respondents have you ever used or do you also use or used in the past year,

which is more a reflection of current use.

So past year use is going to reflect both new cases of use plus persistent use. Overall, we get about nine percent of people who have ever -- who report ever using one of these drugs extra-medically, with about four percent using in the past year.

Analgesics in terms of use are the most commonly used drugs in this group of typically prescribed drugs, with about five to six percent of people ever using them in their lifetime, and about two percent in the past year.

Just some information on sex differences. Males are slightly more likely to use these drugs. The sex differences aren't quite as big as we see for other illicit drugs.

These are just some trends. Just quickly, I'll go over these. Over time looking at the analgesics by sex -- and we see, basically, since the Eighties a decline through the Nineties, and then it's hard to say what's going on at the late Nineties.

We basically -- At the last minute I added the 1999 data, which shows a sharp increase, and I haven't had really a chance to look at what that increase might mean.

In 1999 there were some changes made to

the survey in terms of sample size was increased, and they switched to a computerized interview as opposed to a paper and pencil interview. So there are some methodologic changes which may result in some increases in reporting.

We did compare some trends in other drugs, like cocaine, for example, marijuana. There wasn't the increase for those drugs that there was for analgesics and other prescription drugs, but the increase was most pronounced for the analgesics, and we see increases for both men and women.

This is just for comparison for other types of drugs. A slightly increase for tranquilizers recently, but again we are hesitant to make too much of that yet.

Sedatives: See a decline over time, basically, for both men and women, and stimulants decline over time through the Eighties to the Nineties and then pretty much a leveling off.

Just in terms of the past year use of analgesics for men and women -- this is just by age groups, just to get an idea of who is using, who are current users of these drugs.

We see that the 18-25-year-old age group is the group where the use of these drugs is most

likely to occur, and there actually has been some trend in increase in that age group in terms of analgesics since the Eighties; whereas, other groups tend to look like they are pretty flat.

There's some concern -- we'll have to see what happens -- with this 12-17-year-old age group, that they may be increasing over time.

For women, similar patterns except one concern here is that for the younger girls, 12-17-year-olds, they seem to be pretty much on par with the young adults in terms of their prevalence of use.

This I just put in here just to demonstrate -- There's been a lot of concern about drug use in older individuals, and given the National Household Survey, it's hard to get reliable measures. So that's what that slide kind of shows, that the sample size gets pretty small for age 60, and there really is a need to sort of understand whether or not there is increased use of drugs in this group. So this slide, as I say, is pretty much meaningless and fairly unreliable, but I just gave it as an example that there is a need for better data sources for these older individuals.

This just takes a snapshot in time looking at in 1988 who is using these drugs at different ages

for men and women. Basically, this sort of reflects what we saw before, that the period of young adulthood seems to be the peak period of risk, and it goes down considerably at older ages.

One thing is that we do see some -- Again, we see this pattern that 12-17-year-old women are more likely to use actually than men or similarly likely to use as men.

Just some patterns for tranquilizer use. I can skip over those.

These just show some patterns, age specific prevalences of current analgesic use by race. The thing to garner here is that there are big racial/ethnic differences with whites over twice as likely to use as minorities, particularly in the young adult age group, the 18-25-year-old age group.

This slide kind of just depicts when onset of use starts to occur. So what are kind of the periods over time that use occurs. For both males and females we see, certainly, a sharp increase in young adulthood, from adolescents to young adulthood, and it's still some increase over time, that even into the sixties we see that these curves go up.

For other drugs such as cocaine, we see a much sharper increase from ages right around age 20,

and then it starts to flatten out a little bit more sharply. So there's still some accumulation as people get older when they typically get past the period of risk for other drugs.

This is from 1998, just looking at some of the specific drugs mentioned in the National Household Survey. Here I do have a combination of generic drug names and brand names. I basically pulled them off of what the National Household Survey uses. It gives you an idea of the drugs -- the types of analgesics that people report ever using.

Now the 1999 data does have more drugs listed, and I didn't get time before -- because we just got the data before I had to send my presentation in. But I was just curious for drugs such as Oxycontin what the prevalence was in '99.

Out of 53,000 people interviewed, only 82 people reported ever using Oxycontin, which was about .15 percent was the prevalence of use of that drug. Now, of course, it will be interesting to see from 2000-2001 what those numbers -- if those numbers go up considerably or not, given the attention that's given to that drug and the potential of abuse, to see if the population based reports concur with the anecdotal reports that we hear.

This just shows some sex differences which we saw before for some of the drugs, that generally men are more likely to use almost all the specific groups of drugs, and again the age group difference with 18-25-year-olds being the highest, most likely to be using, and the race differences emerging, that whites are basically more likely to use each of these drugs than minority individuals.

Also there's basically a flat to maybe increasing pattern with income levels, that people with higher incomes may be slightly more likely to have used these drugs extramedically.

Okay. Let me just move over to dependence of prescription drugs. So here we are basically switching to National Comorbidity Study data which is a population based survey of about 8,000 people.

When this survey was carried out, there were about -- overall for any prescription drug there were about almost three percent of individuals had a lifetime history of dependence on prescription drugs. Of course, dependence can include both the physical symptoms of dependence, withdrawal and tolerance, but also some of the behavioral aspects of it in terms of getting the drugs, taking a lot of time using the drugs when you have other responsibilities, things

like that.

So prescription drug use overall, the prevalence of dependence is similar to actually what you see for cocaine. But when you break it down for any particular drugs, it gets smaller. Analgesics actually, even through for the National Household Survey we see them more commonly used than other prescription type drugs, the prevalence of these drugs is -- of dependence, lifetime is about one percent of people have ever had dependence on analgesics, and then it's very small -- It's really an unreliable number for the current dependence.

Okay. In general for prescription drugs, we want to look at comorbidity. Actually, let me just do it for analgesics. So here what we've done is we look at people -- There were 68 people in the National Comorbidity study. So it's a relatively small number, but we wanted to look at what is the prevalence of a variety of other psychiatric disorders for people who have a history of analgesic dependence versus people who do not.

What we see are some striking differences, that almost half the people that had a history of analgesic dependence had also a history of depression compared to 17 percent without analgesic dependence.

They also were more likely to have agoraphobia, about twice as likely to have agoraphobia and other types of phobias.

Also, panic attacks, there's a striking difference. About 30 percent of the people that had analgesic dependence had a history of panic attacks versus seven percent without analgesic dependence. Now we don't know the -- This doesn't test the directionality of these associations. It just gives you a basic idea of the comorbidity of these disorders.

What is extremely striking is the association with antisocial personality disorder where, you know, it's very rare -- relatively rare in the general population. Only about three percent of people have antisocial personality disorder, and well over a third of the people that have a history of analgesic dependence also have antisocial personality disorder or qualify for that diagnosis.

Also there's some issues of shared drug dependence. About 40 percent of the people of analgesic dependent individuals also had a history of cocaine dependence, compared to three percent in the general sample.

We see similar patterns for other

prescription drugs, actually, but maybe slightly more pronounced for analgesics. It's hard to say, because the numbers get rather small. So the confidence intervals around those estimates get relatively wide.

Just for comparison, if we look at cocaine as a disorder, look at cocaine dependent individuals versus those without cocaine dependence and look at the similar disorders, we see that actually the associations for prescription drugs and analgesics are stronger than they are for cocaine dependence.

Briefly, this is just the sort of cumulative incidence of analgesic dependence. So over time, looking at different ages, do people develop -- when they develop dependence. What you see is across the adulthood, we really see a steady kind of increase in dependence.

So the lefthand slide is overall, what's the cumulative incidence of dependence? We see cases of dependence occurring all the way up through the forties for both men and women.

When we look at -- and the next slide is just among people who are users, who becomes dependent. Just basically, if you've ever used analgesics extramedically, by the time you get out to age forty the sort of cumulative incidence tends to be

about less than ten percent. So this is among users, about ten percent of them report becoming dependent. These are extramedical users again.

Just briefly, the transition from use to dependence -- this slide looks at that transition. The people with antisocial personality, for example, are about five times more likely than those without to develop dependence, even once they have used.

Just briefly, this is just some results from another study we published in Archives of General Psychiatry. We were looking at the relationship between PTSD and drug use disorders, and we were looking at directionality.

So the previous slides don't really look at the direction of the relationships, but when we did this, we were trying to test these pathways. Basically, what we found was the pathway that showed up as being potentially meaningful was the pathway from people who had PTSD first, then developed prescription drug dependence -- or drug dependence.

It was really specific for prescription drugs. It wasn't for cocaine. It wasn't for marijuana, and those people with PTSD were about 17 times more likely to develop prescription drug dependence than those without the PTSD.

This just gives you the bottom number here, just shows you the prevalence of prescribed drug dependence is about nine percent versus .6 percent for those without PTSD.

All right. So anyway, I think that basically I just tried to give an overview of some of the data that's out there. There are some limitations in terms of identifying the cases.

There's, obviously, a lot of need for research. There's very little research in the epidemiology of prescription drug dependence, much less analgesic dependence. So there's certainly a need for further research in that area. There's certainly a need for better data.

I think some of these surveys can give you some idea of what's going on. It will be interesting with the new National Comorbidity Study which will be coming available -- the results will be coming available soon, how these associations currently show up in relation to the comorbidity of analgesic use and psychiatric comorbidity.

So with that, I'll conclude. Thank you.

ACTING CHAIRMAN KATZ: Well, thank you very much, Dr. Chilcoat. That's obviously very important information and very germane to our task

today. We are not going to take questions now, because Dr. Chilcoat will be with us and, I'm sure, will speak about it later.

With Dr. Passik's permission, what we'll do now, given the look on everybody's face, is we'll take lunch now, no questions, and then if that's okay with Dr. Passik, we'll begin with his presentation after the lunch break, which will be in exactly one hour. Hang on one second. Sorry, we'll begin at 1:30.

(Whereupon, the foregoing matter went off the record at 10:40 p.m.)

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

(1:35 p.m.)

ACTING CHAIRMAN KATZ: Could we all take our seats, please, and move on to the afternoon session. Is Dr. Passik here?

Let's go ahead and begin the afternoon session. I'd like to introduce Dr. Steven Passik who has been a longstanding contributor to our knowledge on the interface between pain and opioids and chemical dependency. Steve?

DR. PASSIK: Thanks, Nat. It's really a pleasure and an honor for me to get the opportunity to talk to you about the problem of substance abuse and the data that we've gathered in studies that we've done on the problem of substance abuse in people with pain, which I'm happy to be able to talk about, because these folks, meaning to say people with pain, are the ones with the most at stake, I think, at a meeting like this.

This is a very, very broad topic. This is a topic that spans the treatment of pain in many subgroups, from the treatment of pain in people with a known history of addiction who have chronic pain syndromes, HIV related, others, and the special kinds of precautions and issues that surround the treatment

of pain in people with a prior chemical dependence problem.

My interest in this topic started with that. It started back when I was at Sloan Kettering, where I was on Psychiatry service for about ten years and during that time was working with Russ Portenoy and Bill Brightbar, Kathy Foley on the problem of pain in AIDS.

That was largely a problem of articulating management strategies for people who had a previous history of drug abuse. But I don't think that my personal interest in this topic would have been sustained over all this time with just that issue, and I think the expanding use of opioid analgesics for a range of nonmalignant pain syndromes has led to the necessity to look at the problem of noncompliance and addiction related risk in people who are placed on these medicines for pain, and we really have a paucity of data here.

I'm going to show you as we go through this a study that we undertook to try to -- which is a very, very preliminary attempt to try to understand these problems.

We have taken in the -- In the medical community we've undertaken moving a therapy from a

very homogeneous group, meaning to say a chronic opioid therapy that was shown to be very, very advantageous and with low risk in a very homogeneous population, namely, for the most part the tertiary care oncology population, and we have subsequently moved beyond that to take that experience and try to now translate it over the last decade or more to other pain populations.

When we run into difficulties here, it's my view that, when there are difficulties of any kind where the outcomes don't look perhaps as favorable in some studies, it may simply be because we are dealing with a much more heterogeneous population when we move to the chronic pain population.

One of the mistakes that always gets made, to my view, in the chronic pain area is taking any therapy, whether it's relaxation therapy, group psychotherapy for people with chronic pain to chronic opioid therapy and then applying it in the same way to this very, very heterogeneous group of people.

So when we apply this therapy, we are basically trying to effect a good outcome in four very -- four distinct but also very interrelated domains. I think the goals of pain treatment are almost always the same. They are to provide meaningful pain relief

or analgesia.

Herman Weinreb and I have written about the four A's as a mnemonic device for trying to internists and others how to assess people who are on chronic opioid therapy and how to monitor them. Our study that I'll show you a little bit about in just a few minutes uses this as a model.

Basically, in any pain patient, you are trying to effect a good outcome in the areas of analgesia or meaningful pain relief, activities of daily living or improving function. You are trying to minimize and treat side effects, and ultimately the goal, too, is to have as little aberrant drug related behavior that one could hope for.

I think the important issues here are that, when we do this therapy, patients need to be -- and we need to teach physicians and nurses and others how to monitor people in all four of these areas. Now these are very highly intermingled in important ways.

For example, at times you will see aberrant drug related behavior in people in chronic pain who are undermedicated for their pain. That's the so called phenomenon of pseudo-addiction where people are in unrelieved pain, and they act in kind of desperate ways. So the aberrant behavior needs to be

interpreted vis a vis where we are in the other domains of outcome.

With regard to activities of daily living, it is crucial with this therapy that people have a stabilization or improvement in their psychosocial functioning. It's interesting, because opioids treat some -- basically, one major impediment to improved function. That is pain intensity. They lower -- largely lower the volume on pain intensity, but in a lot of instances pain intensity is not the only factor that mitigates against improved psychosocial functioning. So these areas are very intermingled.

I thought mary Baluss this morning raised a very good point about what does improved functioning really mean, and for how long, and how long does a patient get to improve their functioning.

All of these things, I think, are unfortunately poorly defined. For example, a lot of times in pain management we tend to look at the return to work as the gold standard. We feel like heroes if we get a person who has been disabled to return to work.

The problem with using that as a goal of pain treatment is that the best predictor of return to work in disabled pain patients is not pain intensity.

It's not severity of injury. It's pre-morbid job satisfaction.

So ultimately, you know, unless opioids make you like your job more -- it's possible -- ultimately, you know, unless we start using voc rehab as part of what we do in our treatment of chronic pain, that may not be the right goal.

I think what I do as a clinician is I try to sit down with patients, figure out what their goals are, and then I assess these four A's in an ongoing way, and largely what this boils down to in clinical practice is a kind of a good faith, gestalt sense that somebody is making a wholehearted effort to improve their life and that pain medication is a small part of that effort.

Now I want to describe to you a study that used -- that Russ and I undertook, and this is actually a study, I should say up front, that was funded by Janssen Pharmaceutica. Russ and I approached Janssen some years ago before the phenomenon of prescription opioid abuse was all over the media, and we approached them and said there's a broadening use of these drugs out in the community by primary care doctors and others. They need a tool to help them monitor their patients, document importantly

the patient's progress so they can improve their medical recordkeeping in this area, and also have a better understanding of what we should talk to patients about and, in particular, in the addiction related outcomes.

As you are going to see, what we are trying to introduce here, I think, is crucial not only in the clinical world but perhaps in clinical trials on the longer term effects of opioids and their efficacy over time, a different vocabulary for understanding noncompliance behavior; because the traditional definitions of addiction really don't apply to this population.

So Russ and I set out to basically design a series of short questionnaires that could yield ultimately kind of a documentation system for each of these four areas.

We batted this back and forth several times between us, and then actually several people in this room helped us, commented on it, helped us to improve it, including Dr. Katz. Karen Sees helped a great deal with it as well in its development.

Ultimately then we took it, and we handed this -- We gave this to physicians and nurses around the country, internists primarily and some pain experts,

and we had them take it to their pain clinic and assess their own patients one time.

These are all patients who are on opioid therapy for three months or more, and this is a one-shot, one-time cross-sectional snapshot of what outcomes look like in chronic opioid therapy. I'm not just going to restrict my comments now just to the addiction related outcomes. I'll walk you through the summary of the results really quickly.

With regard to the four A's, the first one was analgesia, of course. I think it's very interesting to note here, we basically used a couple of zero to ten scales on average pain and pain at its worst.

You can see that on opioid therapy -- and I know that these don't project too well. I'll walk you through this -- the patient's average pain level was in the moderate range, exacerbated to the severe at its worst. These are people on chronic opioid therapy.

Then a very interesting question that I Think we stumbled upon here. We asked them: Compare your average pain during the past week with the average pain you had before you were treated with your current pain relievers. What percentage of your pain

has been relieved?

For those of you who can't see it, it was 57.8 percent. Now in fairness, there is a large standard deviation that goes all the way up into the eighties and all the way down into the thirties, but the average patient on these drugs is getting about 57.8 percent of their pain relieved.

That is modest, but as you'll see in a moment, meaningful to the vast majority of these patients. But I think it's a very important point to highlight that the average patient apparently -- and this is a study that was not designed to really look at outcomes of chronic opioid therapy; it was more a road testing of this system.

Nevertheless, the average patient, it seems to indicate, is going to have a substantial amount of residual pain to cope with, and ultimately that the goals of therapy will probably best be realized by also bringing in rehabilitative, psychological approaches, and so on.

I think it's a crucial point that we teach, for example, primary care doctors that, if they -- to think about this as their goal as they go into chronic opioid therapy, not to restrict their ability to prescribe but to help them recognize just by asking

themselves which ones of my patients are likely to enjoy a favorable outcome with 57.8 percent pain relief.

If they ask themselves that question going in, they might be able to say, okay, if my gut tells me the answer is yes, nice little old lady with arthritis is going to dance at her children's wedding when she gets 57.8, terrific. That's a patient that probably doesn't have a lot of comorbid psych, probably doesn't have addiction problems, and ultimately will enjoy a good outcome.

If the answer, on the other hand -- the gut tells you the answer is no, it's probably for other psychiatric or deconditioning type reasons for which opioids are not the sole answer. We need to teach physicians, I think, to know when to refer early so they don't end up with bad outcomes based on perhaps inflated expectations about what the drug therapy alone can help realize.

As I said, while the numbers look modest, this is meaningful pain relief. As you can see, we asked the patients, is the amount of pain relief you are now obtaining from your current pain relievers enough to make a real difference in your life? And 90 percent of the patients said yes.

Now interestingly, the physicians agreed in 85 percent of the cases, but more interestingly, when we went back to do the CAPA coefficients on this data, they were exceptionally low, meaning to say that patients and the physicians are not talking about the same people.

So we are now going to go back and analyze the discrepant cases to try to help us understand what makes a physician say the outcome is good versus what makes a patient say the outcome is good. I leave that to your imagination. I'm thinking few phone calls probably is all that drives that.

With regard to activities of daily living -- Now remember, this is meant to help people do this in day to day clinical practice, you know, with people on chronic opioids. So it was done grossly, but we asked the doctors to rate the patients as better, same or worse in the area of physical functioning, mood, family and social relationships, sleep patterns, and overall functioning.

I think it's crucial at a time like now when we are kind of examining this therapy to recognize that in the doctor's judgments four out of five patients were enjoying an improvement in overall functioning.

I would venture a guess that, if we could have predicted ahead of time who was going to need more extensive psych input or perhaps more structure from the point of view of controlling aberrant behavior, that number could be higher if we would tailor the approach and meet those needs earlier as opposed to later.

I think a much more common unfavorable, uncomfortable, if you will, outcome in chronic opioid therapy is not out and out addiction and aberrant behavior. It is a patient on what is a controversial therapy whose function is not gradually improving as they are on the therapy. I think that's what clinicians confront a lot more frequently than out and out anything that smells of addiction.

With regard to adverse effects or side effects, overwhelmingly the patients felt that they could tolerate their pain relievers, despite the fact that two out of three of them had side effects.

In this instance, the only one that rose above threshold that's even worth mentioning was constipation. Four out of five patients had it. It was moderate to severe in a third. It's clear that, when we are using opioid analgesics for the treatment of chronic pain, we do have to be aggressive about the

management of constipation.

Finally, what we are all here to talk about. Russ and I created a checklist on aberrant drug taking behaviors, and this is basically the model that comes from a paper that Russ and I have written, but actually it predates that, comes from some other work that Russ did in Jerry Jaffe's Encyclopedia of Substance Abuse, I believe.

In any case, I think, if I can speak for Russ, he was lying awake one night wondering what all of his patients were doing with all those drugs he was prescribing, and he had the realization, I think, that ultimately this boils down to behavior.

What the clinician will confront in the clinic is not out and out signs of drug addiction. What we will see -- We might see that periodically, but what we are mostly going to see is noncompliance behavior.

What we tried to do was take this notion, that there's a wide, wide range of behaviors that are likely to become manifest in the clinical situation. Some of them are probably innocent and frequent and less predictive of addiction. Some of them, just based on common sense and legal or illegal kinds of issues, are probably more predictive.

We took this, and we tried to embody this in the model of the checklist that we put in, while at the same time trying to take some of the core aspects of addiction -- use despite harm and adverse consequences, uncontrolled use -- and embody those as they might appear to a pain clinician. Again, that need for a kind of translation of the addiction vocabulary into the pain clinician's vocabulary, which I think has a long way to go but, I think, is very important ultimately for inclusion in studies of this kind.

With regard to adverse consequences possibly resulting from drug use, I'm showing you now the numbers of people -- and this is based on the poster data. We now have data on some 450 patients, but we presented a poster at the Pain and chemical Dependency clinic -- pardon me, meeting -- in '99 on these data, and we have the full datasets being analyzed now.

This is data from that poster, and I can tell you the numbers have not changed significantly. What I'm presenting to you here is the number of patients who never did these things -- never did these things. So that these are patients in whom you never saw these behaviors.

So that people sort of taking their medicine to purposely over-sedate themselves -- that happened -- you would have to do the math -- in a little under 11 percent of the patients. Less than eight percent had a negative mood change.

Decline in psychosocial functioning was seen in six percent. Less than five percent had a decline in social functioning. Appearing intoxicated -- as you can see, on down the line, but you can see basically that these adverse consequences were relatively infrequent.

Most of them -- The innocuous ones, as you will see as we go through this, were somewhat higher, in that 10-20 percent of the patients had done them at least once; whereas, some of the more serious ones were down around one or two percent.

What you are going to notice as I walk you through these slides is that the percentage of most of these behaviors comes in somewhere around six percent of the patients, which is a very interesting finding, because six percent or so is basically the -- usually the number that gets thrown around for the amount of addiction in the general population.

I think that's a very important consideration, that the misuse in the form of these

kind of behaviors in pain patients is no more frequent than it might have been based on just predicting it from the general population values.

So here you can see possibly loss of control, requesting frequent early renewals -- you saw that in about 18 percent. Increase of dose occasionally without authorization was in less than 14, and on down the line with the more serious behaviors ultimately coming in at much lower percentages.

Also preoccupation with opioids or other drugs, asking for specific medicines by specific names, fairly innocuous, as Dr. Parris said this morning, about 11 percent of patients did that. Doesn't comply with other recommended treatments, like you ask the patient to also go to marital counseling or physical therapy and the only time they show up is on the day that the narcotics are being renewed -- that was seen in seven percent.

Six percent reports no effects of other medicines, like my pain only responds to opioids, unwilling to do other drug trials.

Misses appointments except for medication renewal, and so and so forth. You can see on down the line that those behaviors were actually in the three

to four to six percent range.

Other occurrences: Patient arrested or detailed, very infrequent -- very, very infrequent, less than two percent of the patients.

What is also very important and very tricky in the assessment of addiction related issues in the chronic pain patient who is on opioids for legitimate purposes is that, when we do see these behaviors, as I intimated earlier, we have to take a step back as clinicians.

This is a very hard thing which ultimately a lot of physicians don't think through. They think of the world as divided into addiction/no addiction when they see aberrant behavior in front of them in the clinical situation. The truth is you have to ultimately -- There are several possibilities that might be driving aberrant behavior in chronic pain patients.

It might be out and out addiction. The patient is losing control. They are using despite harm. I'm going to in a few moments talk a little bit about a very structured approach that can be taken.

We run a clinic in Indianapolis called the Pain and Chemical Dependency Clinic where we take in people who have abused prescription drugs or have bona

fide histories of addiction, and we don't, obviously, manage them the same way that we do little old ladies with arthritis.

Ultimately, I think it's very important to kind of tailor the approach. I have to say that with the right structures like frequent urine tox screens, seeing the patient every three days, having the recovery program that the patient -- recovery group that the patients attend in our clinic, we are able to -- We've had a very kind of sanguine experience. But at the same time not every clinic or physician has anywhere near the ability to bring to bear that much structure.

I think, if that's the case, those are people that need to be referred. The fact that we have a paucity of such treatment settings goes without saying.

Another possibility is pseudo-addiction. As I mentioned earlier, the patient is acting in a way that they are acting not because of addiction but because of desperate attempts to get pain relief. That's another possibility, and with the tremendous amount of undertreatment of pain in our society, clearly something that clinicians need to think through when they try to sort this out.

Other psychiatric diagnoses: Personality disorders, self-medication of depression or anxiety syndromes and so on, also might be driving the behavior, in which case treating those syndromes is sometimes helpful. And there are, of course, the drug diverters who have no pain but are coming in with the sole intent of duping the physician, and all of those things need to be considered, because every one of them has different management strategies that the clinician would take to try to contain the behavior.

Now with regard to defining the problems and understanding the addiction in a pain patient better, there are several problems. The first is we really don't know the risk of aberrant behavior in addiction going in.

We need to get a better handle on what the risk factors are, and then get them out and educate physicians about how to assess them. I'll talk about that a little bit in a moment.

There are tremendous misunderstandings about what addiction is, and the usual definitions simply don't apply well in the pain management situation.

Then finally, there has been an absence of well articulated management strategies for patients

with different substance abuse related problems. Even when they are articulated, they don't lend themselves to solo practice office settings, for example. So that ultimately some of those things are out of the reach of a lot of people who need pain treatment.

I want to just spend the rest of my time talking about the assessment of risk, because I think it's been bantered around over the years and, I think, in some misleading ways.

I think that prior to the sort of revolution in pain management, I think that the prevailing notion was that addiction, for the most part, lived in the drugs themselves and that, if you got exposed to them, you would become addicted. It didn't matter if you had pain, if you had cancer.

In fact, in 1947 the President of the AMA wrote that physicians should spare their terminally ill cancer patients the indignity of morphine addiction, because the prevailing view was that addiction lived in the drugs. So exposure alone would addict everybody or anybody.

I think then the pendulum started to swing, and the revolution that's happened that's helped so many people in pain management started to happen. But I think at the same time, there was a

paucity of real outcomes data on aberrant behavior, on kinds of noncompliance that you might see, and so on.

So there was a lot of data that was cited to help allay fears of addiction that probably didn't have that much to do with what the real risk was. An example is the -- and many of you have probably seen this data quoted many, many times, the so called Boston Collaborative Drug Surveillance Project from Porter and Jick, New England Journal of Medicine, 1980.

In a letter to the editor Porter and Jick reported some four cases of addiction in 12,000 people who were exposed to opioids during a hospital stay in people who had no prior history of abuse and had received those drugs during hospitalization. They could only document four cases of misuse of the drugs in follow-up.

So the prevailing notion came to be that, if you didn't have a history of abuse that the risk of aberrant behavior of any kind was extraordinarily low. But of course, that model doesn't really describe the risk in the chronic pain population. It doesn't describe the risk in people who are going to be exposed to the drugs who have a range of other psychiatric potential problems, as well as a much

longer anticipated duration of exposure.

So what I think Porter and Jick's data really represent is one end of a continuum of risk, short term exposure to opioids in a non-addict population.

The other end of the continuum is represented by people who have a substance abuse problem who are going to get chronic pain treatment. Now as you might imagine, if you go to the literature and look for long term treatment of addicts with opioids for pain, you will not see an extensive literature. But I've pulled out a reference from Dunbar and our very own Nat Katz from 1996, Journal of Pain and symptom Management.

In their experience at Harvard, they followed some 20 patients who had both chronic pain and a history of substance abuse. So this is kind of what we are left with, is drawing conclusions from small case series of 20 patients. But in that study, I think it's very interesting to note that nine out of the 20 patients abused the medication -- nine out of the 20.

Now I don't know how much you want to draw from 20 patients, but it is interesting at least that it's not 20 out of 20. A lot of people, I think,

think that if you try to treat addicts for pain, it's a foregone conclusion that they will abuse the medications and, moreover, treat them as if they themselves, addicts themselves, are a homogeneous group, which they are not. They are a very heterogeneous group.

There are people who never abused opioids. There are people who are opioid abusers. There are people in long term recovery and so on and so forth, and to that point, of the 11 people who did not abuse the medications in the Dunbar and Katz case series, they were all active in recovery programs.

We desperately need to develop these kinds of settings for people. Recovery is not about abstinence. Recovery is about honesty and accountability, and there is nothing incompatible about being in recovery and taking your pain medicine as prescribed, if you have a chronic painful condition. The problem is that methadone maintenance has become the dumping grounds for a lot of those patients.

So just to reiterate: What we really have is a spectrum of risk. When we start people on chronic opioid therapy, the risk of addiction of aberrant behavior depends on their personal

characteristics and history as well as the anticipated length of exposure.

We don't really have a lot of data in patients in whom we expose to these medications over long periods of time, but the risk may be less than one percent on the one hand, or up to as high as perhaps 45 percent, on the other. And the clinician's role is to locate their patient on that continuum.

This is what we need to be treating, again not sort of cutting off physicians' ability to apply this therapy when they think it is medically necessary, but instead to try to help them realize who they are treating so they can bring the appropriate structures to bear when they start that treatment.

I wish I could tell them that it was a straightforward assessment, but of course, it isn't. The literature is a complete mess on this subject, completely unhelpful virtually, but at least theoretically we know that if addiction arises from chemical, psychiatric, social, familial, genetic and spiritual influences, that aberrant behavior during pain management in forms of noncompliance might grow out of those same influences.

I think ultimately we have to teach doctors, nurses, social workers, psychologists and

others to do a full assessment of these issues so that we can bring -- because a lot of our chronic pain populations do indeed have problems in these areas.

They have comorbid psychiatric problems. They have social and familial problems that have grown out of the usual year or more that it takes them to get adequate pain relief. Some of them have spiritual difficulties because of the length of time they have been suffering, and still others are genetically loaded for addiction.

These assessments need to be made so that we can ultimately track people into a tailored approach to their pain management that helps realize better outcomes in a wider range of patients, although if the data from Russ and my study seem to hold to up, seems like 80 percent or so of people did okay with just the kind of usual approach to this therapy.

Pseudo-addiction, of course, can be one of the things that you have to sort out, because, as I've said earlier, when we do see aberrant behavior, it may come from those influences. It may, however, come from inadequately treated pain.

If the patient indeed has a history of drug addiction, I think as a society and as individual clinicians, one of the things we really have to do is

consider the risk of not treating them.

If we are concerned about public health, then we certainly have to be concerned about what kinds of criminal activity and drug abuse is set in motion by refusing to treat populations of people with opioids when they need them, such as the addict population.

In a study that we are just completing now -- this is a NIDA-funded study -- we compared the behavior of drug abusers with AIDS to the behavior of cancer patients. It sounds like there's two groups, but there's really three.

Based on a formula, we have really three groups: Adequately medicated cancer patients, inadequately medicated cancer patients, and virtually all inadequately medicated addicts with HIV-related pain and other chronic pain syndromes.

The results of quite commonsensical and predictable. That is that the little old Hoosier farmers who are inadequately medicated for their pain don't start abusing street drugs. They might try alcohol. They might get depressed. They might become socially withdrawn. But the substance abusers who are HIV-positive in Indianapolis reported commonly turning to street drugs for abuse, diverting prescription

drugs for use, even trading sex -- HIV-positive women trading sex to get pain medicine on the street to treat their pain.

So if we are concerned about the public health consequences, we really ought to be concerned about the underside of this issue that doesn't get nearly enough attention.

Additionally, I think there is a real need for research in an area -- and this is a term that Eduardo Bruerra actually coined. Interestingly enough, he coined it in talking about people with cancer, the so called "chemical coper."

Now a lot of us, as I said earlier, don't see a lot of people with chronic pain who come in with, you know, their pain prescription serving as a gateway to the use of illicit drugs. That is a very rare phenomenon, almost nonexistent.

On the other hand, we do, I think -- at least I do as a psychologist, because I tend to get referred these patients, see a number of people with comorbid psychiatric problems that are not being well addressed, and we see people who develop a syndrome that is kind of referred to in the clinical literature but hasn't been studied at all very well, to my observation.

That is this chemical coping kind of phenomenon wherein people -- and I think it is a syndrome that bears resemblance to addiction, but it's not illegal. It doesn't seem to threaten the public health in any terrible ways, but I do think this is a negative outcome in some people on chronic opioid therapy where the drug just assumes kind of just two central a role in the patient's ability to cope with and live with their disease.

You know, I think when you start a patient that has been undermedicated for periods of time on chronic opioids, I think it's reasonable to have them be very focused on drug procurement and getting more analgesia and so on, because they have been undermedicated, and there's a lot of motivation. But when that sort of never gives way to a broader appreciation that kind of what you see is what you get, this is the amount of relief you have, it's time to start focusing on goal setting and expansion of psychosocial repertoire.

That never happens. That is a worrisome development in some chronic pain scenarios. Very poorly studied and just described, as I say, in the clinical literature. I think these patients need a structured approach. They need psychotherapeutic

approaches, and they need pain treatment that decentralize the medicines, like the sustained release opioids and so on.

So just to reiterate, I think that one of the most important things that I'd like to kind of leave you with is that I think that the decision to start people on opioid therapy should largely be based on medical variables. How severe is the pain? Perhaps to some extent, what kind of pain do they have, since there are some pain syndromes that are slightly less responsible to opioids? What else has been tried?

Ultimately, I think the issue is not, you know, who gets opioids and who doesn't -- and I think that sounds like it was one of the themes of yesterday's discussion -- but who gets opioids in what treatment setting with what kinds of limits to help them also enjoy a favorable outcome?

You know, if I ran a pain clinic, I would have three pain tracks I would try to have people moved into and perhaps moved among, once they had an evaluation initially. There is the uncomplicated patient track who needs minimal structure, easily treated by internists and others.

There is the patient with comorbid

psychiatric and other coping difficulties who needs a moderate amount of structure and a heavy psychological and rehab input, and then there are addicted patients who, depending on where they are in the addiction spectrum, need a highly structured approach, although variable based on those particular variables that you saw there.

So then just finally, there is a difference, I think between addiction as it's been defined in the psychiatric literature and the complex issues of noncompliance and aberrant behavior that become evident during pain management, and this difference has not been well studied.

It's been poorly articulated, and I think in longer term follow-up of people on chronic opioid therapy, we need to start reviewing and looking at aberrant behavior and noncompliance in the longer term.

Finally, the pain population is, of course, as I've been saying, very diverse, and the application of opioid therapy to this diverse population requires careful assessment and consideration. Thank you very much.

ACTING CHAIRMAN KATZ: Thank you, Steve. That was a great presentation on a very complicated

subject with sparse and diverse data. I appreciate it.

In the interest of getting as efficiently as possible to the reason why we are here today, I am going to actually hold questions. I think they will probably come up naturally in our discussion anyway.

We will move right along to Dr. Hertz. Dr. Hertz is a -- Sharon Hertz is a Medical Officer in the Division at the FDA, and she will be speaking with us about regulatory approaches to risk management of prescription opioid abuse.

DR. HERTZ: Thank you, Dr. Katz, and thank you to all of the speakers who have preceded me. There's been some very interesting and useful information provided.

We in the Division, as well as the other division that deals with analgesics, really wrestle with a lot of these issues on a regular basis, and the more information that we have to work with, the easier it is to take a reasoned approach to these problems.

There have been reports of abuse of prescription opioid analgesics that have directed public attention to the known potential for abuse, misuse and diversion of these products. There are several approaches to managing abuse potential that

are considered by the agency.

You have heard about scheduling under the Controlled Substances Act. To some degree, we have discussed a little bit labeling today, including black box warnings. There's been some interesting in updating labels with newer information; risk management plans, formulation changes and restricted distribution.

I am going to focus my discussion right now on risk management plans, which are under consideration with increasing frequency as a tool to address abuse related risk with opioid analgesics.

There are some common features that we are starting to organize with these risk management plans. The first feature that we like to see or that are often provided is identification of key messages.

What are the key events that we need to monitor with this specific product? Is the intent of this particular risk management plan, in fact, the prevention of abuse and diversion or other issues: And when appropriate, what is the importance of proper patient selection with this product?

The identification of risk potential is the next feature in these plans. What are the issues that make a risk management plan an important feature

to consider with a product? Are there issues related to the drug substance? Is it a formulation issue? Is there prior experience with similar products that have tipped us off to anticipate the need for a more proactive approach?

Tracking an quantifying abuse, misuse, and diversion is quite challenging. programs that have been developed for this purpose have included the things that we have heard about: Spontaneous reporting mechanisms through company sponsored hotlines, the MedWatch system, the many databases that have been discussed today and yesterday; state drug control authorities and boards of pharmacy.

Special registries have been created, including pediatric databases. Surveys generated at the pharmacy level have been important in at least one risk management plan in terms of generating important information on the use of some products, as well as getting information from literature and media reports.

Programs to prevent abuse, misuse and diversion often overlap with interventions intended to decrease such activity. Education is paramount. Physician education and pharmacist education can take the forms of continuing education programs, "Dear Health Care Provider" letters, as well as tools such

as patient package inserts to provide information to patients.

We've heard about and seen tamper resistant prescription pads. Are there special storage needs for the physician in their office? What about for the patient in the home environment? Child resistant packaging needs to be addressed, because the regulations only cover this area for oral preparations and, as we have seen, there are some non-oral preparations that have been developed and are being developed for pain management.

We have discussed to a little extent black box warnings. What about restricted access to targeted populations? Is that appropriate to the product?

Expert Advisory Boards have been composed to assist with educational efforts, as well as to assist with the development of surveillance programs. We have also heard about cooperative efforts with law enforcement. These have taken forms such as educational material as well as the use of country-specific indicia or markings to track where products are coming from.

The monitoring efforts, once a plan is generated, are critical. What events are being

reported? How are they going to be monitored? We also need to assess the effects of educational efforts, and we need to audit the promotional efforts. What are the actual messages being delivered by these efforts, and are they reaching the right targets and generating the right message?

I have three vignettes to demonstrate and highlight some past efforts that have met with some measures of success in dealing with issues. Now, clearly, these are based on real products, but I have taken the liberty of altering the facts, mostly simplifying, just to focus our attention on important points for discussion.

Drug A is a parenteral opioid agonist/antagonist that was initially approved for hospital use. The abuse liability was considered to be low, and the product was not scheduled. Little abuse was reported.

Later on a nasal spray formulation was developed for outpatient use. The abuse potential was revised, still considered low but post-marketing surveillance was recommended.

After release, concerns of abuse rose as reports started to come in, and a petition for scheduling by the DEA was raised. Databases were

reviewed to try and gain information on what was actually taking place.

A cooperative effort with FDA and DEA surveyed state authorities, and 80 percent of responding state authorities confirmed cases of nonmedical use and diversion. typical drug seeking behavior was reported, falsification of prescriptions, doctor shopping, everything we have heard about, and these reports continued to increase.

A request was made to DEA to schedule this nasal spray and, in fact, it was placed on Schedule IV of the Controlled Substances scheduling. Following scheduling and, perhaps more importantly or as importantly, following dissemination of relevant educational information, abuse related reports began to decrease in the setting of stable prescribing practices. So this was effective efforts.

The next product was another agonist/antagonist, originally formulated as an oral product. Over the first decade of use, reports of abuse and misuse steadily grew. In particular, intravenous abuse of crushed tablets was noted.

The product was added to Schedule IV, and this had no impact in this instance on the reports of abuse and diversion. As a result, the product was

ultimately reformulated with naloxone, and the original product withdrawn from the American market. Subsequently, there was a dramatic decline in the reports of abuse.

The last vignette, the last product, represented a novel formulation of a drug substance that was already on Schedule II of the Controlled Substances Act. The product was intended for a narrow target pain population.

There were a lot of concerns during the review process for this product, particularly concerns of accidental exposure in non-opioid tolerant individuals, and also concerns about abuse and diversion. A lot of this was really related to the high dose available in this formulation and the potential for easy conversion of this formulation for parenteral abuse.

As a result, a risk management plan was created prior to product approval. Features of this plan included limiting these prescriptions for this product to patients with the labeled indication.

Through surveys of participating pharmacies, off-label prescribing was identified, and corrective letters from the company, not from the government, were sent to physicians trying to inform

them of potential risks and appropriate use.

Detailing by the company was limited to physicians who were known to regularly prescribe to patients in the targeted population, and patient education materials were developed and provided either by the physician or the pharmacy early in the patient's use of the product.

Additionally, cabinet locks were provided to patients for home storage. A temporary storage container was created, and even a locking fanny pack so patients could have product available in a safe manner whenever they needed it.

The results have been quite good. There have been very limited reports of misuse of this product.

The agency is aware of problems of abuse, misuse, and diversion of prescription narcotic analgesics, but we are just as aware of the need for adequate pain management for legitimate pain patients. So in the discussion that is going to entail, we would just like the Committee's input on their opinion of prior approaches and some of the general approaches that we currently have available to us now.

Dr. Katz, I think, is actually going to take care of organizing the questions for this

discussion. Thank you.

ACTING CHAIRMAN KATZ: Thank you, Dr. Hertz. Let me have you stay up there for a minute or two, if you don't mind.

What I'd like to do first is to give Dr. Hertz an opportunity to answer any questions specific to the content of her presentation about regulatory approaches to risk management in this situation, and as soon as she is done answering those questions, we will launch right into the meat of our discussion.

Dr. Portenoy first, then Dr. Carlisle.

DR. PORTENOY: I'm just curious about what happens over time with the risk management program. If a risk management program is in place and the data look good -- for example, vignette number three -- is it revisited by the agency after a year or two, and is the company then allowed to market to a broader population of physicians?

DR. HERTZ: Well, I can answer part of that question. As another feature of that risk management plan, we have quarterly reports of these efforts being provided, so that we can keep a watch on what type of activity is occurring.

The intention there is to provide an opportunity to adjust the plan if trends occur that

suggest there are any significant problems with accidental exposure, misuse or diversion.

I think the fact that misuse has been as low as it has been is because the plan is in effect. So if the plan is removed, you know --

DR. PORTENOY: I'm sorry. Once again, I wasn't totally clear. My's my fault.

I'm more coming at the question in a little bit of a provocative way, from the perspective of the concerns we have about the undertreatment of legitimate pain problems.

We have no data that essentially validates a risk management plan, because you are not doing it in a randomized format. We can't watch one country with it and one country without it. We just put it in place, and then we look at it.

It would be reasonable to think that a very tightly controlled risk management plan has the effect of reducing exposures, at reducing the opportunity for the drug to reach a larger number of legitimate pain patients.

As off-label use grows with the drug, and if the experience suggests that it may be safer than the original risk management plan discerned, is there any effort for the agency to look at it from the

perspective not of, well, there's no abuse, so we're doing a good job, but from the perspective of, well, maybe we are not allowing enough pain patients to have access to it because we have this overburdensome risk management plan in place?

In the absence of validation data, both parts of that argument are appropriate to discuss. Right?

DR. HERTZ: Yes, but I'm going to direct that to Dr. Kweder.

DR. KWEDER: Actually, I can address that more generally. I think that's a great question, and it's exactly the kind of thing that we are facing as we think more broadly about risk management plans for marketed products in general.

There are examples in other therapeutic areas where, when a product, for example, has first come to the market and we have had substantial concerns about how it would be used where we have imposed a very stringent risk management plan and then begun to back down as the data reassured us over time that the things that we feared were not coming to pass and that perhaps more broad access was appropriate, provided, of course, that there weren't other safety or effectiveness concerns.

The real time approaches to these -- you know, the changing environment that we recognize has to be taken into account and built into these plans so that they make sense for the times.

DR. PORTENOY: So my last comment on that is that it would be very helpful, I would think, for the agency to begin to build into the plans up front the kinds of benchmarks that are going to be evaluated not only from the perspective of is it working to reduce abuse but might it also be loosened in order to improve access for pain patients?

DR. KWEDER: Exactly. Yes, exactly. I would agree.

ACTING CHAIRMAN KATZ: Dr. Carlisle?

DR. CARLISLE: Well, my question was actually pretty much the same thing except with one additional question about that. That is, has there been any effort to tease out whether it was the -- in the example 3, whether it was the restriction of the drug or the safeguards that were put in on the patient end of it that resulted in the absence of abuse?

DR. HERTZ: I don't know if I'm free to discuss information obtained in these periodic reports. So I think it's a little hard for me to answer that question. I don't know how much of that

is proprietary.

DR. RAPPAPORT: No, we can't discuss it, but we don't -- What we can tell you is we don't have the information you are asking about. I think that would be interesting to look at, along with the issue of whether the programs are restricting drug use.

ACTING CHAIRMAN KATZ: Dr. Ashburn?

DR. ASHBURN: You mentioned in your strategy slide the several strategies that the agency is considering to use to try to balance the potential for diversion with allowing access of the medications for appropriate use.

One of your suggestions was limiting prescribing to select physicians based on their training and specialty. At least, that's what I got from it, and that's what I was interested in trying to ask whether or not such a strategy has been considered or whether or not it had been implemented.

DR. HERTZ: In the risk management plan for this product, any physician is capable of prescribing the medication, but what was limited in this particular plan was the detailing, in an attempt not -- an attempt to make sure that, because of the potential risk of the product, this wasn't simply embraced as an analgesic that would be widely used

because of the risks involved.

So it wasn't -- It's not that there is any physician in this country who cannot conceivably prescribe it, but what we would like to see is that it is prescribed in a manner consistent with its development and its planned use.

ACTING CHAIRMAN KATZ: Dr. Schuster.

DR. SCHUSTER: In regard to Dr. Portenoy's question, this is not a new problem. For many years those of us who do preclinical abuse liability testing may have predicted that a compound has less abuse than is necessary for scheduling. It is scheduled under the CSA, and then it is not abused.

When we raise the issue "but it's not being abused," we are told that that's because it's scheduled. I'm not -- The government has this problem. I mean, it's just a problem, and we can't do controlled studies with, you know, 25 of the states having it scheduled and 25 not, unfortunately. But it's just a general issue.

What I really wanted to ask was this, and that is: I'm somewhat concerned, and I don't know whether or not there is good data about this but perhaps the FDA or other people here have some indication of this.

When a new product is marketed for an indication in which other marketed products have abuse liability, I can tell you that it goes onto the Web immediately. There are dozens, if not hundreds, of Websites that deal with, hey, what's hot in drug abuse today.

I would not be surprised that, regardless of what this compound is, if it is for an indication in which the vast majority of the medications that are available for that indication are abusable, that it's going to be experimented with when it is marketed. I don't know whether or not how much abuse and how long term does that have to be before it sets up a true signal that this is going to be a long term problem.

I don't have an answer to this. I'm just posing it as an issue that I think must be considered. I can remember when smoking banana skins was the rage for at least a three to four month period, and it died out. Are there any histories of things that have been marketed unscheduled for which there is a period of experimentation and they drop off?

It could be confused if you impose a risk management plan at that point that it's your risk management plan that is responsible for this.

ACTING CHAIRMAN KATZ: Does anybody have

an answer to that question? Does anybody know? Yes, Dr. Leiderman?

DR. LEIDERMAN: Well, I don't know the answer to the question, but I'd like to make a couple of comments more broadly.

One, I think we have all seen, and I tried to make the point, that scheduling alone has very little impact on what actually happens in the real community. Most of the drugs that are under discussion today that we are seeing data about are already Schedule II. That's as restrictive as you can be under the Controlled Substances Act for a medically approved product.

I think what we are trying to do, what Dr. Hertz is trying to do, is broaden the discussion and talk about other ways that we as a public health agency can begin to protect the public health, and it's not just abuse. I mean, it's other kinds of misuse, overdosing, accidental overdose of, you know, potentially very dangerous substances.

Just to sort of balance Dr. Schuster's point, I think we also need to look at the many products that have gone out unscheduled, and we have had to actually, in fact, experience problems in the community and then reevaluate and move things the

other way. In fact, they do move both directions, teasing out, in fact, if you actually do change the behavior and the experience with that drug in the community, what's due to the rescheduling act, the education, natural sort of ebbs and flows in what is popular in drug abuse. Virtually impossible to tease out all of these, but I think the case studies are worth looking at, and I think that's what Dr. Hertz was really raising.

ACTING CHAIRMAN KATZ: Given that we are already starting to discuss what we are here to discuss, I'm going to finally let Dr. Hertz sit down. thank you again. If you would like to sit down -- and launch into the question that we are speaking about, which is -- People can find on their page. That is entitled "Questions to the Committee, Prescription Drug Abuse, January 31."

Just to read the question and continue the discussion: In the context of increasing awareness of the problems of diversion and addiction to prescription opioids among patients and nonpatients, comment on what measures might be appropriate to consider in the development of an overall risk management strategy that could reduce abuse and diversion without restricting access to drugs by

patients in need of treatment.

So it's to the very issue that we have just been discussing. Are we going to lose you at 2:30, Dr. Portenoy? At three? Okay, fine.

So why don't we continue the discussion, and maybe focus it a little further on what risk management programs do people around the table think would be appropriate to consider in this context? Dr. Max?

DR. MAX: I have a question for Dr. Chilcoat before we go on. You did this in a press conference of NIDA where they were announcing some new programs. Can you speculate? Have they set aside money to do opioid prescription drug abuse research?

DR. CHILCOAT: It was a program announcement. So it wasn't particular setaside monies. The money wasn't set aside. So it's just a program of research that's being announced.

DR. MAX: And the scope of that was what?

DR. CHILCOAT: There's a wide range, I think, as I recall, of research in terms of prescription drug abuse, you know, ranging from sort of basic laboratory studies to epidemiologic research, just basically trying to both draw attention to that as -- prescription abuse as a potential problem and an

area that's basically underinvestigated.

DR. MAX: And was -- I'm struck by the fact that the few studies that people here presented were the only ones I've ever known about to estimate the incidence, the risk. Is there something we are missing? Has NIDA been funding prescription drug abuse research besides what you and the people around the table presented?

DR. CHILCOAT: We are not funding -- They are not funding my research, for prescription drug abuse anyway. I just have done this on the side, basically. I'm not sure. Obviously, you would want to talk to someone from NIDA to know their portfolios in that area. Maybe some other people might have --

DR. MAX: I've asked them recently, and they said the person -- the official said nothing.

DR. CHILCOAT: There's very little -- I mean, I --

DR. MAX: He may have not known.

DR. CHILCOAT: Yes, and if you look at the -- Obviously, in terms of literature on epidemiology, especially epidemiologic research in the area of prescription drug abuse and dependence, it's obviously quite sparse, and part of it is, you know, the data available are okay but, you know, they are not

specifically designed with the idea of collecting it for prescription drug misuse, particularly, and I think some maybe recent studies may have had trouble getting funded as well. I'm not sure in terms of getting it through review committees as well. I mean, there's a number of levels that --

ACTING CHAIRMAN KATZ: In the interest of time, I want -- Let's make sure that we do our job today, and I want to make sure we hit the issue of what sorts of risk management --

DR. MAX: I'm finished.

ACTING CHAIRMAN KATZ: Next was Dr. Ashburn. No? Am I calling you twice again accidentally? Oh, sorry. Dr. McNicholas.

DR. McNICHOLAS: I have a question that I'm going to ask Dr. Chilcoat to answer first, but let me put it in the greater context.

One of the things that I have been listening for all day and I have not heard, and I don't think that we can really discuss risk management plans without thinking about this, is what is the source of the diversion of these medications? Is it coming out of doctors' offices? Is it falling off the back of a truck? Is it coming out of -- You know, and where are -- and the reason I am going to address this

to Dr. Chilcoat is, when the National Household Survey, for instance, looks at prescription drug use, you ask did you use prescription drugs?

Is there any indication on how those prescription drugs were obtained? Were they obtained on the street corner or from the pharmacy through a prescription?

So I don't think that we can look at this as the only source of diversion is coming out of prescriptions being then sold on the street corner, and I think we need data on where the various sources of diversion are and how we can address those via risk management plans or something else.

ACTING CHAIRMAN KATZ: Dr. Chilcoat, do you have an answer for that question?

DR. CHILCOAT: Yes. Basically, the National Household Survey doesn't ask specifically about that. Obviously, the problem is that these questions are nested in a survey that takes over an hour anyway, and they are doing 50,000 interviews. So the questions are more, you know, have you used -- They talk about -- describe pain relievers, and then ask about specific use, and the extramedical question lead-in that I presented to begin with. But to my knowledge there is no knowledge in --

ACTING CHAIRMAN KATZ: Mr. Davis from the DEA, is there an answer to that question? What proportion of prescription analgesics that are abused come from what sources, patients legitimate prescribed versus prescription rings versus imports from out of the country versus Internet ordering versus --?

MR. DAVIS: It would depend upon your perspective. There might be more cases involving doctor shoppers and prescription drug rings than actual practitioners diverting controlled substances. However, one practitioner may divert many times the number of controlled substances, pharmaceutical controlled substances, than a street level diverter may.

So in that regard -- So in answer to your question, in that context we don't keep specific statistics on the number of controlled substances diverted by one source or another.

ACTING CHAIRMAN KATZ: Thank you. That's very helpful. So it sounds like -- and this is my understanding as well -- that there are multiple sources of diverted drugs. However, at least the DEA perspective is that the physician source, be it legitimate or nonlegitimate, prescribing remains a source worthy of risk management. Is that a fair

summary, Mr. Davis, of that?

I skipped over you, Dr. Roberts, earlier. We had you on the list. Is it still -- Did you still want to speak to the issue of appropriateness of risk management planning? Please go ahead.

DR. ROBERTS: Well, a couple of thoughts. I mean, as you look at the distribution system, physicians and other prescribers are sort of the sales force, as it were, at the retail level. What I'm hearing is that the number of times that the DEA or other agencies are able to prosecute successfully actions against those prescribers for inappropriate prescribing is actually very rare, 79 out of 950,000 prescribers.

Twenty years in the risk management world has taught me two things about at least doctors' behaviors. The first is regression to the mean, and the second is inertia.

If you give doctors data back on what they are doing and show them to be outliers relative to their peers, most of them will scramble like crazy to get in the middle of that curve.

The second thing is, once they get there, it's damned hard to move them out again, because they tend to sit where they are comfortable. So my piece

of advice on that is with any risk management program, if you can get them where you want them right out of the gate, that's best. But whenever you get them where they are, then leave them alone, because they will stay there.

So that leaves then the second sort of level to this, which is, you know, right or wrong, the sales force has done its job; now what happens?

I think one of the dilemmas that we have as a people is, you know, we are always going to try something, whether it's smoking banana peels or licking frogs or, you know, the latest drug du jour. People are going to be scraping Fentanyl off of patches and trying something.

You can't have it both ways. I mean, we can't say, on the one hand, yep, we expect a certain level of diversionary and addictive behavior and, oh by the way, Mr. and Ms. America, you're on your own once that happens. We've just got to get, I think, more serious about treating addiction as the disease that it is.

That means a fairly comprehensive national strategy that's adequately funded and, to be blunt about it, we haven't done a very good job, whether you talk about the drug czar and the policies we have had

there which have been primarily focused on interdiction rather than prevention and treatment, and even the FDA.

I mean, look at the track record around OTC advertising. It's not left most of us as prescribers exactly sanguine about the ability to positively impact patient and public attitudes around the proper use of medications. So we've got a long way to go.

ACTING CHAIRMAN KATZ: Dr. Portenoy?

DR. PORTENOY: What kind of frog? It's a little bit exciting to me to think that the FDA could influence not only the public health but also the process of gathering the data we need through risk management programs that incorporated outcome measures that were scientifically valid.

I want to understand a little bit better what the FDA can actually ask industry to do. For example, a part of a risk management plan could be education, but we know that education can be done on the cheap and be quite limited or it can be done in a national way using experts and can be extremely expensive.

We know that outcomes collection can be done in a relatively unsophisticated way using

available datasets or it can be done in a way that is very sophisticated involving innovative new data collection, a way of really drilling down and probing to answer some of the questions that have not been answered today.

So I want -- If in fact, the agency would have that kind of authority to work with a company and create a risk management plan that incorporated the outcome data, and one would think that it would then include in that model what would happen with certain outcomes, I think that would be extremely positive. But I just want to understand.

I think we all need to understand what the parameters are.

DR. KWEDER: The answer to your question is, yes, we can do that. I will say that, you know, this is a new area for us. You know, 20 years ago, 15 years ago, ten years ago and even in some places today, the model had been, you know, FDA's job is to put a product on the market and then let the world take it. That has really, really changed.

You know, as public expectations have increased about our ability to influence risk, we have had to look at things very differently. We have several regulatory tools at our disposal, certain

kinds of approvals that allow us to really work very closely with companies to mandate that they provide us with metrics that assure us that risks are being managed for the product appropriately.

Some of the most visible examples of that are the way that thalidomide is marketed -- very, very tight metrics. We have other examples of it that aren't quite so tight, but part of the trick here is to figure out what the questions are.

What are the outcomes you are really interested in? Is the outcome that you want just physicians to be educated, for example, and how can we measure that and know that the people who are prescribing the medicine understand its risks. That's one piece.

We also want to influence behavior. So what are the outcomes that measure behavior are things that we need to think about.

The comment that was made by the gentleman to your left was an important one. Doing that, imposing these risk management plans when the product is first coming out of the box is, we know from years of experience and actually studying this, our greatest opportunity to influence and manage risks in a positive way.

It is extremely difficult for us to work with companies to build successful risk management programs once prescribing patterns are established. We know that from decades of experience, that once prescribing patterns are established, they are extremely resistant to change. We are comfortable where we are.

So some of our questions today really speak as much to how do we do it out of the box, and what are the kinds of things that could be put in place and the kinds of metrics you would be interested in, so that we can do that well?

ACTING CHAIRMAN KATZ: Dr. Portenoy?

DR. PORTENOY: Yes, please. I think this is really terrific, but I do want to -- I want to suggest to you that the clinical community, if I could be so presumptuous as to speak for the clinical community, would be totally on board with that.

The concern is always going to be in several areas. Number one, what sort of delays get built into the drug release process by the need to have a risk management plan? Is it fair to have a product that's been studied, everybody in the community knows it's safe and effective, but then to have it delayed two years to come out while that is

being developed --

The second thing is whether or not the risk management plan appears on the surface, at least, to be unduly influenced by politics. That is a credibility issue. The clinical community gets very nervous when we think that that happens.

The third is: Is the risk management plan appropriately informed by expert review? So if the clinical community gets a feeling that the decisions are being made somewhat capriciously by people who don't treat patients and don't really know the data or know the complexities of the data, then we get nervous.

I would think that it would be extraordinarily positive from both the scientific and the public health perspective to move forward on that kind of initiative, with the provisos being you got to speed up the process, you got to free it from politics, and you got to get appropriate expert review as you move forward in order to create datasets that have appropriate benchmarks.

DR. KWEDER: I certainly wouldn't argue with that. In order to achieve all those objectives, though, the planning and the risk management needs to begin during the development phase. The worst

situation is to get to the point where all the data on an application are before the agency, and all of a sudden say, oh, my goodness, there's a problem here.

That does happen, because we don't necessarily see the data until it comes to us. So that's where the rubber meets the road and it becomes a challenge for us.

I think our approach is to do this increasingly. We have some working groups, for example, with the pharmaceutical industry more generally to try and do some of these sorts of things. In fact, we will probably be holding a public meeting in this calendar year to look at this issue more broadly, because it is absolutely not unique to this therapeutic area.

ACTING CHAIRMAN KATZ: Dr. Portenoy, since you are on a roll, I'm going to ask you to continue. When you first ask your question, it sounded like you were starting to frame out the possible components of a post-marketing risk management model that could be used to address some of the important issues that we heard and mentioned earlier.

I wonder if you could just continue to elaborate on what the elements of that model might consist of, what it would focus on, how it might

address your benchmarking behavioral measures, that sort of -- those issues.

DR. PORTENOY: It seems to me that so much of this kind of preliminary work has been already done in the presentations we just heard, in the sense that if it's a pure mu agonist drug, if it's going to be scheduled under Schedule II, then it's clear that the planning has to be done early on, and it has to be part of the discussions that happen between the agency and industry right off the bat.

If it's an issue of a delivery system that could potentially be misused, it sounds like there are going to be issues related to physician education, patient education, and marketing. Those can be addressed along the way in order to have a reasonable plan that would be informed by expert review sort of divorced from the politics of the situation.

Then I think this issue of data collection and mandating within the appropriate understanding of cost, but mandating some additional creative data collection, some of these prospective, systematic surveys where we are looking at outcomes related to chemical dependency as well as outcomes related to analgesia and side effects and outcomes related to functional -- physical and psychosocial functioning.

That kind of stuff can be done, I think, and really augment some of the available datasets and begin to answer the question which has two sides, the first side being have we prevented more prescription drug abuse, which we all think is important, but the other side which hasn't had the spotlight shone on it yet is does risk management -- does this intensive focus on the drug abuse possibility actually limit access to appropriate patients because of physicians' reluctance to prescribe things that look so dangerous that they have this kind of plan attached to them?

You have to be able to show both, I think, with data over time, and then be willing to release or reverse some of the stringent requirements of a risk management plan if it looks like you are doing harm to patients who have legitimate needs.

ACTING CHAIRMAN KATZ: At the risk of allowing a small number of people to dominate the conversation, that was very helpful, and I'm going to ask you to push it even further now and give us a sense for what specific sorts of elements you think would help meet the goals that you just achieve in terms of how precisely it might be done.

Of course, it's premature, and there are many pros and cons. Many people need to be involved

in the discussion, but let's begin the discussion, if you don't mind, by laying out at least a possibility for how specifically such a program could accomplish its goals.

DR. PORTENOY: Well, I'll only make one comment, and then I really will stop.

A very provocative area nowadays is how do you educate physicians to change practice? I've been lecturing to physicians for a long time, and over the years have gotten less inclined to do it because no one ever listens to me, and it's just like going --

So I would be very interested, for example, in creating outcomes assessment work that would allow us to evaluate quality improvement methodologies and more sophisticated adult educational methodologies, including Internet based methodologies as a way of changing knowledge and skills; because we are talking about skills building here in physicians. We are not just talking about knowledge, and the lowest end is really nothing. A CME -- filling out a CME document to get your Category I credit means nothing.

So we're talking about outcomes assessment that's a little bit more sophisticated from the physician education perspective. Then we are talking

about prospective systematic surveys that have a large enough number of patients so that you can begin to look at primary outcomes, and then do more sophisticated multivariate analyses after, so that we can begin to look at the predictors of negative outcomes; because ultimately it may come to a risk management program that's focused on specific patient populations who are at high risk to develop aberrant behaviors.

Until we do those prospective surveys and collect the data on comorbidities and psychiatric -- other psychiatric and substance abuse covariates, you are never going to be able to get that kind of data.

So in addition to looking at the large datasets like ARCOS and DAWN and all of those, I would think, for example, a risk management program could actually tap into community based prescribers around the country and, in the same sort of methodology that we've been doing for 25 years, do prospective surveys of patients who get exposed to the drug, looking at this range of outcomes in order to answer the question, what actually happens to patients who get exposed to the drug.

ACTING CHAIRMAN KATZ: It sounds like a patient registry of some type. Okay, I'd like to

focus comments specifically on the nuts and bolts of our risk management plans. We have a whole order of folks which I will try to follow as well as I can. Dr. Reidenburg, in fact, you were next.

DR. REIDENBURG: Yes. On this point and looking at the first two questions on the current prevalence of addiction or monitoring addiction, in this patient population I think we would be far better off looking at observational data or behaviors rather than trying to come up to the conclusion of addiction.

For example, when I look at the official definition of addiction, one behavior is compulsive use. I see lots of patients given short acting opiates that last two to three hours on an every four hour schedule having exceptionally compulsive use.

Similarly, continued use despite harm: I will see patients who, after an active day followed by a rainy day like this, they will take opiates to get relief and have what I call side effects that in the presence of a healthy adult recreational user would be called harm.

So I think that it would be far more helpful in this context of looking at patients getting the drug to treat pain in practice to define very specific behaviors or observations that we say in this

context is undesirable rather than letting somebody make up what they think is addiction using this official definition in places that, in my opinion, is inapplicable to the kinds of issues that we want to address.

ACTING CHAIRMAN KATZ: So what you're saying then is that, of all the elements that Dr. Portenoy just outlined he feels would be important in a risk management program to track, from making sure that we are not excessively limiting access of medication to patients who need it, from tracking positive outcomes like efficacy and improvement in quality of life, etcetera, also the variety of negative outcomes we're interested in, one of which is addiction -- you're speaking about that specific issue of how one would measure addiction in the context of that type of program.

What you are suggesting is that it has to be concrete and doable and not overly fanciful or conceptual.

DR. REIDENBURG: And relevant to these kinds of patients.

ACTING CHAIRMAN KATZ: And relevant to these patients, right. Any other comments on the issue of how one would measure addiction in the

setting of this type of measurement program, since that's what we are talking about right now?

Now we do have an order that I will follow as long as people's comments are relevant to the issue at hand, and Dr. Anthony, you were actually next on the list. Is this an issue that you would care to comment on?

DR. ANTHONY: Sure. Let me log just for a moment, though, so that you will get it back on the agenda, the issue of comparison of different risk management plans under experimental or nonexperimental conditions. So that will be for the future.

With respect to measuring, the National Household Survey on Drug Abuse now has a sample of more than 70,000 people a year, and probably will grow a little bit more over the next several years. They are asking seven items on features of dependence, which could be asked routinely in a clinical setting. Not very difficult to ask those questions.

In fact, the methodology is one which can be standardized so that the method in the clinic is essentially the same as in the field. Put on the headset, listen to the questions, see them on the computer screen, and respond to the computer screen.

I don't know that I believe completely the

validity of the measurement of dependence in that context, but having a fidelity and a cross-collaboration between the clinical setting and the epidemiologic field setting would be immensely valuable and would allow you to reference whatever findings you had in your clinic to that accumulating pool of non-patients who are being seen out in the community. So that would be one approach to measurement that I would like to recommend.

ACTING CHAIRMAN KATZ: That's a very important point. Any other comments with respect to the issue of how one would measure addiction in a context of such a risk management program? Dr. Max?

DR. MAX: I heard the speaker say, for one thing, we are not sure what works in risk management. As someone said, it's a shame we can't randomize the 50 states, because we are the Federal government. But actually, as you suggest, we could if it were one company doing it, build some beautiful controlled interventions, like one behavior: People have said that Kentucky has electronic measurement of which patients are going to multiple pharmacies, which I would bet would be a reasonable subset of all the different diversion classes the DEA mentioned to us.

So I think it would be quite easy to go

into Kentucky and randomize counties if one particular company was doing one level of risk management in some counties and one in another and look at the use of multiple pharmacies as one of the outcomes.

ACTING CHAIRMAN KATZ: There are actually -- I think the number is now 17 states with electronic prescription monitoring programs that can be used potentially on that level. My experience with them is that they are quite happy to collaborate in these sorts of projects. We are working with Massachusetts right now.

Any other comments on the issue of how one would measure addiction in a context of a risk management program? Mr. Bloom, you actually were next anyway.

MR. BLOOM: Thank you. Yes. Actually, I would like to agree with the doctor. Certainly, being a person that is medically dependent on the opioids for nine years now, and gone through the whole gamut of being undertreated to finally being properly treated, I think that, you know, looking at the patients and looking at the pain clinics and seeing what pain clinics work and what things that they are doing currently now to manage the patients properly and what procedures they are using would be

extraordinarily helpful.

I know the pain clinic that my partner and I both go to at GW would be certainly -- you know, be able to provide a wealth of information on how they control the management of pain. I found Dr. Passik's presentation to be quite compelling.

One of the questions that I had for him -- I, unfortunately, didn't get to ask the question, but like in the pain clinic that I'm in now, that reduction down to 5.3, while significant, would be considered inadequate pain relief at the pain clinic that I'm on, because on the scale of one to ten, the goal at the pain clinic is to get down to a 2 to 3.

It's by having a baseline therapy, including another treatment for breakthrough pain. I think, if we can do that kind of surveying of existing pain centers now and using the 17 states with some prescription history, we could probably collect some data like we have done with AIDS where we have done some prospective looking back data to get some information about this.

The one problem I have is I am very uncomfortable with the question that says the agency is aware of the growing problem of abuse, misuse. I think it's much better to say the agency is aware of

the growing perception of the problem of abuse and misuse.

When we are saying we don't have enough data to say that statement, and the next question is: Discuss the adequacy of the available data -- it's a little disconnect between the first thing and the second thing.

ACTING CHAIRMAN KATZ: So, certainly, one take-home message from your comments is that any sort of risk management would appropriately be informed by people who already are doing that very type of risk management in the context of their own practices, which gets back to Dr. Portenoy's recommendation on beginning and ongoing expert review by individuals from the clinical community.

Now we are losing you at three, Dr. Portenoy. We're losing you, too, at -- Sorry? 3:30? Have you for a little while. Well, it's a minute or two of three. I want to try to emphasize folks who are leaving shortly and making sure we have thoroughly picked over their brains before they go.

Did you have any final comments in the last few minutes before you go?

DR. PORTENOY: The only comment I would make about the metric to evaluate addiction in

patients is the obvious one, and that is that we really don't know for sure -- at least, I'm not convinced that the standardized interview approach to categorizing patients as having addictive disorder or not having addictive disorder applies across the board to all pain patients receiving opioids for legitimate pain problems.

Because we don't know that, the studies have to be done that validate those sorts of interviews by also comparing them to other kinds of patient behaviors of the type that Steve Passik put on the screen.

If the agency could have a positive effect by actually mandating in an appropriate situation that kind of comparative data to be done at the same time, it would be a very useful approach for perhaps validating a metric that would be useful in the future, and also answering this question that's been out there a long time. How do you define addiction when people have chronic pain?

ACTING CHAIRMAN KATZ: Actually, I'd like to -- Dr. Hertz, go ahead.

DR. HERTZ: Thank you. I just want us to clarify one point. We definitely have tools that provide us the ability to mandate these risk

management plans in certain circumstances for a large number of our products that we are dealing with here today.

We are not going to be putting the product and the risk management in a mandated position. It would be something that would be very extensive and not necessarily a practical thing to do.

So when we perceive a significant public health situation risk and need, we are willing to utilize the tools available in terms of mandating, but what we really need is the cooperation of industry and the cooperation of investigators to help compel the use of these studies and the resources available to help us implement these risk management plans in a prospective manner, to collect data when available, to start collecting data during the studies.

You know, we would have a lot more to inform what to put in the risk management plan if we could start collecting this data early in the process, and that's when the investigators, and a lot of folks here are investigators -- that's when you have your hands on all this great material, your subjects, you know, the hundreds and hundreds of people participating in the trials, that we can use to sort of begin as almost piloting some of this collection of

data and ultimately inform for the risk management plans.

ACTING CHAIRMAN KATZ: I would like to introduce -- to inject one issue now into the conversation before we lose Doctors Portenoy and Passik completely, which is that, if one is monitoring for addiction or other similar outcomes in the post-marketing or clinical setting, is patient self-report with or without the physician reporting sufficient to identify these syndromes that we are concerned about, addition, etcetera, or do we need to do a proper job of this external sources of information as well, such as the electronic prescription monitoring data such as urine toxicology screens, such as spousal reporting, that sort of thing?

There certainly have been a number of studies done in the pain management literature that begin to look at -- scratch the surface of the issue of the validity of self-report in that population. There have actually been four studies done, and without going into the details unless anybody wants, all four of them suggest that patient self-report of medication use in the chronic pain setting is not terribly useful or gives only a very small part of the picture.

So I would ask the Committee to comment on whether they feel it would be appropriate to rely on a measure such as self-report, which at least preliminarily does not seem to be terribly useful.

Dr. Foley?

DR. FOLEY: I think I'm having a lot of -- I'll respond to your question, but it's in the framework of my concern about trying to answer this question.

For a patient to be identified as an addict has consequences that are very, very different than misuse of other drugs, because it then sort of moves into this sort of potential for criminal activity and, if they are identified as an addict, then physicians cannot treat them with opioids. There's a whole variety of rules that follow from that.

So just this terminology is problematic. I would rather use a language that we are trying to prevent diversion and -- prevent drug diversion into another group of individuals that might be using it who should not be using it.

So this language of addiction, I think, we should just like stop with. I think we should talk about criminal activities related to the use of this

drug, because that's what we really are talking about. That's all we can easily identify, and that gets at your point, that the pattern of that individual will be someone who is using a variety of illegal substances, who has a urine toxicology filled with these other substances.

Those kinds of identifications would be a better way, if we talk about this. And I think the risk management issues that we have to address here are very different than they are with other drugs, because of the social and the legal consequences of someone using these drugs.

It's a very, very different perspective. Then it places physicians in the part of being policemen along with something else. I think that isn't coming into this discussion.

So I think that there are clearly a need for risk management plans that should be identified, but I want to hear a way that we talk about this as a medical issue and not as either a political or as a criminal activity.

ACTING CHAIRMAN KATZ: Thank you. Let's try to -- Dr. McNicholas, you were on deck for a while.

DR. McNICHOLAS: Okay. Actually, I want

to second several things that Dr. Foley just said. First of all, if a patient has a legitimate pain need, whether they have a history of substance abuse or not, the legitimate pain need needs to be addressed, and to say that their use of opiates in that context is addiction is meaningless.

You need to manage the patient, and I think that Dr. Passik's data on a patient in a recovery program with the appropriate support doesn't misuse their medication anymore than anybody else does is exactly the point that we need to do here.

The other thing -- and I want to second what Dr. Foley just said. That is we are not talking about patients necessarily misusing their medication. We are talking about diversion to a nonpatient population, and that's where I think that when we are looking at using the databases, etcetera -- and coming back to your question, first of all -- self-report is going to be meaningless, because, first of all, patients don't know what you're asking them.

If you ask them if they are an addict and they think that physical dependence is addiction, they are going to say yes and be wrong. And if they know that they are an addict, they are going to say no and be wrong. So I think that self-report is -- The

people who say yes are the ones who don't understand the question.

So I think that asking for self-report among the patient population is meaningless, frankly. But I think that there are a couple of points that we want to look at when we are looking at diversion to a nonpatient population, and that's where we are looking at databases and that sort of thing.

There are some things that we need to look at, one of which Dr. Schuster brought up earlier. That is: I treat substance abuse. If there's a new kid on the block, my patients are going to try it. So I think that, when we are looking at risk management proposals, we need to build in the ability to see whether or not we are going to have an experimentation phase, because chances are you're going to see a blip.

Now whether the blip continues going up, whether the blip is a blip is really what the risk management program needs to take a look at. We had a medication that came on the market several years ago, and there was a definite blip, and then patients who were real drug addicts when they used it, and you went and asked them whether they would use again, it's ah, I didn't get anything from it.

It came right back down to baseline,

basically, after about a year. But you have to build into the risk management program the known experimentation that is going to occur with a subpopulation of people when there is something out there that says it acts like an opiate. Well, my patients are going to try it.

ACTING CHAIRMAN KATZ: Very important point.

DR. McNICHOLAS: The other thing that I think we need to look at is the denominator. If you write a million-two prescriptions for a medication and you have ten instances of abuse, is that a significant incidence of abuse?

So I think that we need to look at what is the appropriate denominator when we are looking at these databases and instances of abuse and diversion, and what are the appropriate comparisons. Is the appropriate comparison drug fentanyl? Is the appropriate comparison drug morphine? Is the appropriate comparison drug codeine?

If you have no more instances of abuse once you are past the blip than you do with codeine or with morphine or anything else, do you need to continue with this kind of monitoring, and is it anymore of a risk to the public health than other

drugs that are out there and being used appropriately for the benefit of our patients.

ACTING CHAIRMAN KATZ: Very helpful. Thanks. Actually, Dr. Holmboe is next, followed by Dr. Ashburn and Dr. Max.

DR. HOLMBOE: I'd like to more specifically address the issues of abuse and misuse and not as much diversion at the current time, particularly in regard to the risk management program.

Several issues I would raise. The first is I think that there are a number of guidelines that are out there. One of the things, I think, the drug companies could do, and FDA could help assist, would be, one, to try to bring those into some degree of consensus.

More importantly, I think we need to operationalize those guidelines. So learning from the health services research world. We need to get those into the trenches that are more usable form.

We have some lessons that we can learn from the inpatient setting in things such as critical or clinical pathways, standard disorders, algorithms, etcetera. Although they have met with mixed results, we don't have a lot of data in the outpatient setting. I think that's one thing that has been shown to help

operationalize those sorts of guidelines.

Reminders have been shown to be effective, and again I refer people to the Cochran Collaboration systematic database to look at these health source interventions as a source to help guide work in this area.

The second thing I would point out, that when we think about education and communication, it's going to occur at multiple levels, which really adds to the complexity. You have the FDA and government that has to go directly to the public. Also it has to go to the MDs, has to go to the company.

The company has to go to the patients, has to go to the MDs. The MD then has to talk to the patient. The pharmacist has to talk to the patient. So I think there are multiple layers of complexity here that one needs to take into consideration when we decide educational approaches, particularly when we are talking about educating patients, who I think have been left out of this discussion somewhat with regard to how do we best access them in an educational point of view to make them skillful in taking their own medications safely.

One way to do this would be to consider the use of a Mediguide, which has been used by the FDA

for other drugs. That may be appropriate for certain narcotic formulations, and I would recommend to look into that.

The last that I would bring up may be more controversial, but I would consider that perhaps -- and I'm not sure this is the right class of drugs, but we need to do more what I'd call competence based prescribing.

Although the FDA has been successful in restricting the use of certain drugs by restricting the detailing and distribution, we have to look at the other side of the coin. We've talked a lot about being able to educate physicians to use these drugs appropriately.

What we haven't talked about is how do we ensure that they are competent to prescribe these medications safely and appropriately. I think we need to look at that more closely. I think there may be drugs that I think should require a certain level of demonstration of competence to use these drugs, and as Dr. Portenoy talked about, Web-based training has been used in other settings and it has been shown to be successful. I've done a number of them myself for the U.S. Navy in the past. So I think that's a model to look at.

I think, finally, for patients I think we also would recommend looking at the shared decision making programs that have been used successfully in other conditions such as cancer, prostate cancer screening, for example, by Michael Barry up at Harvard.

So those are some of the recommendations I would have to consider for a risk management program.

ACTING CHAIRMAN KATZ: Thanks. It may be of interest that after the JCAHO recommendations came out, which required that all hospitals demonstrate that all of their health care providers are competent to manage pain, we actually produced a Web-based educational program on pain management specifically with that in mind with the institution being the client such that they could use that to help make sure that all of their physicians were competent.

That actually just got launched a few months ago, and it's been widely subscribed to by a number of institutions.

Dr. Ashburn, you were next.

DR. ASHBURN: I'm going to be looking at Steve and Dr. Foley for a few minutes for guidance. I just wanted to start from a little bit higher altitude to try to get my hands around this, and then guide my

comments.

First of all, it sounds to me like we do not currently have good grasp on what brands of opioids are currently being diverted, prescribed opioids. In other words, on the oxycodone issue we really don't know what the prevalence of diversion is and in what flavors they come. Would you tend to agree with that?

We know that some are being diverted, some are not, but we know that oxycodone in general seems to be increasing in interest, by the data we got this morning, but there are no data available to show where the oxycodone is coming from.

In addition, it strikes me that we don't know the source of that medication. Even as importantly, we don't know whether it's coming from the large theft of Oxycontin in Mexico that occurred, 100,000 or 200,000 pills that were stolen, or whether it's really coming from physicians and from people who are doctor shopping. What is the incidence of problems with regard to the area?

That brings me to the area of: When you look at a risk management plan, what is your goal? Is your goal to try to avoid diversion for illegal or illicit use or is your goal for a risk management plan

to not have patients have harm, or both; because if you are looking at thalidomide, the goal is to try to make sure the drug is administered correctly so patients don't die and the wrong patients don't get it, so the patients don't have birth effects.

If you don't look at the goals -- because my concern is that we are mixing the risk of diversion of the drug for illicit use with the concern that patients may not be using it appropriately, which most of us would argue underuse is the biggest problem with opioid prescribing, with the risk of the societal concern about addiction, and we don't even know whether or not prescribed drugs coming from physicians is going to be a source of sustaining addictive behaviors.

With regard to education on that area, that guides how you educate. I mean, I get really nervous when we talk about competence based prescribing, only because it's my opinion that NSAIDs are probably much more dangerous of a drug than opioids with regard to abnormal prescribing patterns, and I doubt seriously whether, politically or otherwise, people would agree that we need to have competence based education for a prescription of ibuprofen, even though I would argue that it's

probably more important to teach people how to prescribe NSAIDs correctly.

So wrapping it up, lastly I just wanted to mention, when you talk about a monitoring program listed with a risk management program, my concerns are that we are -- this community is tending to combine again, like we talked about yesterday, real society needs that for prospective observational studies to get a handle around these issues which really ought to be investigator generated, NIH grant supported stuff, as opposed to things that we ought to expect pharmaceutical companies to do.

I guess -- I just want to share that concern. We really need to know about addiction. We need to know about these things, but how much is appropriate with regard to monitoring for safe use, and how much is monitoring for diversion? I just wanted to express that.

ACTING CHAIRMAN KATZ: Please.

DR. LEIDERMAN: I just wanted to make one comment. I'm really glad you finished up by mentioning safety, because I think we've moved a little bit too far into the sort of criminal or "diversion" arena and need to place this squarely back in the safety realm. And if we even go back to some

of the cases that -- the examples that Dr. Hertz described, many of the signals that began the reassessment of the drugs' proper use were, in fact, death.

Let's talk about that, not being sold on the street and DEA coming to us and saying, you know, gee, we are really concerned about this street problem. We are talking about initially a patient becoming dependent and overusing and dying or a child and a family that contained a patient who was legitimate prescribed it dying.

So let's kind of bring that back to the medical risks. I just want to clarify. There is certainly lots of different interpretations and definitions of the terms abuse and addiction and the way DSM III or IV or another community may use these terms. It's going to vary enormously.

I'd like to come back to -- I think we can all agree on abuse or misuse, and one of our big concerns, of course, is the individual who experiments with -- Again, potentially these are very potent drugs -- for the first time in the wrong setting, and dies or suffers serious sequelae.

So let's come back, I think, to that public health framework.

ACTING CHAIRMAN KATZ: Mitchell?

DR. MAX: I agree with Mike's point, that I see two different types of studies. One is the unit, is the patient evaluation. That's a long term, say one year evaluation of individual patients of a particular diagnostic group, evaluating their benefits and risks, including behavioral effects of the opioids.

The second, a different type of program, is this kind of risk management where we are really looking for fiascos, you know, at the level that you could pick up with the electronic record.

The one thing I want to add on that is that -- Dr. Levy is gone, but I think the state board people -- they are so impressive in what they have given us. They could be some of the people to define the endpoint, because they are so committed to taking whatever we learn from that and working with it.

So that should be that -- That could be that risk management experiment looking for gross diversion fiascos.

The third point is I guess I agree with you, Mike, that in the ideal world NIH should fund a lot of these long term issues, but let's face reality. With Oxycontin screening on every news page, NIDA

doesn't even devote a penny to set aside for this research we need.

So I think it's going to take so long. I think, at this point FDA has the authority to get companies to start funding some of the research and, if NIH wants to come along and chip in, great. But I wouldn't hold my breath.

ACTING CHAIRMAN KATZ: Dr. McLeskey, fortuitously it happens to be your turn to speak.

DR. McLESKEY: Well, I wanted to respond specifically to a comment Dr. Hertz made when she stated that she was seeking the cooperation of industry. And although I am employed by only one member of those industry -- of the members of those industry, I think I can speak for all of the industry in saying that we do want to cooperate.

We are interested in advancing health care and, if what you are describing is a component of that, we want to participate in that with government agencies and potentially with individual practitioners and so forth as the science is advancing.

On the other hand, I like the way the discussion is going, and I want us not to lose perspective of the thing again that Mike Ashburn said just a moment ago, that underserving our patient

population or underprescribing is probably even a greater risk. We want to keep that foremost in our minds.

Also, you mentioned the issue of addiction and abuse being considered a safety issue. I think we all would perceive that as new knowledge, growing knowledge. It's like the QT-interval phenomenon where we didn't look for that years ago. We didn't know that was a safety issue. Well, now we do, and we test for it.

If we as a consensus group come to the conclusion that these kinds of issues really are safety issues and need to be looked for, then so be it, and we potentially should be looking for them. But on the other hand, again I just want to offer some caution, some caveat.

Dr. Portenoy before he left mentioned the fact that how can we keep politics out of this. Could we employ some kind of expert review so that whatever it is that we are looking for is a consensus agreement that something is valuable that we are looking for.

Then finally, can we -- Whatever it is we are looking for, can we make it less cumbersome or cumbersome to a degree or to a minimal degree so that investigators aren't inhibited in the performance of

these various studies, and clinicians who eventually prescribe the medications aren't overly inhibited, and the manufacturers aren't put in a box and eventually patient use of the product also is not so limited that we lose perspective of our first and foremost challenge here, which I think is to make sure that our patients are receiving adequate quantities of whatever the medications happen to be.

ACTING CHAIRMAN KATZ: To follow up on that point, Dr. McLeskey, since we are talking about things that will cost industry money potentially, I wonder whether it would help increase attractiveness on the part of industry to participate in these ventures if the program, while it was simultaneously potentially identifying harm, was also at the same time identifying areas of undertreatment or underutilization of medications? What's your reaction to that possibility?

DR. McLESKEY: Well, it sounds good. If you could be a little more specific, that would be helpful.

ACTING CHAIRMAN KATZ: I can't, but I'm open for anyone else to be more specific. Well, let's see, who is next? Actually, Dr. Schuster, you were next on the batting order.

DR. SCHUSTER: Well, first of all, I'm glad that we are attempting to distinguish between what I've termed iatrogenic dependence and diversion into a drug using subculture, because the risk management strategies that one would use for these two are, in my opinion, very, very different.

I think that -- To move back, I think that there is no question of the fact that we have to begin with insisting that pharmaceutical companies provide educational materials both to the patients and to the physicians who are going to be prescribing any narcotic analgesic that has the potential for overdosage death.

I think that we need to think about what we routinely do in methadone maintenance clinics, and that is with patients who have take-home privileges, we do in fact ask them to secure them in a locked place in their home so that children cannot get them and overdose and die.

I think that these are reasonable things to do, and I think that it's a given that these should be done. I don't think they place any great encumbrance upon anyone, and they certainly can help to both sensitize the physician to the dangers and the patient to the dangers that these medications present

to others in their family.

I'd like to move, though, slightly to the issue of how we can best detect diversion into the drug using subculture as an area, and suggest that one of the things that we need to have -- and I hesitate here, because some of my pharmaceutical company friends may not like this. That is that we need to be able to detect new products in the urine of people.

Having a drug detection system would allow us, for example, in drug use treatment programs around the country with new patients that are coming in to determine whether or not this is -- whether we are picking this up in these substance abusers.

I know that in one post-marketing surveillance program this was done in professionals who were being monitored, and as a consequence, if it were detected in their urine, they would be advised that something that shouldn't be there was there, and it rapidly disappeared.

So the bottom line is that having a means of detecting this in bodily fluids and asking the pharmaceutical companies to provide this might not be a bad idea for us to be able to monitor whether or not this is being abused.

I would also say that those of us who run

detox units are in a unique position. We've just finished a study in which we have looked over the records of about 750 detoxes for opiate dependence, and about 27 percent of them are for marketed opiate analgesics.

Well, we didn't ask the question, where did you get these? I would say that now, you know, I'm sensitized. We are going to now -- In all of our intake forms, we are going to be asking the question were you prescribed these medications, etcetera?

So there's a great deal of data that could be derived if we were to get a system that's sort of like DAWN but utilizing a representative sample of detox programs around the country that could look for the presence of these substances in urine and, as well, for those patients who report these as a substance abuse problem, learning about the means by which they obtained these drugs.

ACTING CHAIRMAN KATZ: Yes. We've also found it very profitable to speak frequently with our detox centers to find out the other side of what we are doing.

Dr. Anthony, you are next.

DR. ANTHONY: Thank you. Just three points on the issue of self-report. This is something

that I struggle with all the time, and I'd like to -- I'm not sanguine about my ability to change fixed beliefs about anything in a short intervention, but denial seems to me to be a state rather than a trait.

Part of our problem is determining the conditions that will influence accuracy and completeness in the reporting of clinical features of the syndromes of interest and to account for both false alarms and falsely negative claims.

So the conditions under which the National Household Survey on Drug Abuse gathers its data are ones that are relatively optimal for completeness of reporting. For example, people of my age, 80 percent of them will report that they have used drugs illegally in that context.

It doesn't seem to me terribly plausible that 100 percent of people my age use drugs illegally, and the value has to be somewhere close to 80 percent, given what we grew up through. So there are conditions under which self-reports can be made to be accurate, and certainly there are conditions under which they cannot be.

I think this may be something that, when we are talking about post-marketing surveillance, we will have to include self-report measures in almost

all of the large sample studies that we do. So rather than discounting them, I would rather approach the problem as ones of optimizing the use of self-report measure and then accounting for false alarms and falsely negative reports.

On the topic of language required to talk about the problems that we are discussing, I created and direct a program that tries to encourage families to get people into treatment as early as possible, once they start developing problems. I find that the language of misuse and abuse and addiction is not only unhelpful but counterproductive in that context.

A public health approach really demands that we are very careful about the language that we use. "Risky sex" has been something that's been rather successful in the public health initiatives about HIV and AIDS and sexually transmitted diseases of earlier eras, and it may be useful to talk about risky drug use or -- You can come up with whatever terms you would like, but paying attention to what you are trying to do with the patient and trying to get them to come in earlier and identify problems earlier -- paying attention to language is crucially important.

I would argue that the terms addiction,

misuse and abuse are absolutely unimportant and counterproductive in a public health approach.

The third issue is this one about the strategies for -- the earlier one that I logged on the agenda, and you may want me to postpone that until later. I can deal with it now, if not.

ACTING CHAIRMAN KATZ: Go ahead.

DR. ANTHONY: Okay. My colleague on the left here, Dr. Schuster, and I think first met one another at an FDA hearing like this one in about 1978 when I came in and suggested to the Drug Abuse Advisory Committee -- I was a wet-behind-the-ears assistant professor, and I suggested to the Drug Abuse Advisory Committee that in order to evaluate their current regulatory approaches to controlled substances, they would have to design methods of doing randomized experiments and that, without randomized experiments either at the city level or at the state level, they would not be able to answer the questions they wanted to answer about the effects of scheduling drugs in one level or another.

I'll repeat that recommendation again some 20 years later and say that we actually do with your 17 states that have electronic reporting systems, the 21 states that are covered -- I'm sorry, the 21

metropolitan areas covered by DAWN -- the increasing cooperative environment between the Federal regulators and the state boards of pharmacy and medicine, we have opportunities to do experimentation on a limited scale, at least early in the introduction of products, on different forms of risk management strategies.

I would hope we wouldn't discount experimentation as an approach to learning more about what we should or should not do, in order to speed the availability of safe and efficacious products to the patients.

The other side of this is, if it is really true that experimentation is not possible, then I would recommend taking a look at a book just published by the National Academy of Science National Research Council panel I served on that essentially talked to this issue at the level of Federal drug controls on cocaine and marijuana and other drugs that are not in the purview of the prescription realm but are on the street.

There is an alternative, which starts with simulation studies and then system research approaches from econometrics. I do think, particularly where we have data systems like IMS, American Provides and other data systems, the RADAR system that Pharma

Purdue is developing, and the like, the are opportunities for systems research to model within the context of error and sensitivity analyses what will happen under different constraints.

The constraints can be increases in cost to the doctor. They can be increases that is more time the doctor has to spend on the problem. They can be increases in the price of the drug. There are different intervention elements that can be modeled.

The results that you get there have limitations of the same type I was mentioning earlier about surveillance data. But if in fact experimentation is not -- formal experimentation is not possible, we don't have to throw in the towel and say, well, all we are going to get is a before and after study and never know whether it was regression to the mean or something else.

We have alternatives with advances in computing and processing speed. They are now at our fingertips where they weren't available 20 years ago when I was talking, and I suggest you look in that direction. Thank you.

ACTING CHAIRMAN KATZ: Thank you very much. Dr. Roberts, you are on deck.

DR. ROBERTS: Thank you. Well, we began

this part of our discussion by asking if there were metrics or outcomes measures around addiction that would be helpful.

My conclusion is no, and the reason I say that is that the special groups that have worked on this that are the experts have only in the last couple of years come up even with a definition of what addiction is, much less tested it for its validity and utility.

So to be somehow, you know, holding a product manufacturer accountable for some outcome on a gold standard that's not even been proven to be gold or tin or brass or whatever, I think, is a little unwise.

I have also learned during these two days that the predictors that we have for this bad outcome of a diversion are not very good, that your risk is somewhere between one and 47 percent, but even if you are in the 47 percent group, you may still have a legitimate need for the medication.

In some ways, the FDA has traditionally handled that problem of prediction with the indications on the label. That was when you were supposed to use the drug, and it's pretty fuzzy stuff right now.

I very much agree with Doctors Foley and Anthony that we would probably be better served by recommending a change in the language that we use and focus more on issues of the behaviors -- in other words, diversion as opposed to using the medication for its intended -- and maybe we need to come up with some new acronym.

Maybe we would use something like MURBS, Medication Use Risk Behaviors, and we can call them MURBS instead of PURBS or whatever it be. I also think you have a real denominator problem here, as was pointed out, in that it's not just, you know, how often do bad things happen against how many times the medication is prescribed. It's also how often was the DEA smart enough to find all the bad things happening, because there are probably lots of folks that never get detected that are diverting all over the place.

So it does come back, to me, to the whole issue of safety. I tend to think of this sort of at two levels, the individual prescriber and then a public level.

For the individual prescriber, as I said, I spent most of my career trying to change physician behavior through guidelines, research and things that I've done. What I've learned from that is, while

continuing education is not the answer, you have to start there. It's like turning the soil and planting the seed, but you got to keep watering and fertilizing and doing all the other stuff before you get the crop to come in.

Once you've got it rolling, hopefully in the right direction, you have to reinforce it. That means point of care tools that the clinician can use right at the point of taking care of the patient. That often means in most doctors' offices getting the nurse to do it, because then you will be sure it's going to get done. That means creating feedback loops so the doctors know where the mean is and can regress to it.

I have a little bit of concern about registries, because again one thing I've learned these two days is, if we have a problem, it's with underutilization, underprescribing, and there's enough stigma attached to these medications that registries, I think, are going to scare people away.

Now most docs expect that they are probably on some kind of a registry. I don't know if we are or not, but I think most of us figure we probably are, that somebody is tracking our DEA number out there somewhere. So it doesn't bother me that you

are looking at my patterns or what my pharmacist is doing.

It does bother me as a potential patient that you might be looking at me as an individual. So that makes me a little bit nervous, and it's one thing to think about.

The other thing I would be concerned about as we think about Phase IV trials to monitor this stuff is, if you put too many barriers in the way of just getting the job done, you are going to dissuade people from perhaps even seeking care.

What I mean by that is in the average family/doctor encounter, average patient, all comers, there are eight major problems to deal with every visit on average, and I'm not talking, you know, left ear, right ear as two problems. I'm talking heart, lung, kidney, depression, whatever.

My experience with people that have chronic pain syndromes is they got lots of other problems. They are depressed. They have heart failure. Their knees hurt. I mean, it's one thing after another. If you make this too complicated, you're not going to get them coming in. They are going to be, you know, figuring out some other way to take care of their problems.

So I think at a public health level, as we move to that level, the thing I would really encourage the agency to do is to consider some of what has worked.

You know, if you look at the history of tobacco use in this country, it's really interesting that in the Sixties when the Federal Communications Commission required equal time advertising and you began to see anti-smoking messages on television for the first time, it was the first time since the turn of the Nineteenth to Twentieth Century there was actually a decline in smoking.

California has seen this with their tobacco tax that's gone into counter advertising. Maybe one of the things to do as a part of the marketing of products as companies increasingly use OTC advertising as one of their strategies is to compel them to have a fairly precise message that really focuses people on the potential concerns around diversion, whatever the issue is.

Frankly, most of those OTC ads right now -- You know, if it's a 30 second spot, you get 26 seconds of somebody running through a field of flowers, and then you get four seconds of some auctioneer saying, oh, by the way, your hair can fall

out and you can die and this and that, you know.

So let's get people to focus and be a little more prescriptive at a Federal level on what we are going to allow the companies and their advertisers to say.

ACTING CHAIRMAN KATZ: That's it?

DR. ROBERTS: God, I hope so.

ACTING CHAIRMAN KATZ: Jeff Bloom, you were next.

MR. BLOOM: Thank you. If I could be so bold as to try to tie together a lot of points that people have brought up. Seems to me that there is certainly widespread agreement that one of the issues is undertreatment, not overtreatment, of people currently.

One of the other issues is post-marketing and safety. The other issue is risk and risk management and, of course, the biggest issue of all, of course, is who is going to pay for this, and how do we get industry and, obviously, NIH is not going to do it.

I would suggest that there is a mechanism in place that the FDA does have experience with and that they are currently working with now and may be the appropriate mechanism to be doing this research,

and that is the CERTS, the Centers for Evaluation and Research in Therapeutics.

Industry has experience in working with them. The FDA is working with them currently now on post-marketing toolkits for risk management for other drugs that would have similar things. They are very good at -- Dr. Portenoy mentioned the QT-interval thing, and that is something that the CERTS discovered through their research.

Perhaps that is the appropriate place, and that is funded through AHRQ, which does not come out of FDA's budget, which is also another plus, and it's university based, and they are up and running. So it's not reinventing the wheel, and it could be a very good mechanism to do a lot of these things and capture a lot of the information, because they can serve a multi -- It could be multi-factorial in their approach, and they have the skills to do this. So it's not something that they would be starting from scratch.

ACTING CHAIRMAN KATZ: Comments from the FDA about that potential funding mechanism?

DR. KWEDER: That is a potential, and right now to my knowledge none of the specific centers that are funded have expertise in this area, but that

is something that could be looked to for the future.

Many of the things that they are looking at, though, are related to some of the things that we have been talking about regarding risk management, such as what are the factors that influence prescriber behavior, what kinds of outcomes should be measured, how do you develop metrics that will get you the information you want.

That would be translatable to this area, but perhaps discussing with the CERTS, expanding their thinking to include some of the specific questions in this therapeutic area would be useful.

ACTING CHAIRMAN KATZ: I'd like to introduce another dimension into this discussion. We've had a lot of discussion about what a potential risk management program could look like, what a light one could look like, what a heavy duty one could look like, the sorts of things that -- the sorts of constructs that it could be trying to address.

We've certainly heard a lot about the potential risks of the risk management program and the ways that it could go very wrong in terms of not having a clear goal, a clear conception, a clear feedback loop such that it could be modulated as time goes on to not be -- need to be a living program, as

Dr. Haddox stated earlier, false alarms.

There are all sorts of ways that it could be gotten wrong. So we've had a long discussion about what potential risk management programs could look like.

I wonder if we could talk for a little bit on when it would be appropriate to think about a risk management program, since we have not really hit that question. If another mu agonist comes on the market, do we need a risk management program for that? Should one automatically be there for every new mu agonist?

Should it be just for new different kinds of opioids, new delivery systems, delivery systems of types that we don't have a lot of experience with as opposed to types that we do, when we are anticipating launching it into populations that may be more vulnerable? When should we be thinking about changing the way things are being done already?

Comments about that? Actually, Dr. Foley, you were on deck for the next comment. So if you would like to address this, it's your turn.

DR. FOLEY: I would, but again I keep arguing for information. I think one of the ways that would help us try to make the decision about the next drug that comes on the market is to ask the FDA to ask

the DEA to give them the real data about where this is coming from and to give any resources we need to the DEA to figure out where this problem is from; because I think we are very, very confused about where it's coming from and, therefore, we can't create the risk management strategy that we need to.

That would be my sort of first strong sense, that any new drug coming out would be based on the past history. If you looked at the MS Contin or all of the slow release -- or controlled release morphine preparations, you would not have predicted this would have happened.

So you enter this without having predicted this. Now you have this, and if you want to predict the next one, then we need to know what the issues were, and we need to know how much is this issue of the drug moved somehow or other into a diverted market and then being widely distributed, and how much it has anything to do with pain, anything to do with patients, and anything to do with the medical arena.

I think we are just lost at this, and I think it's been broadly represented to the media, to the FDA, to all of us, in a very mixed way. Somebody has to get a handle on this to be able to develop the right kind of policy, because I think we may be

wasting a lot of time on the wrong policies, and I would want to call that to attention as the sort of first issue.

ACTING CHAIRMAN KATZ: So it sounds like what you are saying is that, to the extent to which a risk management program is targeted toward addressing the specific issue of diversion to nonpatient communities before we run ahead and start recommending risk management programs, we ought to look harder at the data that we already have and speak more to first determine whether or not it really ought to be something that we should do.

DR. FOLEY: Yes. I think there is no question that any physician who is prescribing an opioid in the setting of understanding what an opioid is, understanding that it's a controlled substance, understanding that it's a Schedule II, understanding that they have to have a DEA license -- those physicians already know a lot of information.

So I think the question is what has gone wrong in this? And if it has nothing to do with that group of individuals but with a whole other marketplace out there, then putting more emphasis on that group isn't going to get us anywhere.

ACTING CHAIRMAN KATZ: Now as we have

heard from a number of other folks around the table, including Dr. Reidenburg who reminded us about the patient oriented outcome being a central focus, patient safety, it seems like risk management programs could have multiple purposes other than getting at the diversion issue, which not in fact be the best purpose for a risk management program.

So to get back to the question I posed, when would it be appropriate to consider risk management programs specifically for the patient level outcomes issues? Let's see, who was next?

DR. ROBERTS: Nat, could I just jump in real quick, so as not to lose Dr. Foley's comment?

ACTING CHAIRMAN KATZ: Yes.

DR. ROBERTS: Well, this is very quick. It seems to me -- and this is the lawyer in me leaking out -- that one way is do this contractually. In other words, there are going to be some drugs that are brand new, innovative therapy, different delivery system. You're kind of nervous about it. You are going to probably say up front we need a risk management program.

There are going to be other drugs, you think, gee, this looks a lot like other stuff that we've already had; probably don't need a risk

management, but you put it in as a codicil to your contract with the company that, if these problems arise, then you have to be prepared to have a risk management program in place.

That, to me, seems a way to deal with Dr. Foley's concern about sort of doing this in a blanket way for every mu opiate that comes down the line.

ACTING CHAIRMAN KATZ: Is that feasible from a regulatory vantage point?

DR. RAPPAPORT: Yes, and that's pretty much what we've been doing at this point.

DR. ROBERTS: I knew it was a good idea.

ACTING CHAIRMAN KATZ: Dr. Reidenburg, you were next.

DR. REIDENBURG: Yes. My answer to your question is to do a risk management program. It's needed when there are specific risks that can be managed by such a program.

I think we are lumping a lot of things as if they are just opiates. For example, we talk about the special storage need and child resistant packaging, and certainly the problems for children and ferrous sulfate is well known and serious, and many of the cardiovascular drugs.

So the issue of protecting accidental

childhood ingestion is a generic one, and opiates are neither more nor less serious than many other drugs I can name.

Something that we didn't talk about that I do think is something to consider is the issue of medication sharing within a family. A person got a prescription for opiate-acetaminophen combination for trauma, shares with a relative following a dental extraction when what the dentist gave wasn't enough. Technically, this is diversion. Medically, I think most of us would turn our backs on it.

I'm worried that this whole idea of the germ risk management as we are expressing the concept can lead to excessive expectations, and that we are promising what we can't do.

Another example -- and here again, I think splitting, as we do in research, is helpful. Most of us have our DEA numbers printed on our prescription pads. We hear that this is wrong. If this is really a problem, then what we need is a program to get us physicians to stop printing our DEA numbers, if that's a source of diversion. Yet I don't hear any of that being considered in the risk management that we are talking about.

We've been talking a lot about the need

for all kinds of research, and yet the ERISA requirements for patient confidentiality to be implemented this year gives us a whole new level. It's one thing when we are talking about getting information for law enforcement or requirement regulations, but where we are talking about research, then we really need to rethink what can we do with the regulations of ERISA that we are all going to have to live with.

I think that this will influence a lot of these recommendations. As I looked at the list of things that Mr. Davis presented, as a physician if I have a legitimate patient who is doctor shopping, I don't have a way to know who else that person is seeing in New York.

As I go down the whole list, there isn't anything here that I as a physician have the capacity to be involved with, other than this criminal prescribing which is just criminal behavior.

So that these were the thoughts. The last thought I wanted to express is that an awful lot of what we've been saying these two days, particularly with respect to comprehensive centers and referral to groups, is establishing what I'll call a very ideal standard of care, but if that becomes the standard of

care, then there are an awful lot of people who, for either financial, geographic or other reasons, can't get it.

If we are saying that those of us that don't have access to this kind of a referral pattern shouldn't start, then we are really raising a barrier that I don't think most of us here mean to raise. I think we need to clearly differentiate what's the ideal care, what standard of care, and what's necessary for rational drug development.

ACTING CHAIRMAN KATZ: Dr. Schuster, you are next, followed by Dr. Max.

DR. SCHUSTER: Well, the question of when one should consider the development of a risk management plan, I think, has already been covered. Many of us have been -- Well, let me back back.

The College on Problems of Drug Dependence began 50-60 years ago, and it's goal was to find a nonaddicting replacement for opiate analgesics with equal efficacy and, obviously, greater safety.

It was a meritorious goal, and remains a meritorious goal, but obviously one that has not borne fruit. Nevertheless, I think that we have to think about the future where I would hope it would be, as has been already alluded to, the discovery of multiple

subtypes of morphine, opiate receptors, mu opiate receptors and other kinds of potentially new mechanisms for effecting analgesia, that we are going to be moving perhaps into an era where we have to be able to help the Food and Drug Administration to not reflexively put something into Schedule II because it has an opiate-like structure.

I would remind you that nalorphine has an opiate-like structure, too, but it's an antagonist. The point I'm making is that, if we are going to be trying to encourage pharmaceutical companies to develop either new preparations or new moieties that are going to have analgesic efficacy, we have to be in a position to think about methods that will allow the Food and Drug Administration to say, okay, well, we'll consider putting this one in Schedule III as opposed to II, but we are going to have to really follow it very closely to make sure that we've not made a mistake.

That's the kind of program that I think is important, because industry -- if they can't get a marketing advantage, they are not going to try to continue to develop new products that are going to be safer from the abuse viewpoint.

I think that that's a direction I would

encourage us to think about in terms of risk management and what kinds of risk management procedures we could have that would allow the FDA to think about even lower scheduling for these substances.

ACTING CHAIRMAN KATZ: Dr. Max?

DR. MAX: Well, let me continue on Bob's theme that a carrot is better than a stick. If you meant by risk management program one where you really look for diversion and disasters, I think Sharon already said that they are just going to do that if there is already evidences of big blow-up. That's the only time they are going to make the drug companies do that. However, if what you mean by risk management, getting some data where none exists now about at one year in the broad population what's the balance of benefit versus impairment of function from opioids, I would propose that for every opioid that comes up, the FDA try to establish a carrot by considering a several tier labeling system using as a model the rheumatoid arthritis guidelines where, if they want to spend extra money to do a few million dollar study to follow a lot of people over a year, they can be the first product to label that we know this is beneficial long term.

You know, I think this would take a lot of work, because it's different. The rheumatoid arthritis guidelines were constructed in a setting where there's a mature research field, and they know how to measure joint erosions and do clinical trials.

This is an area that is a just beginning research field with very few junior investigators, and it would need a lot of validation. So this would take a lot of pilot studies and working out, but I would propose this for every product with a several tier approval system.

ACTING CHAIRMAN KATZ: Could you describe the rheumatoid arthritis labeling approach in more detail?

DR. MAX: I just know about it from one talk I heard Jim Witter give. He said that there was a meeting, a long term task group in the people that are interested in arthritis in CDER, CBER, and Devices, and they constructed five different levels of labeling, of which only the first two have been reached by anyone.

The first level, you need to do, say, two trials of an anti-rheumatoid arthritis drug, and make people have less pain or feel better, with a short study.

Jim, do you want to tell, or Lee?

ACTING CHAIRMAN KATZ: Anybody ever see that Woody Allen movie where Woody Allen is talking to somebody online who is saying some nonsense about the movie, and then he happened to have the director right here, and he pulls him out of the background. I never thought I would see a real life example of that until now.

DR. WITTER: Good afternoon. Yes, Mitchell and I have talked about this in the past, because we have a mutual interest in several things.

The RA guidances -- I think he's got it pretty much straight. There are various claim structures, and the thinking behind it for rheumatoid arthritis were to act more as carrots, as he said, versus sticks.

So it's a structure that builds. For example, the first approval is on signs and symptoms, because based upon what we know about compounds in this area, that's achievable for most compounds, and it's a clinically important outcome.

Then since we have a good understanding, or did anyway, about other outcomes such as structural damage, that then would be a separate claim. Trials would be longer. Outcomes have been specified, and

sponsors, for the most part, have gone after that. So we are getting more robust data. Again, this is going for a disease modification idea.

Then other kinds of claims that are built in, for example, prevention of disability, remission, again looking for most robust datasets, longer datasets, but also different kinds of patient outcomes.

So I think what Mitchell is getting at is, if we could do something similar in the analgesic spheres where we could get to an agreed to consensus on what kind of outcomes those should be, then how could we develop the carrots at the FDA to kind of accomplish that.

ACTING CHAIRMAN KATZ: Any other FDA comments about how that system worked for rheumatology?

DR. SIMON: Since I'm a new kid on the block, I just want to make sure that everybody knows that I'm Lee Simon. I'm the Division Director for 550, Analgesics, Anti-inflammatories and Ophthalmologics. It's either Ophthalmics or Ophthalmologics. I'm not sure.

I think that the structure of the RA guidance document is really a very lovely model. It

is also something that needs to be seen as an evolving model. It was written at a time when we had little evidence, but we thought these are the ways to go.

In that it has been used as a reward system for the pharmaceutical industry, the sponsors have actually allowed us to now create and collect data that allows us to now, using evidence, reevaluate where we are at.

In fact, we are quite thrilled with the datasets that have allowed us to understand the signs and symptoms, which is what people come to see us about, meaning they are hurting. They have arthritis. They need to be treated for that.

It has also allowed us to understand the destructive nature of the disease and how we can modify it. So for the first time, we actually have drugs that are labeled as being true disease modifying drugs by either retarding or inhibiting structural damage.

We are still grappling with the issue of the health related quality of life measures, since I'm not entirely sure I understand what health related quality of life means nor how to measure it as opposed to disability or preservation of function.

I think that the kinds of things that we

would like to see happen in the analgesic arena are extremely similar. We would like to see layers of approval that would allow the sponsor, the FDA, the academic environment, and the other stakeholders such as patients to learn more about how the therapies actually take place.

ACTING CHAIRMAN KATZ: Are there FDA comments about that approach, in particular how the reception was by industry to that approach?

DR. SIMON: We actually were urged into this approach by industry. The sponsors felt that, if we were going to grapple with the idea of applying various different indications like this, a -- they had input into this, because they were involved in the creation of the guidance document.

The process actually responded to what they perceive they could achieve, and because it was a carrot, it became very competitive. The idea was between sponsors that one drug might be actually able to look like this versus that. So that now we are actually able to distinguish between nonsteroidal anti-inflammatory drugs those vaunted anti-inflammatory analgesic agents and drugs that actually treat disease as opposed to just signs and symptoms.

So without such a guidance document, we

would still be stuck in a realm of having equal therapeutics, theoretically, because of their approval, yet really doing very different things.

So I think sponsors have really been quite appreciative of it.

ACTING CHAIRMAN KATZ: Mitchell, since you brought the whole thing up, I wonder if you could take a moment to speculate about how such a hierarchical labeling procedure might look for opioid analgesics, and then, Dr. McLeskey, I would be interested in your reaction to that proposal.

DR. MAX: I think this is a very hard thing which goes beyond my clinical expertise, but I would think that the most important thing for a claim at, say, one year is I think you need some degree of controlled experiments where you see if people are better off being on opioids than if they were just on, you know, multi-disciplinary pain therapy for back pain.

You need a controlled experiment, number one. That would let you see if there tolerance wipes all your effect and you are just left with a physically dependent person in the same boat they were in before they started.

It would take a lot of thought into

deciding what the patient spectrum is. Probably you should say what you claim is what you study. I think it would be very -- You asked here whether you should include people who have a history of substance abuse. There are probably ten or 20 percent of people who have a history of substance abuse, depending how you define it. It could be a big market, but I don't know if -- It might not be every company's cup of tea.

I think to have a measure of function that would be -- You don't have to call somebody an addict, but you can assess -- or you want to know -- Some of my patients just take more and more drug, and they lie around in their bed and watch TV and can't do anything else. You can tell that from going to work and being perky easier than if they are an addict or not.

Yes, I think there would need to be a program where we got the best -- encouraged the best in academics to try to -- but that would be up to industry, if they are funding it, to have a lot of small pilot studies, a lot of validation studies. But I think probably the market and the race would solve a lot of it.

I think, you know, to assess the best of these things, I'm not sure the agency would have the personnel inside to be able to assess the fine points

of it completely. So you would -- You know, you would get help when you needed it. But those are my only thoughts so far.

I also want to mention, over lunchtime I talked to a few of the higher level people who produce these drugs, and I said would you be wanting to spend a lot of money to do great science and go for an additional labeling that you could promote, and they said absolutely, as long as we didn't go broke, you know, during the design.

ACTING CHAIRMAN KATZ: Dr. McLeskey, any reaction to the concept of a hierarchical labeling procedure similar to the rheumatology drugs in the setting of opioids?

DR. McLESKEY: Well, I am familiar with the rheumatoid arthritis model, and I believe all of us would respond positively to a carrot rather than to the stick approach. So we would encourage that.

The concerns are, though, that our understanding of the analgesic effects and addiction far lags behind our understanding of the disease process associated with rheumatoid arthritis. So again with that as a caveat, then how could we move forward?

This is such a diverse area that, if

anything like this were to come about, I would encourage a working group with multiple of the pharmaceutical industry players involved, because I'm sure not all of us would be thinking exactly the same along those lines, and maybe then some kind of a guidance document could be created. But I think it's a good idea, but my concerns are we just don't know enough about the field to make it practical yet at this point.

ACTING CHAIRMAN KATZ: Dr. Smiley, I've been keeping you on hold for a little while. Your floor.

DR. SMILEY: I'm trying to remember what I was going to say. I will make it short.

I'm actually sort of gratified with the last couple of comments. We moved from this discussion of the structure of risk management schemes. Dr. Foley just left, but I want to emphasize from someone who is not an addiction person or particularly a pain management person that, sitting here all day, it's actually been rather frustrating, almost getting a little angry trying to figure out why I'm being asked or why we all even are being asked to come up with suggestions on managing the risks when law enforcement or the FDA or anyone can't even tell

us whether the problem with Oxycontin was, you know, five docs in Kentucky writing thousands of extra prescriptions or, you know, five truck hijackings or what it was.

So the idea that -- I mean, I think Dr. Foley said this very clearly. So I won't say it anymore, but it is actually kind of frustrating to be put in the position of being asked to solve a problem that can't even be defined to us.

I can't solve problems that I understand. So I certainly can't solve problems I don't understand and can't be given the facts on.

Then I guess in the same context, my only comments of the afternoon then will be that I am concerned that there's a tendency when evaluating risk management strategies -- there's only one success in the kind of context we are talking about, and that's no diversion, very little abuse.

There really -- Despite nice words that some of us say, it's very unlikely, in my mind, that an evaluation of risk management strategy will include how well are patients doing and is the drug being restricted too much.

There is a tendency, and this certainly is an issue in lots of other areas of our national

consciousness this year, to sacrifice freedom and even efficacy for security. I think we need to be concerned about that, and I know I am.

ACTING CHAIRMAN KATZ: Sounds like you are echoing Dr. Portenoy's concern earlier.

I'm prepared to leave the risk management arena unless folks from FDA have any continuing questions on that. Have we done a job on that question? We could move on to the other questions that were originally outlined for this afternoon.

I wonder if maybe, Bob, you could give me a sense at this point of how much more information you would find helpful for today on the clinical trials issues and the prevalence issues that are questions 1 and 2 on our page today.

DR. RAPPAPORT: Well, I think that the -- Which questions are you talking about? You're talking about the ones I gave you this morning or the --

ACTING CHAIRMAN KATZ: No. There's this question Number 2 about discuss the methods for assessing and monitoring addiction in the clinical setting; should these be extended to the clinical trials. That's something that we haven't really spoken about. I'm not sure how --

ACTING CHAIRMAN KATZ: No, I think briefly

bring that up. That would be useful, yes.

ACTING CHAIRMAN KATZ: Let's move on to that then. I'll reread that question, since I just mumbled it out a moment ago: Discuss the methods for assessing and monitoring addiction in the clinical setting.

I think we have already spoken at length about that. Dr. Passik spoke to us about that. I alluded to the difficulties of self-report and the possibilities of urine toxicology and other options.

Are there methods that may be extended to the clinical trials setting? So I guess in my mind, what this question is getting at is that, if there are negative outcomes that we are concerned about on a patient level with the prescription of opioids, specific safety issues on a patient level, are there ways that we should be monitoring this in the clinical trials setting that we are not doing right now?

Dr. Schuster?

DR. SCHUSTER: Well, two things. First of all, although it is not -- These are simply indications. These are not strong measures, but I think, number one, in most clinical trials people are provided with extra medication in case they happen to drop their current supply down the toilet. Does that

happen to a greater extent with this medication than it does with placebo? Simple -- you know, I mean, it's easily done. That data is easily collected.

Secondly, at the end of the time that the clinical trial is over -- Now I have to confess that here I don't know -- Because these are opiate analgesics and they are being used for the treatment of pain, this complicates life for me.

Often with other classes of drugs, we not only look for signs, in quotes -- and I know that physical dependence is not addiction, and I'm quite aware of that. But we could look at least as a subset of individuals, at whether or not there is the emergence of a withdrawal syndrome. That includes strong drug craving.

Now the problem here, of course, is that if the person is relenting to pain, it's unlike when I'm dealing with -- I'm talking about a different class of agents, and I realize as I'm saying this that it probably is not applicable in this setting. But the only time that we are interested in physical withdrawal is when it has a motivational component for drug seeking behavior, and if there is some way of doing that in a controlled fashion that is over and above that which is seen simply because of the

reemergence of pain, then that clearly would be an indication that this is a substance that we have to watch.

ACTING CHAIRMAN KATZ: So it sounds like you are saying that at a minimum, it would be appropriate to look at simple compliance metrics that are collected anyway, and then if one wanted to go beyond that, you would think about monitoring for withdrawal craving, that sort of thing.

Any other thoughts about how one could -- about the appropriateness of enhancing monitoring in the clinical trials setting? Dr. Roberts?

DR. ROBERTS: Well, I think it's important if the concern here is diversion, which is what I think we are talking about.

ACTING CHAIRMAN KATZ: I'm actually referring to specific patient safety issues.

DR. ROBERTS: Well, let me go on with that. I mean, if that is the concern, though, I mean ultimately, you have the patient before you who has been prescribed a drug, and the question is are they using it appropriately or not.

As we've heard time and again these two days, you may need huge amounts for an individual patient. So I'm not sure you can use any kind of a

benchmark against which to measure them. So I'm not sure urine levels are going to be helpful, because they are going to have the drug in their system. They are getting it appropriately prescribed.

The question is are they having to do other things behaviorally to get additional drugs, but again you still have the problem are we just undermedicating them? Is it pseudo-addiction?

So it seems to me that the bigger concern is other folks getting their hands on the drug that shouldn't have it in the first place, and that you are going to have to rely on things other than medical measurements, clinical measurements. You are going to have to rely on the criminal justice system and, you know, doctor shopping and electronic monitoring of what happens with the scripts.

So I don't think I can in the individual patient talk about addiction here, because all of what I've learned these two days is that people that tend to be addicted sort of come to the narcotics prescribing with their addiction because of post-traumatic stress disorder or they had a predisposition to addiction in the first place. It's not that they got this new drug for their pain as the cause of their addiction.

ACTING CHAIRMAN KATZ: Are you suggesting that we should more carefully track psychiatric or psychological comorbidities in opioid clinical trials for chronic pain?

DR. ROBERT: Well, I think it will help you understand this phenomenon we've called addiction, and yet I'm a little hesitant, as Dr. Foley and Anthony and others have said, to even use that term; because I'm not sure what it means anymore.

More importantly is, if the concern is having somebody use a drug inappropriately, that is going to relate to their behaviors, not to their clinical status per se, you know, how much drug am I taking. Well, if I'm actually swallowing all the pills that I'm supposed to be taking, unless I do it in a suicidal fashion, you're not going to know the upper threshold for my pain management. So that's a problem for you.

The other group, which I said may be easier to manage, you're going to manage through social measurements, you know, criminal convictions, DEA investigations, doctor shopping, prescription hopping, that kind of stuff.

ACTING CHAIRMAN KATZ: That sounded like a yes to the psychiatric comorbidities issue. Are you

also then suggesting that we track aberrant drug taking behaviors formally in opioid analgesic trials for chronic pain?

DR. ROBERTS: I would, and I wasn't being completely facetious when I talked about coining a new acronym, something like Medication Use Risk Behaviors, because that has worked well in the context of HIV disease.

People can understand when they do something that may put them at greater risk. That makes sense to people. They don't like being labeled, however, and that's what using terms like addiction does.

ACTING CHAIRMAN KATZ: Clearly, there are stigmatization risks that we want to strive to avoid. I think everybody in the room understands that. Anybody else feel that we should be tracking psychiatric comorbidities and aberrant drug taking behavior in opioid trials for chronic pain? Dr. Tobin?

DR. TOBIN: I think it's necessary that we do that and, secondly, to subcategorize the patients as they are entering into the protocols; because we may find that, either by specific diagnosis or having a parallel diagnosis, it is actually going to be the

predictor of the comorbid other drug use. Then secondarily, not only identify that psychiatric description or other comorbid diagnosis that exists upon entry. We need to have potentially some uniform, widespread screen of all the other potential drugs of abuse that we think those patients would be at risk to go coadminister, and measure them either by blood or urine levels.

That's a pretty far-reaching statement that is not very easy to accomplish. Talking about everything from acetaminophen, nonsteroidals, other opioids, amphetamines, tricyclics and on and on. There are probably at least two dozen different classifications there.

I think that those will be necessary to track in order to determine whether this new drug that we are actually trying to measure is evoking other behaviors.

I think the more expensive way is to put them in an inpatient hospitalization, and that's going to reduce our willingness to come in and be in the studies, at least many, and it's going to be a lot more expensive.

ACTING CHAIRMAN KATZ: Are you suggesting that we monitor comprehensive urine toxicology screens

as an outcome measure in opioid trials for chronic pain?

DR. TOBIN: I think I am.

ACTING CHAIRMAN KATZ: That wasn't as hard as I thought it was going to be.

DR. TOBIN: You asked a leading question.

ACTING CHAIRMAN KATZ: That's what they pay me the big bucks for. I want to continue to go in order. Jeff Bloom, you were next.

MR. BLOOM: Just before I get nauseous and I hear "doctor shopping" one more time, let me just say as from a patient perspective that there is this perception that people would doctor shop simply to seek drugs and for drug diversion, and there may be some situation of that. But there is also a situation, and this is a very real life situation for patients, where they have to doctor shop because they can't find a doctor that is willing to write them the prescriptions necessary to treat their pain adequately.

I will give you a perfect example, and I don't mind revealing this, and it's my partner who is on 900 milligrams of MS Contin, 450 of oxycodone and 100 -- 300, I'm sorry, 10mg Valiums a month, which is a very large prescription.

Now it doesn't take a genius to figure out that, yeah, you might have to go see four or five doctors until you find the right doctor to do that. In his case -- and then this might be a useful thing -- is he was put in the hospital, and it was found -- to find what was the level of appropriate opiate treatment to get his pain under control after being undertreated for many, many, many years. But this concept of people are just doctor shopping randomly to sort of just play around with medicine, I think, is insulting.

While there may be some cases like that, I think it's more frequently that there is a very real problem with patients having problems and doctors being very frightened over the DEA and their licenses writing those kind of prescriptions for patients that desperately need their pain to be under control.

ACTING CHAIRMAN KATZ: You're next. I just want to introduce one or two -- You're next, I promise. Let me blab on for just one minute.

I think you are raising a very important point, which is that all these things are really surrogate measures of what we are interested in. The aberrant drug taking behaviors, as Dr. Portenoy and Dr. Passik pointed out earlier, we're not really sure

exactly what those mean.

You know, if the patient is calling the clinic all the time or all these other things, is that a problem with the clinic, with their home situation? We don't know.

We just completed a study of 122 patients looking at their urine toxicology screens. It was all of our patients over a three-year period of time being treated with opioids long term for chronic pain. It was presented in abstract form a few months ago, and it's submitted for publication now.

We found that about one-third of our patients had what we call positive urine toxicology screens, meaning either an illicit substance, marijuana, cocaine, what have you, a nonprescribed controlled substance, another opioid we weren't prescribing, etcetera.

We don't know what that means. Those patients may have been doing all fine with their opioids. They may all have had a real addiction problem. We really just don't know. So by itself these things are surrogate measures.

We also completed another trial that was sponsored by a pharmaceutical company where we required a comprehensive urine toxicology screen on

entry, since one of the entry criteria was no active substance abuse, you know, whatever that means, and why ever we were doing that.

We found that about -- Despite a self-report of taking no other concomitant medications, etcetera, we wound up excluding something like ten percent of our patients because they in fact subsequently were shown to have a positive urine toxicology screen at the time of their incorrect self-report.

What does that mean? Does that mean those patients would have done less well, more well? We really don't know what these surrogate measures mean. So we have to be careful. But it sounds like there is a feeling like there may be a hint, a signal, maybe telling us something useful that needs to be evaluated further.

Dr. Parris, I'm sorry, I interrupted you before.

DR. PARRIS: Thank you. The comments of Mr. Bloom are well taken, and his partner clearly needed -- required the care and support of the medical profession. It's also important to recognize that there are some patients who use that very same principle, and they don't need that kind of care. The

task of the physician is to try to differentiate, and you can be wrong sometimes.

Now there are some patients who have given up on doctor shopping. The studies -- I think there was a study in New England Journal of Medicine in 1998 that showed that one in three Americans have given up on the medical profession and have turned to alternative medicine, and we don't know what kind of medicine they are getting from those alternative sources, and some of them may be getting opioids and other analgesics. Where is it coming from?

Are there other health care professionals prescribing medications that are not under the purview of the DEA or the FDA or whatever agencies? I refer to nurse practitioners or are there any other health care professionals writing those prescriptions?

So that's a whole area that we have not addressed, that of alternative medicine.

ACTING CHAIRMAN KATZ: Dr. McNicholas, followed by Dr. Max.

DR. McNICHOLAS: Yes. I would like to endorse the idea of doing a psychiatric assessment on patients coming in for clinical trials on opiates, for two reasons.

First of all, I think that one of the

things that has come up repeatedly over the past two days, and certainly in this morning's presentations, is not only with patients with substance abuse issues are you going to have psychiatric comorbidity. A lot of your patients with pain are going to have depression, anxiety, etcetera.

Perhaps some of those are maybe not in Dr. Portenoy's program but in other programs not being appropriately managed with things other than opiates, and perhaps treating their depression may decrease their reliance on opiates for their pain management.

So what we might do is get a better idea of what patients entering pain management treatment look like, so that we can better manage the entire patient.

The other thing that I would like to endorse is Dr. Tobin's suggestion that you do urine testing on these patients, because for one thing, if they are going outside to get benzodiazepines, other opiates, etcetera, something is not being attended to.

I think that you can use some of the surrogate measures that we normally use in some of our substance abuse trials to look at whether or not patients are inappropriately using medications.

You can use computerized tops to tell you

when the medication was taken. Was it taken on schedule? Was it taken early? Did they take it late? Sometimes what we find is the patient said I didn't think I needed it, so I just didn't take it on that one. That tells you something, too.

So I think that there are a variety of surrogate measures that you can use. Do they need take-home medication more often? Do they need rescue more often? Are they using, by computerized chips, the medication as it's prescribed, etcetera?

Just on the data that you presented on your patients, you eliminated ten percent of your potential subjects on the basis of a urine tox. What did you do for alcohol?

ACTING CHAIRMAN KATZ: I don't remember offhand, but my guess is that, if they had alcohol in their urine at the time that they came to the clinic, we probably would have excluded those patients as well. But I don't remember that for sure.

DR. McNICHOLAS: I keep hearing these things of six and seven percent for substance abuse. Jim, I think your data showed, what, 15 percent of the population at risk or with a diagnosis, a lifetime diagnosis of alcohol dependence?

DR. ANTHONY: That would be a little high,

but not necessarily for the pain population but in the general population, it would be closer to eight to ten percent. But active alcohol or drug dependence would be not ignorable. It would be two to four percent if you combine all of the controlled substances and alcohol together.

DR. ROBERTS: And tobacco, about 20 to 25 percent, if you want to talk about lethal drugs.

DR. ANTHONY: If you count tobacco, you're talking about 24-25 percent.

ACTING CHAIRMAN KATZ: So it sounds certainly like one of the suggestions that I want to make sure wasn't lost that you just made is that monitoring of urine toxicology screens during an opioid clinical trial for chronic pain might not only be a potential outcome measure, as Dr. Tobin said, but also would be a potential safety measure of safety of the patients during the conduct of the trial, and that's a very interesting point.

Dr. Max, you were next.

DR. MAX: Particularly in the longer outcome studies, I think, you should absolutely have a psychiatric evaluation, not only for stratification of risk to understand who has what risk, looking at mood disorders, PTSD, and so on, but also for the outcome

to see what opioids do.

I recall that in your four-month study of opioid treatment of back pain patients, there was a striking improvement in anxiety. So it was really -- You know, it was a really good anti-anxiety agent.

I would add, be sure to include the multi-somatoform disorder, a primary care somatoform disorder, because a lot of people would think that you should not treat people with multiple unexplained symptoms like fibromyalgia, etcetera.

ACTING CHAIRMAN KATZ: Any other -- Jeff Bloom?

MR. BLOOM: I just wanted to add a couple of things and endorse the point that she made.

One of the things about the psychiatric part that I think is extraordinarily important is, getting back to my partner again, he does suffer from PTSD, and he's a victim of childhood sexual abuse; and because of that, his pain threshold is much lower, and he experiences pain in a much different way, and it's not an uncommon phenomenon.

In terms of the way they work things, he's under a pain contract, and at anytime -- He is given a month's supply of drug, and he is going to be given a two-month supply of drug soon. But at anytime they

can call him up, and he can be called in at anytime for a random urine test.

That's part of the contract, but the contract is a two-way contract where the pain clinic has certain things that they assure him, and the patient has certain responsibilities, and it's a two-way street. In that way, it's not making it, you know, a good guy/bad guy kind of thing, but it's a mutual responsibility thing.

I think there is nothing wrong with that at all, especially in terms of those kind of levels of opiates.

ACTING CHAIRMAN KATZ: Sure. Dr. Chilcoat.

DR. CHILCOAT: A number of issues related to psychiatric comorbidity. Obviously, the data we showed today from, say, the National Comorbidity Study showed very strong associations, but it's hard to tell where the source of the drug, whether it was analgesics, whether it was diverted versus used -- prescribed by a physician and then the use took off.

One of the things we did find from that study of PTSD, which I just briefly mentioned at the end, we found support for the self-medication hypothesis, but we're not really sure whether they

were self-medicating or not, but there were two questions, two ways that people -- in terms of prescription drug use -- could quality for a diagnosis based on the instrument that we used, the Diagnostic Interview Schedule.

One was people who used the drug, were prescribed by a physician and then went on to develop problems, and then also people who used on their own and developed problems.

Both groups -- The probability of developing drug dependence, prescription drug dependence, was extremely high -- relatively high for the people who had PTSD versus not. So PTSD put people at risk, regardless of whether the dependence -- drug dependence was due to use as prescribed by a physician and then took off on its own or was used on their own.

ACTING CHAIRMAN KATZ: Just a point of clarification. I may have missed what you just said. It sounds like you were saying that from the database that you alluded to you could divide patients into two groups, patients with active dependence who were originally started on the medication by a physician in the medical setting versus those who started on their own. Is that correct?

DR. CHILCOAT: Yes. The question -- There's kind of two ways to get into the dependence questions, but one is basically people who -- If you don't use a lot of other drugs very much, one to five times, I think, you get sort of put into this. You do get asked about whether you -- were you prescribed the drug by a physician for treatment of pain, a number of different issues, and then if they did, then they ask -- there are some questions about using -- I can't remember the exact questions, but they then were asked about dependence related to the use of those drugs.

So you can start to -- It's not a perfect question, but there are some ways to sort of tease it apart in that particular instrument. But in other instruments like the Household Survey obviously don't separate out those uses, but we found that with the odds of developing dependence, regardless of whether it was prescribed by a physician or on your own, it was about -- for people with PTSD versus not, it was about, I think, 12 for the physician prescribed, then dependence; and then about -- I don't know, it was about 20 or so for the dependence on your own.

ACTING CHAIRMAN KATZ: Overall, of the patients who eventually developed dependence, what proportion developed it beginning in the medical

context versus beginning on their own in that particular database?

DR. CHILCOAT: Boy. I can't remember exactly. There weren't very many prescription drug abusers anyway in the whole sample. So it was probably -- I don't know, maybe two-thirds were on their own, and maybe a third for physician, something like that.

ACTING CHAIRMAN KATZ: Other comments about methodology for detecting these adverse outcomes that should be incorporated into the clinical trials setting? For example, should we be monitoring neuropsychological function routinely in opioid clinical trials for chronic pain? Dr. Schuster?

DR. SCHUSTER: Let me just ask one question, because I am not acquainted with how people -- either of the experts -- how you do long term clinical trials. It's been suggested that there should be clinical trials that look over the course of a year, and we're talking about psychiatric comorbidity.

You talk about stratification. Are we talking about treatment of those psychiatric comorbid conditions or -- We certainly can in an ethical fashion have people go for a year without treatment.

Are we going to ensure that the treatment is uniform across all the sites that these people are coming to, because if it's not, then you've got really troubles in terms of interpreting the interaction of that treatment with the outcome for the treatment with the analgesic agent.

What's the usual standard here?

ACTING CHAIRMAN KATZ: The usual standard is that patients with any significant comorbid -- The usual standard is that it's not even looked at. If it is looked at, that creates problems, of course, and patients with significant psychopathology are excluded from the trial almost universally in opioid chronic pain analgesic trials, although typically that's done by investigator judgment. Sometimes it's done by questionnaires.

If it is done by -- There have been instances that I can point to. For example, we just finished and reported a 690 patient study of a nonsteroidal anti-inflammatory drug for chronic low back pain where patients with significant psychopathology by the judgment of the investigator were to be excluded. But of course, there was this pesky questionnaire that they also filled out, and it turned out that something like 10 to 15 percent of the

patients, despite having been included by the investigator, had moderate to severe either anxiety or depression, but there was no mechanism in the trial built in a priori to deal with that. So it's never been really dealt with.

The question of neuropsychological testing in clinical trials -- should that be monitored? Are you going to answer this question?

DR. MAX: No. I want to just respond to Bob. I'm the chair of our IRB. I think that if this is an intervention into the medical system, one has to give some people opioids, some not. I think it's very reasonable -- My IRB just reviewed that I could do a psychiatric assessment if some issue came up just during the -- The patient says, oh, I'm disturbed about this. Talk to your doctor.

I don't think we are obligated as long as the patient is informed that this is purely for future knowledge, and extensive psychiatric is not mandated.

DR. SCHUSTER: Well, I guess, obviously, IRBs differ depending upon where you are. All I can say is that, obviously, it would -- We would not admit anyone, clearly, for example, who had significant major depressive disorders with suicidal ideation.

I mean, you know, these kinds of things

are clear, but I just wondered whether or not people were being treated for these, because if you are going to then be monitoring the urine for other substances, as was suggested -- if they are suffering from generalized anxiety disorder and they are showing up with diazepam in their urine, you know, this may be self-medication as opposed to abuse of these things, and that should be known.

DR. MAX: But in terms of neuropsychological testing, there have already been many short term studies that show within about three days of increasing the dose, people perform pretty well, and a number of controlled trials showing that at six to eight weeks there is normal function on stable doses of opioid. So I wouldn't make that a high priority.

ACTING CHAIRMAN KATZ: There is actually no prospective controlled trial looking at before and after neuropsychological function in patients given opioids for chronic pain. The only study that's available is Jennifer Haythornthwaite's study.

That was a simple pre/post, single arm, open label study, taking patients already on opioids, organizing their opioids, and seeing what happened to their neuropsychological function, which actually

improved in that particular trial. But there is no other published controlled study.

DR. MAX: There are the two abstracts I talked about that will be out in the next year, the Rowbathan and the Raja.

ACTING CHAIRMAN KATZ: What are the results?

DR. MAY: The results in Haythornethwaite then tested people given placebo or opioid or nortriptyline for about seven weeks, and there was absolutely no effect on a whole battery of tests of either of the medicines and morphine 90 milligrams a day, nortriptyline 90 versus an inactive placebo.

ACTING CHAIRMAN KATZ: Super. Thanks.

DR. SCHUSTER: I would also point out there's a literature from methadone maintenance treatment where cognitive testing has been done, and it has been impossible to distinguish individuals maintained on very high doses of methadone even from matched normal controls.

ACTING CHAIRMAN KATZ: I still would introduce a note of caution, that we are sitting here with very advanced practitioners aware of even unpublished studies, and there's still a wide perception out there in the community that

deterioration of neuropsychological function is one of the potential risks of long term opioid therapy.

It would seem to me that a company that is considering marketing a product would do well by continuing to shore up evidence that that indeed is not a problem. I wouldn't be so quick to throw it away, because a few of us here are aware that it may not be an issue.

Dr. McNicholas.

DR. McNICHOLAS: Just to comment on that, I would absolutely agree in shorting up the evidence base, but I would also urge somebody to perhaps organize the present evidence and make it available for education, whether or not we can alter practices, but certainly I think that that would be an educational opportunity that people who are marketing these drugs should not miss.

ACTING CHAIRMAN KATZ: Are there any other burning questions about how one monitors these adverse events in the clinical trial setting? Are there any other burning questions? Dr. Tobin.

DR. TOBIN: Just a question, because I'm not a toxicologist, and I need someone in drug detoxification to potentially answer this or someone in toxicology.

Is urine screening -- Even if we know all the substances and metabolites we are going to look for, is that sufficiently sensitive for what I'm proposing compared with needing recurrent plasma samples, or are they even complementary?

ACTING CHAIRMAN KATZ: Dr. Reidenburg?

DR. REIDENBURG: Yes. I can address that with respect to compliance with other medications. That is that often the urine screens are more sensitive, because of the concentration of the urine.

The issue is that for many drugs you need to measure metabolite which, being more water soluble, often is harder to measure, because the old fashioned extraction methods won't pick them up.

Another thing that is known from the compliance measurements in hypertension is that everybody has any hypertensive medication in their urine when they visit the clinic, but when you use the computerized bottle caps, you see that compliance is misrepresented by urine testing.

ACTING CHAIRMAN KATZ: Are there any other questions or comments? Jeff Bloom?

MR. BLOOM: Just one other comment. I would be remiss if I did not mention this. That is to dispel the common myth about opioids and the drug

load. It might sound like my partner, given the load of medication that he is on -- you might think he would be a zombie, but actually he has his life back. He's more productive than he's ever been. He's painting again. He actually feels like a human being again.

For people that think that, you know, opiates are a fun trip for people, that it's just a vacation, they are not. It's actually a way to have a functional life from a very painful existence, and I really hope everyone keeps that in mind, that it's not a joy ride for people.

You know, there are a few people that certainly abuse it, but for most of us it's a difference between having a quality of life and not having a life at all.

ACTING CHAIRMAN KATZ: Thank you. Well, if there are no other comments or questions -- I'm giving everybody a last chance -- then I'll proceed and adjourn the meeting with expression of -- Oh, Dr. Kweder, did you have some comment?

DR. KWEDER: Yes. As you adjourn, I would just like to thank the panel for your willingness to tackle these difficult issues that are often like Jello. They are often like Jello for us, too.

In particular, I want to respond to Dr. Smiley's frustration. You know, the questions that you asked about, you know, well, what's the diagnosis -- those are the questions that we ask as well. We have scoured the earth, believe me, looking for answers to some of those.

Unfortunately, you know, as a public health agency, we find ourselves in a situation of not having a specific diagnosis or one with the acumen we would like, but being put in the uncomfortable position of being told we will do something.

Whether or not that's politics or public health is, you know, in the eye of the beholder, but we live in a very political society, and we live in a society that places demands on us, whether one considers them political or not.

So a lot of your frustration is exactly the frustration that we feel, and we apologize for sometimes not being able to be a little bit more specific, but you have given us some great insights that we will take back and try and create into some concrete efforts as we go forward.

Many of the questions that we've brought to you today, hopefully, we'll be able to bring back to this panel in more focused, specific ways as we

look toward specific risk management programs or ideas to implement. So thanks, as well as the clinical trials arena. Your discussion has been very helpful. Thank you.

ACTING CHAIRMAN KATZ: Dr. Rappaport, any last words?

DR. RAPPAPORT: I would just like to add my thanks. We have received a lot of interesting comments over the last two days, and it's going to be enormously useful to us.

ACTING CHAIRMAN KATZ: Let me thank the Committee for helping me in having a very constructive discussion on some very difficult issues, and to you all for coming. Safe travels.

(Whereupon, the foregoing matter went off the record at 4:42 p.m.)