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

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MEETING

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WEDNESDAY,

JANUARY 30, 2002

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

PRESENT:

NATHANIEL P. KATZ, M.D.

JIM ANTHONY, Ph.D.

MICHAEL A. ASHBURN, M.D., M.P.H.

JANICE BITETTI, M.D.

JEFF BLOOM

AMANDA S. CARLISLE, PH.D., M.D.

MARIA K. CONNOLLY, D.N.Sc.

PRESENT (Continued):

DEBRA FRIEDMAN, M.D.

KATHLEEN M. FOLEY, M.D.

ERIC S. HOLMBOE, M.D.

TERESE T. HORLOCKER, M.D.

BRUCE ALLEN LEVY, M.D., J.D., Guest

LLYN A. LLOYD, R.Ph.

MITCHELL B. MAX, M.D.

CHARLES H. McLESKEY, M.D.

LAURA F. McNICHOLAS, M.D., Ph.D.

WINSTON C.V. PARRIS, M.D., FACPM

RUSSELL PORTENOY, M.D., Guest

MARCUS M. REIDENBURG, M.D.

RICHARD G. ROBERTS

NEIL L. SCHECHTER, M.D.

MARK SCHREINER, M.D.

CHARLES SCHUSTER, M.D.

RICHARD M. SMILEY

JOSEPH R. TOBIN, M.D.

C O N T E N T S

C O N T E N T S (Continued)

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

(8:14 a.m.)

ACTING CHAIRMAN KATZ: Good morning. Can everybody hear?

I'd like to call the meeting to order. I'd like to thank everybody for coming. My name is Nathaniel Katz. I'll be chairing the meeting this morning.

This is the Anesthetic and Life Support Drugs Advisory Committee meeting. The topic for the next two days will be opioids. So if you're in the wrong place, you can make yourself aware of that right now.

Let me begin by again thanking all of you for coming and thanking the folks at the FDA for inviting me to participate in this meeting.

What I'll be doing first is I'll begin with a few moments of introductory comments to try to set a context for today's meeting.

The subject as you all know is opioids, and I'd like to just take a moment and provide a historical context for the discussions that we'll be having over the next two days.

As many of you may know, opioids have been used for therapeutic purposes for a long, long time.

The first reports that we have of the use of opioids come from actually the first historical writings which were from ancient Sumeria in about 4000 B.C., and there were clear-cut writings then about the therapeutic of opioids.

And we have awareness of the use of opioids from most cultures since that time. Already in about 300 B.C., there was a vociferous argument going on in the literature where some people were saying, some physicians were saying that opioids should never be used because of their horrible side effects and complications, whereas others, including Galen in the 2nd Century A.D., decided that opioids should be used for everything because they cure all illnesses.

And since that time up until the present day, we've seen that the discussions of opioids have typically been framed in that context, where people have taken either one dramatic view or another one and have sort of shouted at each other over these gulfs.

And that applies up until the present day, I think, in the year 2002. Today I think we have an opportunity to start to discuss these issues in a different way in that we can actually in one of the few occasions in history start to have a rational

discussion where we all try to understand differing points of view and get them all on the table so that we can inform each other and understand the issues rather than just shouting from our positions, and so that we don't take the risk of being like the blind men feeling the elephant where the one on the tail thinks that he's feeling a rope and the one on the leg thinks that it's a tree, and all of them suffering because they don't really see the whole picture. They just know what their one little part is.

So today and tomorrow what we're going to try to do is understand the whole picture.

So with that context, I'd like to set forth what the goals of the meeting are for the next two days, which are to share ideas about opioids with each other, exchange information, synthesize the whole picture for ourselves, help inform this division of the FDA about these issues.

What we're not going to be doing over the next two days or what the goals are not are necessarily to come to any consensus or agreement on some of the major issues. I think it will be enough if we can simply inform each other and understand these issues better.

The goal of this meeting is not to take

any particular drugs off the market. It's not to focus on any specific drugs. We're trying to deal with the opioids as a class since they all share very similar properties; not to focus on any particular members of that class. We're not going to try to come up with any black and white prescriptions for what anybody ought or ought not to do about some of the issues that we'll be discussing today, but to really try to bring all of these issues to light and understand them better, and I'll look forward to the help and support of the Advisory Committee in achieving the goals of getting all of these issues on the tabled without necessarily being overly prescriptive if it's premature to do so.

So those are our goals, and I look forward to everybody's support in achieving those goals. There are a few housekeeping rules that I'll want to mention to help us achieve those goals. My main role will be to make sure that everybody gets heard today in the light of getting all of this information out there on the table.

And so in order to do that, we're all going to have to stay on time. So I'm going to be the big, bad guy that's rude and obnoxious when people spill over their allotted time. That will be

particularly important for the public speakers.

We have a very packed agenda today. There were a huge number of pieces of information received for this meeting. The last count that I heard is that there were over 1,600 submissions of opinions to this meeting. When I asked how many more that is than one usually gets at a meeting like this, the answer was, oh, about 1,500 more than we usually get.

(Laughter.)

ACTING CHAIRMAN KATZ: So I guess there was a lot of excitement about this issue. So it's going to be very important for people to stay within their focus and within their allotted time, and I'll deal more with that later.

So I'll be the rude guy, and I'll ask for everybody's forgiveness in advance if I cut off your microphone or do something obnoxious like that so that everyone can have their opinions heard.

With that, I'll introduce Kimberly Topper, the Executive Secretary of the committee, who will read the conflict of interest statement.

MS. TOPPER: The Food and Drug Administration has prepared general matters waivers for the following individual special government employees: 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 and Amanda Carlisle, who are attending today's meeting.

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

The committee will also discuss 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 to give rise to waivers for participation in meetings in which particular products are at issue. Unlike issues before committee on which a particular product is discussed, the issues of broad 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 of general topics' impact on so many institutions, it's not prudent to recite all potential conflicts of interest 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 only to matters of general interest.

With respect to 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 contacts 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 consults for Eli Lilly, Janssen, Ortho Biotech. Additionally, he's the scientific advisor to Eli Lilly, Janssen and Adolor. 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 Detro 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 served on Astra-Zeneca's Speaker Bureau.

Dr. Mark Schreiner is a Medical Director for Children's Clinical Research Institute, AFSA (phonetic), and he's involved in clinical trials sponsored by Baxter Pharmaceutical, Sanofi Synthelabo, Novartis, Purdue Pharma, L.P., King Pharmaceuticals, Abbott and Glaxo SmithKline. He receives no direct compensation for the pharmaceutical sponsors.

Dr. Kathleen Foley in the past ten years has consulted with of the companies that make analgesic drugs. In the past year she's worked with

Purdue Pharma, Janssen, Knoll, and Abbott.

She is also on the Speaker's Bureau for Purdue Pharma, Knoll, and Janssen. Additionally she is a Scientific Advisory for 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, Direct, and Chrysalis. Additionally, he reports involvements on contracts and grants with Parke-Davis, Boehringer Ingelheim, Elan, Ortho Biotech, Endo, Ametek, Medtronic, Purdue Pharma, Pfizer, Janssen, Abbott, Curatech, Ortho-McNeil, Elon, Pfizer, and Searle.

In addition, we'd like to disclose that Dr. Charles McLeskey is participating in this meeting as our industry representative acting on behalf of regulated industry. As such he has not been screened for any conflicts of interest.

In the event that any discussions involve any other products or firms not already on the agenda for which FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion

will be noted for the record.

ACTING CHAIRMAN KATZ: Thank you, Kimberly.

What I'd like to do now is to do introductions. I'd like to go around the table and to have everybody on the committee and invited guests take a moment to introduce themselves, tell us who you are and what you do.

Why don't we start at that end of the table, please?

DR. KWEDER: Good morning, everyone. I'm Sandra Kweder. I'm the Director of the Office of Drug Evaluation II at FDA. What that means is my office oversees the work of the Anesthetics, Critical Care Life Support Division, as well as several others.

DR. RAPPAPORT: Good morning. I'm Bob Rappaport. I'm the Deputy Division Director of the Division of Anesthetics, Critical Care and Addiction Drug Products at the FDA.

DR. DalPAN: Good morning. I'm Gerald DalPan. I'm a medical reviewer in the Division of Anesthetics, Critical Care and Addiction Drug Products at FDA.

DR. MAX: My name is Mitchell Max. I'm a neurologist, and I do chronic pain clinical trials at

the National Institutes of Health and the Dental Institute.

DR. LLOYD: I'm Llyn Lloyd. I'm the Executive Director of the Arizona State Board of Pharmacy.

DR. REIDENBURG: I'm Marcus Reidenburg. I'm an internist and pharmacologist, head of the Division of Clinical Pharmacology at Cornell Medical College.

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

DR. ASHBURN: My name is Michael Ashburn. I'm the Director of Pain Programs at the University of Utah and at Primary Children's Medical Center in Salt Lake City.

DR. McNICHOLAS: Good morning. My name is Laura McNicholas. I'm from the University of Pennsylvania in the Philadelphia VA. I'm a psychiatrist specializing in the treatment of substance abuse.

DR. HORLOCKER: I'm Terese Horlocker from the Mayo Clinic. I'm also Vice President of American Society of Regional Anesthesia and Pain Medicine.

DR. SMILEY: Good morning. I'm Rich Smiley, Director of Obstetric Anesthesia at Columbia

University.

DR. ROBIN: Good morning. I'm Joe Tobin. I'm a pediatric anesthesiologist and intensive care specialist at Wake Forest University.

ACTING CHAIRMAN KATZ: As I said earlier, my name is Nathaniel Katz. I'm a neurologist. I run the Pain Clinical Trial Center at Brigham Women's Hospital in Boston, and for many years I ran the Pain and Symptom Management Program at the Dana Farber Cancer Institute at Brigham Women's Hospital in Boston, as well.

DR. CARLISLE: Good morning. I'm Sue Carlisle. I am an anesthesiologist and intensivist and Chief of Anesthesia at San Francisco General Hospital in San Francisco.

DR. PARRIS: Good morning. I'm Winston Parris. I'm a pain consultant at the Tampa Pain Relief Center and clinical professor of anesthesiology, University of South Florida in Tampa.

DR. BITETTI: And I'm Janice Bitetti. I'm an anesthesiologist/intensivist at George Washington University here in Washington, D.C.

DR. McLESKEY: Charlie McLeskey, an anesthesiologist by training. I work at Abbott Labs and serving as industry consultant to the committee.

MR. BLOOM: My name is Jeff Bloom, and I'm a retired AIDS patient advocate since 1994. I retired with complications from myelopathy, and since 1994 I've been an AIDS patient advocate volunteer in Washington, D.C.

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

DR. ROBERTS: Good morning. I'm Richard Roberts. I'm a simple country doctor in Belleville, Wisconsin, where I'm a professor of family medicine at the University of Wisconsin.

DR. SCHREINER: I'm Mark Schreiner. I'm a pediatric anesthesiologist at the Children's Hospital of Philadelphia, and I'm the Medical Director for Children's Clinical Research Institute.

DR. ANTHONY: Good morning. I'm Jim Anthony. I'm a professor at Johns Hopkins, Bloomberg School of Public Health and School of Medicine. I direct a drug dependence epidemiology training program and am an epidemiologist.

DR. SCHUSTER: My name is Charles Schuster. I'm 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 at Memorial Sloan Kettering Cancer Center, and I direct a project on "Death in America" to improve the care of the dying, and I am an expert consultant to the WHO for developing initiatives in drug availability in developing countries for the treatment of cancer and aids.

DR. LEVY: Good morning. My name is Bruce Levy. In my prior life I was an anesthesiologist and a pain specialist, but since 1993 I'm a regulator, and I was Executive Director of the Texas State Board of Medical Examiners for eight years. In the past year, until a few months ago, I was a Deputy Executive Vice President of the Federation of State Medical Boards of the United States.

DR. FRIEDMAN: Good morning. My name is Debra Friedman. I'm a pediatric oncologist at Children's Hospital and Regional Medical Center in Seattle, Washington, and I'm also a member of the End of Life Task Force for the Children's Oncology Group.

ACTING CHAIRMAN KATZ: Thank you very much, everybody.

With that I'd like to reintroduce Dr. Bob Rappaport, who is Deputy Director of the Division of

Anesthetic Critical Care and Addiction and Drug Products, who will deliver some welcoming and introductory comments.

DR. RAPPAPORT: Dr. Katz -- can you hear me? -- Dr. Katz, members of the committee, ladies and gentlemen, I'd like to thank you for joining us here today to participate in what we hope will be an educational and enlightening experience for all of us.

The cover memo that Dr. McCormick included in the front of our briefing materials eloquently addressed the purpose of this two day meeting. Unfortunately Dr. McCormick is not going to be able to participate in this meeting due to a medical problem.

So I'm going to read from her memo some of the words with which I think she had hoped to unify our sense of purpose in this room.

This year begins the decade of pain. After a long struggle to raise pain management to a new level of importance among medical specialties and to begin to remove some of the stigmata associated with pain therapies, particularly the opioids, pain management will certain gain greater visibility in the next ten years.

Pain management guidelines are proliferating. Many states have adopted legislation

to insure that quality of life and pain relief are taken into full consideration in the terminally ill patient.

There are many challenges ahead, and we have a great opportunity to continue this effort in a studied and responsible way.

There are newer and more elegant opioid formulations and drug delivery systems on the market and in the development pipeline. These have the ability to provide opiates to the patient in more convenient, palatable, and effective ways.

The awareness of the importance of good pain management has made its way into new populations, such as the pediatric treatment community. In spite of the difficulties in characterizing pain in the child and the infant and in conducting adequate clinical studies to assess proper dosing, the FDA will invite discussion about the unmet needs in this age group, the kinds of delivery systems and agents that might be appropriate at various ages, the risks of having these medications in the home where small children may have access, and how these risks should be communicated and managed.

Our hope for this meeting is that you as the experts in pain management and addiction treatment

will provide the agency your views on what is need in the arena of drug development and risk management. It is our hope that you will bring the FDA up to date on your views regarding the unmet needs of the pain community and assist the FDA in thinking about ways in which we can carry out our mission responsibly with solid programs to develop good drugs while managing the risks associated with them, always keeping in balance the needs of the public.

Thank you.

ACTING CHAIRMAN KATZ: Thank you, Dr. Rappaport.

What we'll do now is we'll proceed to the public speaker portion of our agenda. I do want to go over a few housekeeping rules with our public speakers to make sure that everybody gets heard in a reasonable way.

Everybody from the public has three minutes to speak. There will be a light on, a yellow light for -- I'm sorry -- a green light for the first two minutes, and then a yellow light for your third minute, and then once that third minute is up, there will be a red light, and I understand also a very obnoxious buzzer will go off at that point in time, and then we can even cut off your microphone if you're

still speaking beyond that point. Hopefully that won't be an issue.

And then we have even worse punishments for you after that that I'm not privileged to divulge at this point in time.

(Laughter.)

ACTING CHAIRMAN KATZ: So there is a list of all speakers that everybody should have. So if you see that you're up next and you're on deck, go sit in one of those speaker ready chairs, and there are some folks from the FDA who will help chaperon you to the right place so that we don't waste a lot of time blundering back and forth.

Now, all of the public speakers, you need to begin with your disclosure. So if there are any potential conflicts that you think people ought to be aware of, please lay those out right up front. Anybody funded your trip down here, any financial relationship you have, research relationships, if you belong to an organization that's funded by anybody in particular, please lay that all out right up front.

If you have no such disclosures, just say, "I have no disclosures." And if you begin your discussion without a disclosure statement, I'll probably rudely interrupt you and remind you that we

need to hear that. And we do appreciate that.

There have been two cancellations from the original list that we had. So there will be two folks who will be able to be popped in from the top of the waiting list. That will be Dr. Babul today and Dr. Van Zee tomorrow. You'll be at the end of all of the regular speakers for today.

So with that, why don't we proceed?

MR. GIGLIO: Thank you.

I'm John Giglio, the Executive Director, American Pain Foundation.

We have received unrestricted grants from several pharmaceutical companies, some of whom make opioids, including Purdue Pharma. We also receive funds from nonprofit foundations and many individuals. Our single largest grant was from an individual who died in serious pain.

In our last fiscal year, we received approximately 60 percent of our unrestricted funds from industry. Purdue did not ask us to testify.

We are a national nonprofit that supports people with pain through information, education, and advocacy, including a Web site and a toll free number. In the last year we've logged several thousand calls from consumers.

We're the largest nonprofit representing the interests of consumers with pain, and our goal is to help people with pain get the care they need.

We're deeply concerned that in an effort to stop the abuse of Oxycontin, FDA and DEA will take steps that will severely hurt consumers who use opioids for legitimate medical purposes. As you know, for many people with moderate to severe chronic pain, opioids are the most effective treatment available and often the only one.

In the last few months, we've received requests for help from consumers. They've doubled, mostly as a result of fear from stories generated in the media. Many people are telling us that they're worried about being taken off their opioid medication, including products than Oxycontin.

Others have been telling us that doctors have already done so or reduced their dosage to an ineffective level. Still others have expressed concerns about becoming addicted to or even dying from their prescribed opioid.

On several occasions we have had people who were literally threatening suicide as they were speaking to us. Unfortunately most of the media reports fail to convey the other side of the story,

that millions of people suffer from serious chronic pain; yet most go untreated or under treated, especially the elder, minorities, the poor, and children.

The fact is when prescribed appropriately by a physician and taken as directed, opioids are safe, effective, and rarely lead to addiction. They give relief and allow people to resume their lives.

We recognize that opioids are sometimes diverted by criminals and abused by thrill seekers and people with addictive disorders. We acknowledge that regulation is needed to minimize diversion and abuse, and we agree that those who produce, prescribe, and dispense opioids must understand these risks and comply with all laws.

Yet even the DEA agrees that we already have a powerful regulatory scheme to pursue these bad guys, and we believe that adding new restrictions will have the unintended effect of killing the legitimate use of opioids. It will unravel years of slow progress that has been made in their acceptance by physicians and the use of patients.

We ask that as regulators you should be tough in combatting diversion and abuse, but you must do so in a way that doesn't inhibit the legitimate use

of opioids.

Thank you.

ACTING CHAIRMAN KATZ: Thank you very much. You win an award for not using all of your three minutes.

(Laughter.)

ACTING CHAIRMAN KATZ: Next, please.

MS. MULLIKIN: Good morning. My name is Chris Mullikin, and I've been a registered nurse for the past 38 years.

For the past three years I've been fortunate enough to be an active member of the Purdue Pharma's National Speakers Bureau, which has afforded me the opportunity to provide much needed education to both public and professional groups about the inadequate and inappropriate pain management.

I entered nursing for the same reasons that most of us do: a desire to help our fellow man and to advocate for those in need. After many years in a variety of nursing roles, I find myself working in an area of medicine where the need for patient advocacy is greater than almost anywhere else, that discipline being pain management.

About 15 years ago, I found myself in the uncomfortable position of caring for my mother, who

was dying of pancreatic cancer. Dealing with the death of a loved one is traumatic enough without feeling helplessness associated with my inability to manage her rapidly increasing pain.

I questioned the logic behind her physician's concerns about respiratory depression or even addiction.

After Mom died, I decided to switch my career focus to pain management. As I said, this was 15 years ago, and there was a lot of ignorance and misunderstanding out there. Education about pain management and the use of opioid medication was practically nonexistent.

Well, we've come a long way, or have we? I now manage the Pain Management Center at Shore Memorial Hospital. It's a small health care system on Maryland's Eastern Shore. Our program consists of an in-patient acute pain management team and an out-patient pain center that treats primarily chronic pain patients.

Patients' statements such as, "You've given me my life back," and daily hugs are part of our routine. This patient population is one of the most labeled and under treated in the history of medicine.

Pain is described as the universal human

experience. It affects all of us at some point in time in some way. So why do we try to cover it up, ignore it, or tell our patients just to live with it?

We have the knowledge, the medical research, and treatment modalities to successfully manage most pain that our patients can suffer. So what's stopping us? We have the same fears and concerns of 15 years ago. They're still with us today.

We are allowing the abuse and the ignorance of the few to affect the potential health for the many. The restricted use of opioid medication in non-cancer pain will do a disservice to the population already living with many unfounded fears and restrictions.

Please do not through misguided intentions inhibit the quality of care that we can easily provide to that population. Remember the biggest form of drug abuse today is under treatment, and this is a crime that we can all eradicate.

Thank you for this opportunity to be an advocate for that population that I serve daily.

ACTING CHAIRMAN KATZ: Thank you very much.

Next please.

MS. REEVES: My name is Lorraine Reeves, and I'm Executive Director of the Chronic Pain Advocacy League, and I have no disclosures.

I've also been coping with my own pain for 16 years now. So I understand too well what it's like to try to get treatment and also to be treated with respect.

While no one wants to interfere with the treatment for those who need it while addressing the drug problem, outdated attitudes and fears are already doing that. A clinic that did not want to deal with the hassles of their patients on opiate therapy dumps them even though they previously agreed not to.

A local pharmacy announced suddenly that it would no longer fill prescriptions for anyone unless they are with Hospice. Their longstanding clients were left scrambling trying to find their meds.

A doctor, while giving a lecture on pain management, is asked what would she do if one of her patients lost a prescription. They could be lying. Would she rewrite it?

She said, no, they're adults. They'd have to tough it out for a month.

No one would do that to a patient with

heart disease or diabetes.

Another woman who has had great success taking Oxycontin, has a career, has a life because of the pain relief it affords here, is informed by her doctor he wants her off of it. There's too much media coverage.

This is just a sampling of what I hear every day. I get calls from people desperate in need of pain relief who are struggling to find care and just want to have a life. My own situation, I take Oxycontin, and without it I would not be here today. At the very least I'd be in bed. At the worst, I don't even want to think about it.

Yet following an interview I did a while back, the reporter informed me that he got a number of calls from people who said, "I shouldn't take anything for my pain. God gave me the pain. I should live with it."

Now, this may sound extreme, but attitudes like this, that pain won't kill you, it's all in your head, you're weak if you take something, are causing very serious problems. And now we are caught in the middle of a failed drug war, which is actually the reason for the increase in addiction, not the use of opiate therapy.

We are fighting for our lives. Chronic pain kills who you are, destroys your self of self while slowly destroying the body. Don't let us become casualties in a misdirected war.

ACTING CHAIRMAN KATZ: Thank you very much.

MS. KOWAL: My name is Nancy Kowal. I'm immediate past President of the American Society of Pain Management Nurses, and I stand before you today as not only a patient advocate because the nursing component of who I am says that I must be, but also for my patients that I care for on a daily basis.

I do do lecturing for multiple pharmaceutical companies, and I also have been involved in research projects through professional venues in university settings.

Today I wish to make a statement for my patients and as a representative for pain management nursing. To insure that the 21st Century provides a healthier quality of life regarding pain management issues, let us stop as professionals and reflect on the health care issues surrounding inadequate pain management.

The ASPMN organization has always fully supported education and clinical expertise in pain

management. Grave concerns have surfaced regarding the recent negative discussion resounding around the utilization of opioid analgesics in all patient populations. Many populations are at risk currently for the non-treatment of pain.

If pain management's use of opioids becomes criminalized in the public's eye, further barriers to pain treatment will occur. The continued discussion of abuse potential, diversion, and addiction, as well as the politicizing of quality pain management can only prove detrimental to the clinical outcomes of our patients.

As immediate past President of the American Society of Pain Management Nurses, I stand for education, for research, for standards, and most of all for patient advocacy. The organization encourages and supports the systematic study of pain, along with evaluation of clinical care and research.

Built into this mission is the ultimate responsibility to speak for pain management as a profession publicly and in the government forum. If routine practice does not meet the patient's needs, then we are responsible to change the practice. The mission of ASPMN is to promote and provide optimal care to pain patients, including the management of its

sequelae.

This includes the option of opioid analgesic based on a quality pain assessment, an appropriate evaluation of outcome, the risk-to-benefit ratio of providing opioid analgesia to all patients must be determined with a picture of the patient in mind.

As a professional organization, quality of life and patient outcomes are our key concern. We must advocate for those that are too weak and debilitated to speak for themselves. Hear the plea of pain professionals and the patients who surround them daily. As the issue of opioid analgesic use is evaluated and discussed --

ACTING CHAIRMAN KATZ: I'm sorry. Could you close your comments? Your three minutes are finished.

Sorry.

MS. KOWAL: Yes. Common goals and process must be established with pain clinicians to provide the best outcomes for our one focus, the patients.

Thank you.

ACTING CHAIRMAN KATZ: Thank you very much.

Next speaker, please.

MS. CUSIMANO: My name is Cheryll Cusimano, and I am a pain management nurse. I take care of chronic nonmalignant pain patients.

I am speaking today, a pain nurse clinician, as an advocate for free choice of long acting opiates in an equal position amongst all of the treatments for pain management. We now have drugs that for both the long term and short term can both relieve pain and maintain function.

Although these drugs are potentially addicting, this represents, in fact, a very narrow view of the situation. If you were a diabetic on insulin as a model for prescribing, you can see how a patient can be adjusted safely on a very dangerous drug. Pain prescribing should be no different.

Carrying a patient on an opiate medication is guided by clinical skills and not fear. Just as with the insulin, we adjust the doses and we document responses. In the end, everything relies on knowing and following the patient.

I am the nursing specialist for a chronic pain service which has functioned continually for over 23 years. Our care of patients, including opiates, as well as other modalities, follow guidelines and goals based on successful outcome studies. Although we

stabilize patients on opiates, many of them are able to transfer to alternative therapies. When we decide to use a long-term opiate, we have an up front agreement with our patients about goals and ending points.

If we encounter opiate abuse by a patient, then we treat this as a problem in its own right, but this situation is rare given our guidelines.

Since there is proper technology for the use of opiates, we must not withhold this choice for this care. The policies and guidelines for a proper practice may be the same as those for any other dangerous drug.

As Americans committed to patients' rights, we must not discriminate. Decisions are made on our skills and our patients' needs without threats or fears of policies that are too rigid or the abuse problems of a small but very visible subgroup of patients.

All of us who are clinicians and policy makers are walking the same tightrope. We all need to focus on education and guidelines for proper practice. We should not fool ourselves. There will always be unskilled and misbehaving clinicians, just as there are abusing and even criminal patients.

The policies and disciplinary actions for violations should follow a parallel but separate agenda under public law and policy making. At all costs we must develop regulations to protect and guide the skilled and the honest efforts of good clinicians and the proper needs of our patients.

Thank you.

ACTING CHAIRMAN KATZ: Thank you.

Next speaker, please.

MS. GARRETT: My name is Rhonda Garrett, and I'm here representing the Interstitial Cystitis Association.

The ICA is a nonprofit, voluntary health organization that receives funding in part from the pharmaceutical industry via educational grants to support programs and services for IC patients.

Interstitial cystitis, known as IC, is a nonmalignant, chronic inflammatory disease of the bladder that causes severe pelvic pain, urinary urgency and frequency, up to every 20 minutes both day and night. The cause is unknown, and there are no uniformly effective treatments.

A diagnosis of IC is made on the basis of symptoms and the absence of other definable causes, such as infection or bladder cancer. At the present

time there's no specific diagnostic test for IC.

Approximately one million people in the U.S. suffer from IC, an incidence similar to Parkinson's disease. Epidemiological studies reveal that it takes an average five to seven years to get diagnosed, and sometimes even longer.

The quality of life for IC patients has been shown to be worse than that of patients undergoing dialysis for end stage renal disease.

Economic impact is estimated at 1.7 billion per year.

Suicides occur every year because patients are left in severe pain with nowhere to turn to for help. Because physicians are often not familiar with the condition, patients are frequently told that their symptoms are all in their heads or caused by stress, thereby minimizing or invalidating the patient and compounding an already devastating condition.

Opioids are an absolute necessity for many patients with IC, particularly for those who do not respond to any of the available treatments. For IC patients it can mean the difference between life and death.

I am an IC patient currently on MS continin, and it has given me the opportunity to come

here today.

Opioids, when used appropriately, rarely cause dependency. Addicts use pain medication to escape life while people in chronic pain use pain medications to get their lives back.

While preparing for this testimony, we received the following E-mail from an IC patients. "I'm having a very hard time finding a urologist that understands IC. I'm in constant chronic severe pain, and every doctor I see seems to be afraid to give me the pain medication I need for fear of dependency problems. What they don't understand is that my life can be no worse than it is now. I am unable to leave the house and am struggling with severe pain, hopelessness, and depression. Please help me."

When we contacted this patient to offer our help and support, we also asked her permission to present her poignant statement at this meeting today, and this was her response.

"You have my permission if it is at all necessary to use my name. I'm not ashamed of this disease. It is the medical profession that should be ashamed of themselves."

Physicians confronted with patients in severe pain due to IC often ask themselves whether

this patient should receive treatment for their pain. Perhaps the question should be why should this person be left in pain.

Thank you.

ACTING CHAIRMAN KATZ: Thank you.

Next, please.

DR. SWERDLOW: Good morning. I represent the Sickle Cell Disease Advisory Committee of the National Heart, Lung and Blood Institute at the NIH. This committee includes ten outside experts plus governmental representatives to provide policy advice to the NHLBI.

Sickle cell disease is characterized by intermittent, unpredictable episodes of severe disabling pain beginning early in childhood. Many patients develop chronic pain. Those with very mild disease may have efficacy from non-opioids, but the vast majority of patients require opioid therapy to control their acute and chronic pain.

The pain of sickle cell may well be different from other pain states in that it is quite severe, unpredictably intermittent, involves both acute and chronic pain, and begins early in childhood, possibly altering pain sensations and coping skills.

Patient are routinely accused of being

addicted to opioids. Substance abuse behaviors may just be desperate attempts to get badly needed opioids. Many patients require extraordinary doses for pain control, which is a long considered addiction by many physicians. The average dose of long acting opioid upon discharge from our hospital for a pain episode is one gram of morphine equivalent per 24 hours.

The more tolerant patients require doses over ten grams of morphine equivalent for 24 hours. Lack of stronger dosage forms can be a major inconvenience when patients have to literally take ten to 50 tablets at a time for a single dose of pain medication.

Those who treat sickle cell patients and the patients themselves are in a constant battle with physicians in emergency departments in hospitals, not to mention pharmacists and insurers, to provide adequate amounts of pain medication.

Current barriers are excessive and often discourage or prevent adequate treatment.

Children over seven can generally learn to take tablets and use patient controlled analgesia device as well. The greatest practical difficulty for pediatric patients is finding plain opioid

preparations to avoid acetaminophen or NSAID toxicity.

Acetaminophen toxicity is the single greatest substance abuse risk to the sickle cell population. Desperate patients will consume large amounts of combination medications if that is all that is prescribed.

Additional pure opioid preparations and dosage strengths would be most helpful in treatment of this disease.

Despite the high dosage requirements, opioid addiction is highly unusual in the sickle cell population, possibly because of the great degree and frequency of pain. We see far more opioid abuse by proxy with a parent or housemate taking the patient's medications, but such abuses are usually easily detected with accurate pill counts and frequent patient visits and review of patient diaries.

Diversion is rare in the adult sickle cell population because the patients place such high importance on the medication for themselves.

ACTING CHAIRMAN KATZ: Thank you, Dr. Swerdlow. Did you have any disclosures to make?

DR. SWERDLOW: The committee has no disclosures. I have been on the Purdue Frederick Speakers Bureau, but not within the last year.

ACTING CHAIRMAN KATZ: Thank you very much.

Let me just remind the subsequent speakers to begin with your disclosures, if you don't mind.

Next, please.

DR. HANDEL: Good morning. It's an honor to be here on behalf of the Pain and Palliative Care Service at the NIH. I am speaking in the place of Ann Berger, who is the department chair, and I have the disclosure that I have in the past been, but am not currently on the Speakers Bureau for Purdue Frederick and Janssen Pharmaceuticals.

In speaking for our service, I see the founder of our service, Mitchell Max, is here and present, and I wanted to make a couple of comments about suffering.

My belief is that our service is and has been founded at the NIH specifically to deal with suffering of patients on protocols in our institution, and we have found that there are many sources of suffering, one of which is fear.

Our patients commonly find themselves in situations where they have significantly uncomfortable conditions, are under intense therapy, and then find themselves in situations where they're going back to

their communities to continue trying to live in between their courses of therapy.

Our patients find that while they may have significant dedication towards comfort and increased quality of life while they're in-patients, they oftentimes find a very different situation upon leaving the institution.

We find that this is, because of a number of different factors, one of which is fear, one of which is lack of education in the community both in professionals and in the lay community.

There are fears about safety and there are fears about actually accessing the appropriate medications. We have found that there is a pattern where patients will be calling back on a regular basis asking if there's a way that we could either liaison with their physicians or their community or actually at time talks to their family.

Our hope in presenting to you is that there is a way that you can balance this very difficult job that you have, the job of assuring safety for patients who are on these significant medications that are necessary and are important for their quality of life with the opportunity to give them appropriate access to these medications.

And I believe that only in dealing with both of those sides of this balance will we stop dealing with the tail of the comment, the effects of abuse, and start getting ahead of the comment to maybe redirect the course towards better care.

Finally, I believe that -- and I know I speak as many of you know about sustained opioids simply being tools, and that tools can be used or misused. We have two populations using them: those that absolutely need them and have to have access and need to be managed expertly -- we need to assure that -- and those who misuse. I think we need to address those populations very separately.

Thank you.

ACTING CHAIRMAN KATZ: Thank you very much.

The next speaker, please.

MR. BROATCH: Good morning. My name is Jim Broatch, and I'm Executive Director of the Reflex Sympathetic Dystrophy Syndrome Association of America. We're dedicated to promoting greater awareness of an encouraging research into reflex sympathetic dystrophy, or RSD, also known as complex regional pain syndrome.

About ten to 15 percent of our budget is

provided by unrestricted grants from pharmaceutical medical device companies.

RSD is a neurological syndrome characterized by intense burning pain, pathological changes in skin and bone, sweating, tissue swelling, and extreme sensitivity to touch. It generally results from some kind of trauma, and the consequence pain is much greater than the original injury.

Some patients report that a breeze created by a ceiling fan causes excruciating pain. A Johns Hopkins spokesperson remarked about RSD severity thus, "If hell were a clinical medical condition, it might look like RSD."

Anyone could get it. Most people have it between 25 and 55. It's more frequently seen in women than men. The incidence is unknown, but it's estimated between 1.2 million and six million individuals in the U.S. have it. It could literally rip your life apart, destroying your career, social network, finances, marriage, and family.

I'm here today to present this committee with hundreds of personal communications from our members and others in the chronic pain community who are incredibly fearful that the FDA will restrict the availability of opioids or withdraw or restrict

Oxycontin in the market. It's not a farfetched notion.

Already in a number of states Medicaid has restricted patients' access to Oxycontin. Increasingly we are receiving reports that patients are switching chronic pain patients from Oxycontins to often less effective pain killers because of their fear of increased regulatory scrutiny.

To help chronic pain sufferers in the medical community manage the use of opioid painkillers, we have published the opioid contract on our Web site. The testimonies that I'm presenting to the committee are from concerned patients, patients with RSD, others suffering with chronic pain. They represent a wide range of educational, socioeconomic levels, including disabled police officers, registered nurse, truckers, stay at home moms, the formerly rich, and the poor.

Their message to the committee and to the FDA is simple. Using opioids for chronic pain has improved the quality of their lives, although most are not working and subsist on some kind of disability related compensation. Opioids, especially Oxycontin, have allowed them to be more productive members of our society.

Donna Isaacs, a six year RSD sufferer, summarized the current situation well when she wrote, "I take Oxycontin every day for my pain. I'm find it more and more difficult to get my medicine because of all the media coverage. I've been to at least four drug stores that don't carry my medication because of the media coverage, and I panic every day I go to get my medicine praying that I'll be able on that day to get it filled. I need my medication every day just to get out of bed."

Thank you.

And I'm going to present this to the committee, and I hope you'll have time.

ACTING CHAIRMAN KATZ: Thank you, sir.

Next, please.

MS. ANDERSON: Good morning. My name is Kathleen Anderson. I'm the Director of Governmental Affairs for the American society for RSD/CRPS. I have no disclosures.

The recent bad press regarding Oxycontin and the future of opioids is of great concern to the members of the American Society for RFD and the community of patients and caregivers we represent. Reflex sympathetic dystrophy has one of the highest chronic pain ratings as indicated on the McGill pain

index. Placing additional restrictions on opioid analgesics will prolong the suffering of RSD patients.

Presently pain management centers are limited. Treatments revolve around medications, physical therapy, psychological therapy, and invasive surgical procedures. It takes an average of two years to be diagnosed with reflex sympathetic dystrophy, and once diagnosed, most patients must see an average of 4.5 physicians before their pain is treated.

How much longer will it take these patients to get relief if tighter restrictions are enforced? Will they live that long?

Suicide is one of the leading causes of death in RSD patients in the United States today. Until more facilities are established and HMOs cover their costs, patients will continue to use primary care doctors and a variety of specialists to obtain medications for pain relief.

Knowing these facts, we cannot limit the dispensing of opioids.

I am the parent of an 18 year old who has been suffering with reflex sympathetic dystrophy for the past three years. Do I worry about the effects of her medications? Yes, of course I do. But my worries about the effects of these drugs are secondary to the

torture she endures with this illness. The pain is debilitating and relentless. It is inhumane.

Last week I watched with a broken heart as my dear friend buried her 20 year old daughter, Britney McMurty of Glastonbury, Connecticut. Her spirit was much stronger than her body after being ravaged by the pain of the RSD for the past four years.

Is that the same fate I have to look forward to?

The federal government needs to appropriate fund to establish multi-disciplinary pain clinics to insure that RSD and other chronic pain patients get timely and proper medical treatments. It would eventually allow a majority of opioids to be prescribed from centralized facilities by the pain experts. These facilities could house training seminars to educate the medical community.

I ask this committee to rethink the idea of enforcing additional restrictions on the dispensing of opioid analgesics. People in pain are a vulnerable population. We need to pursue education, awareness, and research in the area of chronic pain. Until pain is better understood, we need to place the burden on those responsible for opioid abuse, not the victims

themselves.

Thank you.

(Applause.)

ACTING CHAIRMAN KATZ: Thank you very much for your comments.

Next please.

MS. McLAUGHLIN: Hi. My name is Kathy McLaughlin from Hospice in Northern Virginia. I'm representing the Hospice and Palliative Nurses Association Board of Directors today.

The HPNA has received small amounts of pharmaceutical monies to assist in publication costs for clinical publication tools. That's the only thing I can disclose at this point.

Our membership represents about 4,000 professional nurses across the nation, and I'm a registered nurse, a member of the Hospice and Palliative Nurses Association, and I'm a Board certified Hospice palliative nurse.

I'm presently practicing as the nurse case manager of children and adult patients and their families in their own homes through the Hospital of Northern Virginia.

Every day thousands of patients with unrelieved pain are referred to Hospice or palliative

care programs across the nation. Opiate analgesics are a critical element in the appropriate management of pain, especially cancer pain.

Time released opiate analgesics available in multiple strengths have been the mainstay of most of our programs. They're prescribed in increasing amounts because of the simple reason that they're cost effective and they work.

Unfortunately, though they work well for adults, the present available formulations are not always appropriate for children and dying patients.

At present Hospice care providers of at least two groups are confronted with the task of tailoring the adult preparations of the market for diverse size patients. Calculating initial dosages are based upon the patient's height, weight, age, and medical status. The doses are then titrated to patient response and by frequent medical and nursing assessment.

The concentrated oral solutions are the easiest to administer due to the small volume needed. Extreme care in calculating dosage and instruction of the caregivers is paramount for safe delivery. These can be administered via feeding tube if present, but most of our patients don't have that.

Unfortunately, these preparations are relatively short acting in duration and require frequent dosing, a burden to patients' families and caregivers, especially in a home setting.

The long acting tablets are not often the answer because they can't be crushed, and as we've seen in the news, it's not a good thing.

The transdermal patch in the long acting, microencapsulated forms are often too high a dosage for the children in our population, as well as the very old and some of the dying.

Intravenous, subcutaneous, and rectal routes are also other choices for administration, but need to be used judiciously since they are invasive and often anxiety provoking for many of the children and their families.

All of the above-mentioned preparations have helped maintain many children comfortably in their own homes with the support of the Hospice interdisciplinary team. By my own practice, it would seem that a long acting opiate analgesic solution or suspension would be extremely beneficial not just for infants and children in a population, but for all those who have difficulty swallowing tablets.

And also the HPNA Board of Directors urges

very careful consideration surrounding any action that might restrict the availability of opiate analgesics and any further action to limit the availability of opiate analgesics either by decreasing production or require any sort of preauthorization for the medication would undoubtedly serve to inhibit affected pain management. The result would be unnecessary and unrelieved pain and suffering.

Thank you very much.

ACTING CHAIRMAN KATZ: Thank you.

Next, please.

DR. LEVY: Good morning. My name is Michael Levy. I'm the Director of the Pain Management Center of the Fox Chase Cancer Center in Philadelphia. I'm here on my own accord and support as a pain expert from an NCI designated comprehensive cancer center.

In the past 20 years, I've received research support and been on the Speakers Bureau of ANESTA, Janssen, Knoll, Purdue Pharma, Ortho-Biotech, and Centicor.

We are in the midst of two epidemics: the epidemic of unrelieved chronic pain and the epidemic of Oxycontin abuse. I speak today on behalf of the patients with chronic pain and the health care

providers that treat them.

The cure for the current Oxycontin abuse epidemic must not increase the suffering of legitimate patients with chronic pain. Ready access to Oxycontin is essential to our ability to provide safe and effective comfort and function to thousands of patients throughout this country.

Despite heroic efforts over the past 20 years by individuals and organizations to teach clinicians how to properly assess and treat chronic pain, surveys still show that half of the chronic pain patients in this country are under medicated. Last year the Joint Commission on Accreditation of Health Care Organizations enacted new standards for pain control to try to correct these system-wide inadequacies. Just when physicians are advocating or being pressured to provide better pain management, one of their best tools is being threatened.

Over the past six years Oxycontin has set a new standard for the relief of chronic cancer and non-cancer pain. Oxycontin has been shown to be a safe and effective analgesic in the control of pain caused by cancer, osteoarthritis, post hepatic neuralgia, major surgery, and degenerative spine disease.

Oxycontin has the characteristics of an ideal opioid analgesic, short half-life, long duration of action, predictable pharmacokinetics, absence of clinically active metabolites, rapid onset of action, easy titration, no preset ceiling dose, and minimal adverse effects.

The escalating abuse of Oxycontin is a double tragedy. The first tragedy is the fact that individuals with a disease of addiction have found a new substance to abuse. Oxycontin abuse has led to violent crimes by abusers, pushers, and prescription diversion by deviant physicians and pharmacists.

The popularity of Oxycontin abuse has also resulted in the inadvertent deaths of inexperienced drug abusers.

The second tragedy of Oxycontin abuse is the fact that legitimate pain patients are having increasing difficulty utilizing their appropriate prescribed Oxycontin. Patients are afraid of taking their Oxycontin, afraid of becoming victims of violent crime, afraid of being ridiculed by their friends, family, and uninformed health care professionals, and afraid of not being able to obtain adequate prescriptions.

In conclusion, the interventions aimed at

reducing the public problem of Oxycontin must not interfere with the safe and effective use of the patient problem of unrelieved chronic pain. Substance abusers need to be kept from obtaining their Oxycontin and need comprehensive mental health care services to deal with their addiction.

Legitimate pain patients need ready access to Oxycontin. Legislators, regulators, and law enforcement agents and health care professionals must work together to heal our society and reduce the suffering of our citizens.

Thank you.

ACTING CHAIRMAN KATZ: Thank you, Dr. Levy.

Next, please.

DR. WILSON: Good morning. I'm Peter Wilson, professor of anesthesiology and pain medicine at Mayo Clinic, Rochester, Minnesota. I represent the American Society of Anesthesiologists, some 35,000 physician anesthesiologists.

I've been working in the anesthesia subspecialty field of pain management for more than 20 years, and although I've published animal and clinical studies in opiates, I haven't received pharmaceutical industry support for this. I have not received

pharmaceutical industry support.

It's quite clear that opioids are essential for the control of pain during surgery, other acute pain states, cancer, AIDS, other terminal illnesses and for some chronic pain states.

Long acting opioids provide a more stable blood level orally than short acting opioids and are, therefore, more effective for pain management. Methadone is the only clinically available oral opioid with an intrinsically long half-life, but it's extremely variable and quite tricky to use.

Other opioids have to be formulated at a sustained release preparations.

Misuse or aberrant behavior and diversion of appropriately prescribed opioids by legitimate chronic pain patients is rare. The use of patient contracts and/or random blood or urine screening for substances has note been shown to improve compliance or reduce diversion.

Inappropriate patient selection, inappropriate prescribing usually reflects a lack of training and experience of the prescribers rather than malfeasance. Aberrant patient behaviors with respect to opioids, including doctor shopping, really should be monitored by the DEA and state medical and pharmacy

boards, not by the FDA.

The DEA and state medical board should also monitor and enforce legislation and regulations against aberrant prescriber behavior, including unethical, inappropriate, and illegal activities, pill mills, Internet, and absentee prescribers.

Aberrant prescriber behavior leading to diversion is a function of the prescriber, not the medication, and again, the DEA and state medical and pharmacy board should address this, not the FDA, and we do not believe that any non-physician representative should be in the position of making clinical judgments.

Restriction of a legitimate supply of opioids will lead to rationing, which will adversely affect provision of pain relief to all pain patients, acute, chronic, terminal, the young, the old the disabled and the disadvantaged.

Thank you.

ACTING CHAIRMAN KATZ: Thank you, Dr. Wilson.

Next, please.

DR. RAMIREZ: My name is Jeff Ramirez. I'm representing the Veterans Health Administration. I have no personal disclosures, though my agency does

conduct medical research that is funded by the pharmaceutical industry, and we do receive educational grants.

Many veterans, like 20 to 30 percent of civilians, annually suffer from pain. Further, these veterans had devastating injuries related to the service to their country that may have resulted in chronic pain. In many cases their suffering has not lessened with time, but rather made worse by the accompanying degeneration occurring with age.

In some cases, surgical interventions may provide some relief. However, in most patients with chronic pain related to chronic disease or musculoskeletal injuries, there is no simple procedural cure. In these patients, the use of chronic opioids has provided a means of controlling their pain and increasing their ability to participate in society.

The VA has been in the forefront of recognizing the treatment of the significant health care problem of pain. We have implemented pain as the fifth vital sign throughout all of our medical facilities, in recognition of its importance and to emphasize assessment and treatment.

In addition, there are large scale efforts

to develop provider and patient educational programs, treatment guidelines, and promotion of research activities and training programs related to the understanding and treatment of pain that has been undertaken throughout the VA. Within these efforts are programs specifically to address opiate prescriptions and management.

Proactive, aggressive management of both acute and chronic pain is universally recognized as an essential component of health care. However, substantial evidence indicates that neither acute nor chronic pain is adequately treated within most United States health care systems.

This has been recognized as a new standard of care regarding the assessment and treatment of pain as we have implemented it throughout the VA. When patients report with pain, we teach our physicians and other health care providers to believe their statement of pain.

When encountered by patients in pain, we would all like to provide them relief if possible. In many cases the most important treatment is opiate therapy.

When patients are prescribed opiates for pain control, there's no question that there is a

potential for diversion or misuse of the medication. These problems, which are infrequent, can be minimized by the prescribing physician for following things like having careful discussions with a patient on the use of opioids before the first prescription is written, and entering into opiate contracts with patients and maintaining appropriate records.

The VA is responding to concerns about diversion by developing guidelines in this area and utilizing many of our electronic medical records and our electronic prescription records in order to check for patients who do try to get opiate medications from various medications.

But to summarize, the currently available, long acting opioid pain medications have improved pain control for patients needing these medications. The misuse of these medications by a small number of individuals does not negate the very positive impact that these sustained delivery systems have on patients with chronic pain from a variety of conditions. The removal of these medication or excessive regulation will have a negative impact on the willingness of health care practitioners to provide pain treatment throughout the VA and throughout the United States.

Thank you.

ACTING CHAIRMAN KATZ: Thank you.

Next, please.

DR. MERRICK: Good morning. My name is Randy Merrick. I am a Board certified family physician from a rural county in Virginia. I'm here speaking on behalf of myself and my patients. I am self-funded with no disclosures.

I appreciate being invited to comment today as a practicing family physician who has treated Hospice and non-cancer chronic pain patients for over ten years.

The use of opioids to treat these patients has been a cornerstone with other complementary treatments if available.

Once visited by an intimidating group of State Police and Board of Health profession officers, I took advantage of my situation and became a member of a task force for the Medical Society for the State of Virginia and helped co-author guidelines for the State of Virginia for the treatment of chronic non-cancer pain.

These guidelines later became one of the templates for the National Federation of Medical Board's guidelines published. I have long held the belief that the family physician who deals with all of

the bio-psychosocial aspects of our patients, children and adults, are one of the best trained physicians to deal with our patients in chronic pain.

After the attempts of our colleagues in the specialties, such as neurosurgery and orthopedics, failed, eventually the buck stops here with me, the family physician. Testimony after testimony from those I treat who have been returned to qualify of life faced with chronic pain proved to me that my treatment of their pain is as legitimate as my treatment for their diabetes, hypertension, depression, et cetera.

As the buck stops here, I also realized that I have an obligation and a responsibility to insure that my patients adhere to my patient-doctor contract that allows me to use opioids to treat the chronic pain.

When I hear of even the slightest insinuation by any source that one of my patients may be diverting their opioid medication or exhibiting addictive behavior, I take action by informing my local authorities of possible diversion or requiring my patients to be evaluated for substance abuse and treated for addiction.

We have an obligation as family physicians

to assume that what our patients tell us is true regarding their pain. There lies the essence of the doctor-patient relationship. When nothing else is left to be offered for treatment of their chronic pain, we as family physicians are obligated to use whatever we need, whatever message, whatever medications that we need to treat these patients, to allow them to return to a quality of life.

As a coroner for two counties, I have recently investigated over the last two years three suicides because patients were unable to gain treatment for the chronic pain. We certainly have a job to do.

The American Academy of Family Physicians and my state chapter are aggressively educating all of our physicians in the treatment of chronic pain.

Thank you.

ACTING CHAIRMAN KATZ: Thank you, sir.

What I'd like to do now since all of the speakers have come up is just make sure that some of the folks on the list for this morning haven't lost the opportunity to go, and what I'll do is read through the names very quickly of people who are on the list for this morning, and if you're here, please come up and take your turn. If I mispronounce your

name, I apologize.

Dr. Manchikanti, Skip Baker, Cynthia Simonson, Barbara Ann, Stephen Plotnick, Aaron Gilson, Ronald Kurstin, Myron Yaster, F. Michael Gloth, Michael Kaplan. Any of those folks here?

Since we do have a little bit of time, we'll proceed on to the list of folks who requested an opportunity to speak and were put on a waiting list. Let me read through your names quickly, too, so you can prepare yourselves if you're still interested in speaking to come up and sit in the speaker ready chairs.

Dr. Babul, you'll go first.

Dr. Van Zee, if you're here, you'll be next.

And the other folks in order are Mary Kelly Sohm, Laurie Torres, Cyn Hoard, Katt Morris, Jay Steffler, Lynda Langhorne, Mary Winfield, Robert Root, Lonna Gutierrez, and Dr. Dahlquist.

I'm not sure we'll have time for everybody, but if you're around, please prepare yourself to come to the speaker ready position.

Dr. Babul, please.

DR. BABUL: Good morning. My name is Najib Babul. I'm with TheraQuest Biosciences in East

Norriton, Pennsylvania. I've been involved with analgesic drug development for over a decade. I'm here on my own accord due to my scientific interest in opioid drug development and my interest in public policy issues surrounding patient access to opioids.

I do consult with a number of pharmaceutical companies in analgesic drug development, some of whom market or are developing opioid analgesics.

I would like to speak to the committee on the issue of a core development program for analgesic drug development, which is the subject, I believe, of your morning deliberations.

I think the committee and the division need to consider a number of key questions in the development of analgesic agents, and I'd like to identify at least some of the questions that may help the committee with its discussions.

The first issue really is whether if a drug is pharmacological effective in acute pain and in chronic pain and there are no formulation related barriers to its developments for both indications, whether the agency should consider approving the drug just for acute pain or just for chronic pain or whether it should be a requirement that both

indications be studied simultaneously.

The other issue is whether acute pain data in any way support the efficacy of a drug in chronic pain. How many chronic pain disorders or models, as we like to call them, need to be evaluated? What are some of the suitable models that we are to consider? Is it reasonable to study mixed models given the clinicians often see a very heterogeneous group of patients?

What is an appropriate duration for a clinical trial in chronic pain? And should cancer pain be in the mix of studies in chronic pain or should that be a separate indication?

And if it is a separate indication, is it likely to become orphaned, given that cancer pain studies, as a number of us know, are challenging?

Now, I would like to in the interest of time restrict my comments just to new chemical entities that are the subject of a 505(b)(1) approval and would like to suggest that drugs that are in process right now at the FDA perhaps require different consideration.

I would suggest that it's important for us to do a proof of concept study to very carefully identify a no effect dose or a minimum effective dose

for any new chemical entity that's approved as an opiate analgesic; that we need to carefully characterize the dose response characteristics of the drug, and that we need to establish very carefully prospectively the dosing frequency of such drugs.

In addition, I would suggest that at least one and possibly replicate evidence should be necessary for the approval of drugs involving at least a 12 week duration of efficacy so that we can clearly assess not just efficacy, but the durability of response which is a question that clinicians have.

And finally, that if cancer pain is part of the mix, then we ought to have at least one adequate and well controlled study in cancer pain involving a minimum two week duration.

One additional point is that for centrally acting drugs, as opioids are, clinicians need guidance on acute and chronic effects on psychomotor and cognitive skills, and this is something that perhaps the committee and the agency ought to look at for approval of such drugs.

Thank you.

ACTING CHAIRMAN KATZ: Thank you, Dr. Babul.

Next, please. Dr. Van Zee, are you here?

Please begin with any disclosures.

DR. VAN ZEE: Yeah, my name is Dr. Art Van Zee. I have no disclosures.

I've practiced general internal medicine in a small Appalachian coal mining town, St. Charles, Virginia, for the last 25 years. My region of the country, as you probably well know, was one of the earliest areas affected by Oxycontin abuse and addiction.

It would be very difficult to overstate the degree of devastation this has brought to central Appalachia and now widespread in many regions of the country. There have been at least three major factors which have played a major role in this epidemic of Oxycontin abuse.

First, there's been an obvious problem with misprescribing and over prescribing of this drug.

Second, this epidemic has been a vicious indicator of the extent of prescription drug abuse in our society.

Thirdly, and the one which might be closest to the FDA here is that of the promotion and marketing of Oxycontin by Purdue Pharma, which I think has played a major role in the problem.

Purdue Pharma in the most extensive opioid

promotion in the history of the industry has used sophisticated marketing data to determine which physicians in the country prescribe opioids most liberally or least discriminately, if you will, and couple this data with lucrative financial incentives to their sales representatives.

One sales representative in Florida made $100,000 over and above their $50,000 of salary in the year 2000 based on the high Oxycontin sales in her territory.

Purdue has used thousands of company sponsored talks and seminars that have been well documented in the medical literature to influence physician prescribing and practices. Purdue has lobbied the primary care physician to a great extent, and primary care physicians as a general rule have the least amount of skills in pain management and addiction issues, at least suboptimum.

Purdue continued free Oxycontin promotion pills up until July 2000 in a campaign to promote it. The company has had an extensive and sophisticated non-branded promotion of opioids in general in which the benefits of opioids for chronic, nonmalignant pain have been much overstated and the risk trivialized. And all of this has contributed to the commercial

success for Purdue at the expense of the public health.

This now is the opportunity for the FDA simply that the current regulations governing the way the pharmaceutical industry can market and promote opioids or any controlled abusable drug has not served well the public health. Not to radically change those type of regulations at this point would give sanction and safe harbor to the drug companies for the continuation of such business practices, which do not serve any of us well.

Thank you.

ACTING CHAIRMAN KATZ: Thank you, Dr. Van Zee.

To my surprise we have time left in this open session, and so what I would like to do now is in the few minutes that we have if there is anybody in the audience among us who would like to take three minutes to share an thoughts, then people come forward and have a seat in the speaker ready chair, and we'll take you in turn as time allows.

Please begin by saying who you are and what you do and if you have any disclosures to make. Go ahead.

MR. STEFFLER: Hi. My name is Jay

Steffler. I've no disclosures to make.

I've suffered from RSD since 1992. I spent eight years with my doctor, doctors, trying every modality known to medicine to try to cure me of the RSD, and from all of the sympathetic lumbar blocks that they gave me, I developed myofacial syndrome and arthritis.

After finishing all and trying every modality, the doctors would give me small amounts of opioid medication when, in fact, it was not enough, and too little actually is worse than taking the proper amount.

And the only way that a chronic pain patient can abuse their medication is to give it to someone to whom it's not prescribed. The only other way is if the doctor that they are seeing is not giving them enough medication. then they are forced to go see several doctors which ends up in mixed medication which can kill the patient.

When the patient with RSD sees one physician who is regulating their medication, they're entire life returns to them. I feel like I have come out of a coma. I haven't had to use a cane for two years. I was bedridden for those eight years. I am now going back to work, working through OVR. Before

that I was, as I said, completely bedridden.

And now the only problems I have now is that I'm a slave to the insurance company. I am only allowed to -- because they will only dispense so many days of my medication at a time, I'm only allowed to leave my house for ten days at a time maximum.

So the opioid therapy -- when they took me off all of the experimental medications that they tried me on, I came out of a coma. I literally do not remember what went on during those eight years from the Soma (phonetic) and all of the different families of antidepressants, not for depression, but for the side effects. I couldn't remember what happened during those eight years, and I literally feel like I've got a second chance at life. I feel like I've just been born, and it's a whole new world to me.

In the past two years since I've started the opioid therapy, I've been getting my body back into shape. Atrophies muscles over eight years do not come back after a couple of months. It takes quite a while.

So after the two years -- it's been two years, and I am now working. I'm going back to college, get my second degree, and I'm also teaching, and it has given me a whole new life.

And in fact, even the pharmacists are shocked when they see the medication that I take. They say themselves, "How are you standing here?" when, in fact, before I couldn't do anything and I couldn't stand there when I was on the other medications that didn't work.

Suddenly my mind came back. I'm able to think again. Movies that I saw during that eight year period I don't remember, I have no recollection of. Now my mind is back. My desire for life and everything, my who life has come back to me.

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

MR. STEFFLER: The problems with the Oxycontin, I think the DEA needs to focus more on the people who are healthy who abuse the medication instead of focusing on the chronic pain patients and doctors who are for people who need it.

ACTING CHAIRMAN KATZ: Thank you very much.

MR. STEFFLER: Thank you.

ACTING CHAIRMAN KATZ: Next speaker, please.

DR. DAHLQUIST: I'm Glenda Dahlquist. I'm

a chronic pain management physician from Dayton Ohio. I'm a member of the American Academy of Pain Medicine, and I'm also the Chairperson for the local pain society in Dayton, Ohio, and we are currently in the process of gaining state chaptership from the national organization, the AAPM.

I am a speaker on the Board for Purdue Pharma and Janssen. I have no other disclosures, no research grants.

And I'd like to make one comment. I'm not on the Speaker Bureau for Purdue. I mean, I don't use Oxycontin because I'm a speaker. I'm on the Speakers Bureau because I believe that Oxycontin has benefitted so many of my patients, and they finally asked me to speak on their bureau after I had prescribed it for four years, seen the benefits that it's given to my patients when used appropriately.

One other comment I'd like to make is with our local pain society. With the recent media coverage and fears of license or sanctions, even chronic pain physicians in our area have decreased their prescribing of Oxycontin, and I think this is very sad because we as chronic pain physicians, we're the top of the ladder when it comes to dealing with chronic pain patients. The family doctors may not

feel comfortable prescribing high doses of opioids. The internal medicine specialists may not feel comfortable delivering high doses of opioids to patients who have high drug tolerances and high needs in order to function appropriately.

We as chronic pain physicians are the ones who deal with these most severe patients, and now we're seeing an epidemic of chronic pain physicians who are afraid they're going to lose their licenses, and nobody in the community will treat these patients.

I'd like to point out real quickly, too, I haven't heard anybody speak about not the detriments just relating to the humane part of treating pain management, but what about the medical problems? When a patient is in pain, their stress hormones increase. This can lead to worsening other chronic diseases such as hypertension, heart disease, diabetes. They have to increase their insulin doses if the blood sugar goes up too high because they're under too much stress.

Suicide rates. I had a patient who finally did commit suicide because she had left my practice and gone to another pain physician who wouldn't treat her appropriately, and we heard just from another coroner that he has done an autopsy on

patients who have committed suicide because of that.

These patients, if they're not given the appropriate pain medicine, will turn to over-the-counter medications, nonsteroidal anti-inflammatory agents, handfuls of nonsteroidal anti-inflammatory agents causing GI bleeding and things like that.

We really need to be able to treat these patients appropriately before we cause worsening medical problems --

ACTING CHAIRMAN KATZ: I'm sorry. I'm going to have to --

DR. DAHLQUIST: -- people on the welfare system --

ACTING CHAIRMAN KATZ: -- ask you to bring it to a close.

DR. DAHLQUIST: -- and people not being able to be treated appropriately because of the inadequacies of the medical profession.

ACTING CHAIRMAN KATZ: Thank you very much.

Why don't we then call the open session to a close? Let me thank all the folks who took time out of their schedules and made the effort to make it here to share their thoughts with us, in particular, the folks with chronic pain themselves. Thanks very much

for coming.

It seems like there are one or two folks on the Advisory Committee or guests that have drifted in since we did our morning introduction. So perhaps they could take a moment to introduce themselves and let us know what your names are and who you are.

Dr. Connolly, would you like to begin?

DR. CONNOLLY: I'm Maria Connolly.

ACTING CHAIRMAN KATZ: You have to press the red button on your mic.

DR. CONNOLLY: I'm Maria Connolly, and I'm a consumer representative on this panel. And I flew in from Chicago with a big snow storm, but in San Diego yesterday afternoon it was pretty nice.

ACTING CHAIRMAN KATZ: Thanks.

Dr. Schechter.

DR. SCHECHTER: Hi. I'm Neil Schechter. I'm a pediatrician, and I run the pain relief program at the Connecticut Children's Hospital, and I'm interested in pediatric pain specifically.

ACTING CHAIRMAN KATZ: Thanks.

Was there anybody else that drifted in that I didn't notice?

(No response.)

ACTING CHAIRMAN KATZ: All right. Then

what we'll do now is I'll reintroduced Dr. Rappaport from the FDA, who will give some introductory comments for our morning session, which will be on opiate analgesic development and use.

DR. RAPPAPORT: This morning's session is on opiate analgesic development and use. The framework for the agency decisions includes the regulatory restrictions and requirements defined by the Food, Drug, and Cosmetic Act.

This allows not only for decisions to be based on scientific integrity. It also provides a level playing field for the commercial sponsors of the new drug applications, thereby preventing arbitrary and capricious decisions by the FDA.

One of the final products of our labor is the product labeling. The label may contain only information supported by data submitted in the new drug application. However, this data may lead to difficult choices on how the label is written.

For instance, for new, modified release opiate analgesics studied in only low back pain patients, we may result in an indication limiting the drug's use to the low back pain patient population.

In your discussions this morning, keep in mind the difficulties we at the agency face daily when

we try to mesh the available data with the regulatory framework in order to provide product labeling that clearly states the findings of the clinical studies in a manner which will be most beneficial to prescribers and patients.

We hope that the following presentations will provide you with a foundation upon which you can build your discussion of the points we have raised in the background package for this meeting.

Thank you.

ACTING CHAIRMAN KATZ: Thank you, Dr. Rappaport.

Dr. Levy will now get up and give us a discussion on pain treatment guidelines.

Dr. Levy.

DR. LEVY: Good morning, everybody. We've been sitting here for a while. Let's take two minutes to stand up and relax for a second before you start listening to lectures.

Don't go outside. Just relax.

(Pause in proceeding.s)

DR. LEVY: Okay. Now you can sit down. We don't want anybody getting chronic pain here just from sitting and having dependent limbs.

This morning I will try to speak to you on

three specific issues. One, just to describe my background from an historical perspective very briefly because I may be probably the person who has treated pain here the longest, or one of them, over the years.

Two, I'd then like to tell you about the Texas perspective and how that led to the first guidelines in the country, and then the federation guidelines, which were a result of those in some other states.

Twenty-six years ago I was attending in the pain clinic at the University of Washington, which was probably the first multi-disciplinary pain clinic in the United States. That was the days before any of these initial organizations ever existed.

We created the International Association for the Study of Pain then, and that was an innovative creation. None of this had occurred before.

I tell you this for one reason: because when I started treating pain, opioids were an anathema. None of us were to use opioids in any way, shape or form, except to put people on pain cocktails which were a combination of methadone and sedatives to get them off narcotics. And that was the whole purpose, and it was that way for many years until the writings of Dr. Portenoy and others that led us to

believe that these drugs had a basis for treatment in chronic pain, end of life care, et cetera.

So my mindset had to go full circle to get from where I started to where we came in '93, and now, like anything else, we may have gone a little too far, and we have to come back.

I tell you that because that is the history of what you do when you look at different aspects of things.

Now, in Texas, we had an intractable pain statute in 1989. It did nothing. It did not increase the use of drugs or help patients get treatment, and the reason being is that doctors were still afraid that if they prescribed, they would be disciplined by the Board.

Now, I was recruited by then the governor's office, et cetera, and I became the Executive Director of the Texas State Board of Medical Examiners, which regulates the practice of medicine in the State of Texas.

At that point there were really no states with guidelines or ways of prescribing or advice to physicians. In fact, the word was that if you prescribed, you were going to be disciplined.

Now, the reason was we were given a count

from the Department of Public Safety on every narcotic written, and I would get a readout every month of all the narcotics written or opioids and sedatives written by physicians in that state.

And prior to 1993, investigations would be open just on prescribing habits. When I became the Director, that stopped. What we did was bring all the pain directors together in that state. We brought the professors. We brought the public groups, et cetera, and we got together and decided how pain should be practiced.

And that's what led to our guidelines. And we had some definitions that other people then came to accept. Nontherapeutic prescribing was a medical use or purpose that is not legitimate. That goes back to the law of the 19-teens.

A prescribing pharmaceuticals are practicing consistent with public health and welfare, is prescribing pharmaceuticals and practicing medicine for legitimate medical purpose in the usual course of professional practice.

What is intractable pain? A pain state in which the cause of the pain cannot be removed or otherwise treated and which in the generally accepted course of medical practice no relief or cure of the

cause of the pain is possible or none has been found after reasonable efforts.

You're all familiar with this, but in 1994 when we wrote these, no state had ever taken this position before. We basically that if you're going to prescribe narcotics, counting pills is not the issue. The issue is: are you going to practice good medicine?

And how to determine whether you practice good medicine is whether you take a documented medical history; you do a proper physical examination; you do and have recognized medical indications for the use of those drugs; you have a written treatment plan; you discuss the risk and benefits of the medications with the patients; you do periodic review at reasonable interviews; you keep complete and accurate records; and you closely monitor the patients with any kind of history of substance abuse.

If you do this, you're not going to get in trouble. If you don't, you were, and it became very obvious which physicians were having a problem in the State of Texas because they didn't practice this way. You would go and look at their medical records, and they would write, "Low back pain. Dispense 100" -- whatever the drug was, and that was it.

Well, you don't have to be a rocket scientist to figure out this is not good medical practice, and those physicians we disciplined. But the ones who followed the guidelines were not.

What are the red flags? Issuing prescriptions for large amounts of controlled substances or in excess of prescribed dosage, but knowing certain physicians' practices and how they practice, this became less of an issue as time went on. But failing to keep accurate records, failing to evaluate or monitor their patients, prescribing to drug dependent persons without adequate consultation, evaluation, or monitoring, these were red flags that enabled us to discipline physicians that were not practicing good medicine.

When you look at these numbers, those are the number of disciplinary actions against physicians in the United States from 1993 till 2000 that we've tabulated. The numbers, they're a little rising, but they're pretty much the same in that proportion.

What you can see thought is that controlled substances violations have stayed down pretty low since the time that guidelines have come into play. Prior to this, there were a large number of disciplinary actions solely on the writing of

narcotics.

The other thing is contrary to what you heard today, there are not a lot of suspensions or revocations of licenses because of controlled substances writing. They are not happening. They are only happening when there is improper prescribing and improper management of the patient.

They are old wives' tales. They are fear tactics, but they are not occurring.

Now, what's the challenge? The challenge is to protect the medical uses of controlled substances and simultaneously preventing drug diversion and abuse. That's the challenge we all have here.

But in the same time we have to insure public access to effective pain control. We have to weigh both. If you overregulate, the public doesn't get adequate care. If you under regulate, you don't have the proper vehicle for proper medication and proper treatment. This is what the boards must do.

The present status is that only eight states have no policy. In 1993, only two states had policy, Texas and California. So this has been a major jump in the last seven or eight years.

Those that have guidelines and statements

amount to the majority of the states. You'll see that the numbers overlap. It's not that I can't count. It's that certain states have more than just a guideline. They may have a statute, et cetera, and they have chosen to either create regulations or create statements or guidelines or a combination.

The real critical factor here is that only eight states have not taken action on this. At that point, after the Texas guidelines came out, the Federation of State Medical Boards then felt that this was an issue and brought together a committee on which I served, as well as, I believe, another seven or eight members, and we created national guidelines that the federation would publish. We had public hearings, and then were recognized by all the states and used as model guidelines.

That was funded by the Robert Wood Johnson Foundation.

We developed those model guidelines for the use by state medical boards and other health care regulatory agencies to promote the appropriate prescribing of controlled substances in the management of chronic malignant and nonmalignant pain.

Our objectives were to establish consistent standards for managing chronic pain based

on current research data. And we wanted to promote a nonlegislative approach, a regulatory approach that the state boards could advocate to address the use of controlled substances in the management of chronic pain.

Why was that important? Because we wanted a mechanism in which those people that were regulating the practice of medicine -- and most boards are made up of usually about two thirds physicians and one third public members, who had been in this kind of practice or could get the information from that kind of practice without making it a statute, but still have the regulatory aspects.

Why is a regulation so much important versus a statute? Statutes are difficult to change. Regulations are not. If the research had changed or there was some other issue that had come up, a board could change their regulations in a few months. They could tweak them, but you can't do that with a statute.

So the recommendation was to keep this on a regulatory aspect, and that has worked well in most states.

So what do these model guidelines really advocate? I'm not going to read all of them to you.

I'm going to basically tell you this. When it's all said and done, they dome down to if you do a physical examination of the patient, treatment plan, informed consent of the patient, periodic review of drug treatment, consultation and referral if necessary, accurate, timely, and complete medical records, you will not get in trouble with the medical board.

You will if you're writing prescriptions and people are hanging out of your office around the block.

The grant was extended through last year. We created workshops for board investigators. We developed position papers. We communicated with all of the member boards. We created the position, the model guidelines, and we targeted those eight states without policy to work on those.

The next phase will be to improve the quality of patient care through appropriate and effective pain control and build relationships to increase physician knowledge of current standards for appropriate pain treatment. And we must insist and inform the license population of state specific regulations regarding physician responsibilities and treating pain.

Thank you very much.

ACTING CHAIRMAN KATZ: Thank you, Dr. Levy, for a very lucid presentation.

Dr. Levy, why don't you stay there for one minute?

Does anybody sitting around this U-shaped table have any questions for Dr. Levy about his presentation?

DR. LEVY: Yes, sir.

DR. HOLMBOE: Hi. Eric Holmboe from Yale University.

Just out of curiosity, as we know, there are a proliferation of guidelines for a myriad of conditions, and one of the biggest problems is to get physicians to use them. Simply putting out a guidelines has not been shown to be effective in changing the quality of care.

I'd be curious if you could just spend a moment or two describing how you disseminated these guidelines to your physicians and whether or not that was effective.

DR. LEVY: One, I will tell you that guidelines that are practice guidelines must be differentiated between regulatory guidelines. For the first time, the medical board took a position in saying in this condition, we require this to be the

good practice of medicine.

We didn't do that for diabetes of hypertension or heart disease, et cetera. We did do it for chronic and malignant pain and acute pain in this management. So that was a unique difference.

If the physician's license is on the line for these kind of guidelines, they listen a lot more than if it's recommended by their society, et cetera.

The second issue is I went out and promoted them. I taught in my position as a director. I went to all of the medical schools in the state, and I spoke to each of the senior classes, each one of the eight years, and I promoted these guidelines and spoke with all of the students, but at the same time I spoke with the residents as well.

The second issue was I went to the pain societies in our state and spoke to them.

The third issue was they were promulgated in our news report which came out boldly printed in the Texas letter.

The fourth issue was that the Texas Medical Association was very helpful in this regard, and they published them as well, as well as the Texas Osteopathic Medical Association in their bulletins. And so this became an issue.

We also had certain reporters around the state who wrote articles in our newspapers promoting this and speaking about this change on the Texas board.

I will tell you that after this time, it became much easier to discipline those physicians who were off the site. But the ones that practiced good medicine found that they were hassled less and were able to practice with less difficulty from intervention by the state medical board.

And my belief, after running a medical board, is that 98, 99 percent of the physicians are there to practice good medicine and do a good job, and your outliers are one or two percent. And when you can set up a regimen where you can really define who those outliers are, it's a lot easier to get at, and they don't make up a large percentage.

DR. MAX: I want to congratulate you on a very wise, beautiful document in our handout on your policies, but let me ask. Now a big issue is doctors who might be sloppy or naive or inexperienced getting deceived by patients who can say they have symptoms. Do you have a position on something like -- and doctors don't know the patients are going to multiple pharmacies.

Does your federation of boards have a position on, say, electronic data collection from pharmacies to inform physicians when multiple doctors are prescribing?

DR. LEVY: Well, you have asked a multi-phasic question. The first one is what do you do about those physicians who are naive.

You give them one bite of the apple. If they have those problems, if they're sloppy in record keeping, you bring them in for a little talk in front of your board. And if they are deficient, then they shouldn't be because that may be a symptom of their entire practice, and it might just not be with pain, but with every other disease they treat. And if that's their practice, they need some remedial help.

If they get it, fine. If that physician would come before us again for the same reason, that physician would be disciplined. So that's the first issue.

The second issue, the federation has not taken a position on the issue that you're describing as of yet.

DR. MAX: Do you have an opinion on that?

DR. LEVY: Ask your question again. I want to be specific in what you want me to have an

opinion on. Ask me my opinion.

DR. MAX: Specifically, I think more interestingly we heard the doctor from Virginia, from the Epicenter of the Oxycontin.

DR. LEVY: Right.

DR. MAX: You're sounding like there really isn't much of a problem if you leave it to the state boards. So what do you have to say to that physician from Virginia?

DR. LEVY: I say that the regulations are written already for the states. It is up to the state boards to do their jobs and evaluate these physicians, and if those physicians are allowing diversion, allowing doctor shopping; if they're practicing irresponsibly, then those physicians must be disciplined by the Board.

And then you get into other issues of whether there should be criminal prosecution of those physicians if they knowingly or intentionally did something that was absolutely harmful to a patient.

Your second issue is whether you should collect information on the Internet if you're doctor shopping. Well, you have a responsibility. We have not taken a position on the collection of information at this point.

But if you're going to manage these patients, you have a responsibility to manage them in the best care, and one of the aspects of informed consent is to tell them you are going to take care of them and not to doctor shop.

DR. MAX: But how do you know if patients are doctor shopping? Can you expect a doctor to call all of the pharmacies?

DR. LEVY: No, you cannot.

ACTING CHAIRMAN KATZ: Dr. Foley.

DR. FOLEY: Thank you very much for your presentation.

What has been the role from the federation's perspective of really educating doctors about pain management? Are there any guidelines related to that and any responsibilities?

It is the responsibility of the boards -- I've recently been talking with the board in Florida -- for them to try to make these kinds of guidelines available, but they've stated that they don't have funds to send them out every member in the state, and many states don't, in fact, provide these guidelines to every physician at the time that they're licensed.

So what, in fact, is the role of the

boards in setting these guidelines to also play a role in educating physicians about proper pain management?

DR. LEVY: Well, that was part of our second phase. We believe that it is the responsibility of the Boards to educate their physicians, and when I was the Director in Texas, every physician to get a license had to pass a jurisprudence exam and have a visit with me. And part of that visit was to understand pain guidelines, et cetera.

So we presented them to all physicians as well as publishing them in our newsletter periodically, and it doesn't cost any money to publish them as part of your articles in your newsletters, which --

DR. FOLEY: Yeah, I think I'm confusing it. It's teaching about pain as opposed to teaching them the guidelines.

DR. LEVY: That's a unique issue that we all have seen. There has not been any increased teaching of pain in the 25, 26 years that I've been involved in pain work, and I think you have the same experience, Dr. Foley. We haven't seen this great increase in training physicians in the management of pain.

ACTING CHAIRMAN KATZ: Dr. Smiley.

DR. SMILEY: Yeah, I just want to maybe have you elaborate or respond to the following question. You state that the anecdotes that we've been hearing today from patients and from professionals about sort of a chilling effect of medical board actions or regulation in general on physician prescribing for patients in pain, prescribing of opioids, pharmacies not stocking drugs, those kind of problems that we hear that you kind of say are just anecdotes.

And you know, we all know -- at least I do -- that there are certainly physicians I deal with who have problems, who hesitate to prescribe opioids when they're indicated. There are patients who can't get drugs at various pharmacies. Is it your position that this is doctors not knowing what they're supposed to do? Is it the fault of the medical board, or is it, in fact, sort of a nationwide anti-drug hysteria and it's just easier to ignore pain and not deal with it?

And doesn't the medical board, I guess, have a responsibility to be promoting good medical care and not just being many DEAs?

DR. LEVY: Well, one, I believe that medical boards do promote good medical care by

creating these guidelines.

Two, if you look at most of the medical practice acts though, they don't specifically tell you that you should create guidelines for every treatment of every type of disease.

Third, I would never question anecdotes. These are experiences people had. My opinion is that they are anecdotes though; that if you look at the regulation, that physicians can practice this way. They can practice good medical care in chronic pain management, and if they are not practicing good medical care, one could be an excuse by that physician that they don't want to or, two, they could be uneducated.

Now, it is the responsibility of the medical boards to educate those physicians on guidelines. It's not the responsibility of medical boards to educate them on practice.

Yes, sir.

ACTING CHAIRMAN KATZ: Dr. Ashburn.

DR. ASHBURN: Thank you very much.

I have a couple quick questions. On two of your slides you talked about the number of violations that have occurred. I wanted to refer back to those --

DR. LEVY: Okay.

DR. ASHBURN: -- for a minute because if I understood you correctly, you felt that these were evidence that the perception that physicians were at risk for regulatory scrutiny that might cause them to lose their license or undergo other issues was actually not valid.

So on the first slide entitled "Controlled Substances Violations by Prescribing Physicians" --

DR. LEVY: Yeah, I'm trying to get back there.

DR. ASHBURN: One more.

DR. LEVY: That one?

DR. ASHBURN: That one.

DR. LEVY: Yeah.

DR. ASHBURN: Is this -- I wanted to make sure I understood. Now, this slide is based on national data.

DR. LEVY: This is the federation data of all the boards collected from the year 2000.

DR. ASHBURN: Okay. So this is not violation of the Controlled Substances Act.

DR. LEVY: This is all violation --

DR. ASHBURN: This is violation of state medical board -- these are lists of state medical

board actions.

DR. LEVY: These are disciplinary actions against --

DR. ASHBURN: Okay.

DR. LEVY: -- physicians in all the states of the Union for these years.

DR. ASHBURN: Okay. So one thing that should be pointed out is that physicians can get into trouble with regard to prescribing of opioids in two ways essentially, maybe more, but we worry about actions against our medical license, which this is represented by, as well as scrutiny for violation of the Controlled Substances Act, which one would be subject to investigation by Department of Justice and the DEA.

DR. LEVY: Well, let me try to explain this then. When you look at these total actions, the majority of those are for quality of care cases, and others may be sexual abuse of patients or --

DR. ASHBURN: Sure, I understand.

DR. LEVY: -- et cetera. What I'm trying to point out is of those 4,600 disciplinary actions only 319 were directly related to controlled substances.

DR. ASHBURN: No, and I appreciate that,

but as somebody who has to listen to other physicians who express a little bit of the paranoia, I just want to also point out that 319 disciplinary actions against physicians is one action a business day. I mean, that's not an insignificant number of nationwide areas with regard to physicians being concerned about actions.

On your second slide on actions' percentage by total, the numbers didn't add up, and I was wondering whether or not these were, again, national numbers on state medical board actions, revocations, suspensions, probations, and miscellaneous. These usually are about 100, give or take. The actions under controlled substances usually are about 300 a year, give or take.

These are percentages?

DR. LEVY: Yeah, these are percentages.

DR. ASHBURN: All right. I just don't know how to read well.

DR. LEVY: Can we go back to your last comment though?

DR. ASHBURN: Sure.

DR. LEVY: You said 319 were significant or 300 are significant. When you add that up, that's approximately of 700,000 physicians in this country.

You believe that is a significant number of physicians who are disciplined? Six maybe per state?

DR. ASHBURN: No, it doesn't surprise me. I'm just -- you know, I know anecdotally, again, of only one or two cases where physicians have been disciplined for under prescribing of opioids. So I'm just presenting this scenario.

Now, you know, frequently in policy making and frequently in physician practices, the decisions are based on their perception of reality as well as what reality is, and if I'm an odds maker and I'm looking at the risk of being sanctioned for doing nothing, which is extremely low, or the risk of scrutiny by doing something, then I'm going to tend to shy away particularly with all of the publicity about risk with opioids, tend to shy away from prescribing opioids for my patients based on concern of regulatory scrutiny whether it exists or not.

And I think I was just -- I wanted to make that observation.

DR. LEVY: Since I've seen most of these actions and have read the orders, I would say that these people are what I would describe as true outliers Okay? By and large, and for the physician who's practicing good medicine are not going to fall

in this 319 in any way, shape or form.

So to equate that this should concern physicians is incorrect. That it does you may be correct, that the perception is there.

What I'm trying to point out is that the reality is not there.

DR. ASHBURN: Okay. Thank you.

ACTING CHAIRMAN KATZ: Dr. Carlisle.

DR. CARLISLE: Do you have any idea of what percentage of that 319 that you actually found violations -- the question is: what is the n for that? How many investigations produced this 319?

DR. LEVY: That I can't tell you because this is an aggregate data of all the states, and we don't collect investigation numbers. Each state does, but the federation doesn't. It only collects final actions against physicians.

DR. CARLISLE: Do you have any sense of that number?

DR. LEVY: I can only speak from Texas, and I would open approximately 1,300 to 1,500 investigations a year on physicians and would discipline anywhere from on the average of about 150 to 170 physicians a year. Of that, I would say that no higher than fifth in propensity of disciplinary

actions were controlled substance violation. Over half were just quality of care cases.

So you're really looking at much smaller numbers here, and especially with the educational approach that we took in Texas to align all of the physicians of what was accepted practice. I think that helped a great deal.

ACTING CHAIRMAN KATZ: Let's take one more question. Dr. Parris.

DR. PARRIS: Yes, Bill. You said you spoke to the senior class that year. Did you speak to the directors of curricula of that particular medical school?

Because, after all, that's where the problem really starts.

DR. LEVY: Each year we would meet with the deans and some of the faculty of the medical school. I would do that every year. We also talked about curriculum.

Now, medical school curriculum is very difficult to get into somebody else's turf, and our issue was not just pain management, but ethical and moral behavior, and that was a greater issue for me and proper behavior physicians. That had been incorporated in some of the faculty.

Dr. McLeskey may still remember when he was still teaching at Scott & White, of my visits there and speaking with the residents and the students.

So pain management was only a small part. It was more ethical and moral and judicial behavior that we expected of the students and physicians, and that was incorporated in the faculty of all eight medical schools in Texas.

ACTING CHAIRMAN KATZ: I'm going to take the last question, Dr. Levy, if I may. The slide that you have up there right now portrays the total number of sanctions by state medical boards, and just to follow up on Dr. Ashburn's point, any idea of what the total number would be of sanctions by DEA, law enforcement, other agencies on physician --

DR. LEVY: That I can't answer. We'd have to get someone from that field.

ACTING CHAIRMAN KATZ: Well, thank you very much for your presentation.

DR. LEVY: Thank you.

ACTING CHAIRMAN KATZ: I appreciate it.

DR. LEVY: Thank you for listening.

ACTING CHAIRMAN KATZ: What we'll do next is go to Dr. Russell Portenoy from Beth Israel

Hospital in New York to give a presentation on opioid therapy of chronic pain involving trends.

DR. PORTENOY: Good morning. It's a great pleasure to be here.

I've been privileged to be working in pain management and opioid pharmacology as an investigator and educator and a clinician for a long time, and when Dr. McCormick called me up and asked me to address the panel, I was very honored to do that, but I sort of struggled with what I could talk about.

After a conversation, I pointed out to her that I was old. She agreed --

(Laughter.)

DR. PORTENOY: -- and jumped at the chance for me to provide sort of a historical perspective, to try to contextualize the meetings for today and tomorrow., and I really plan to do that imminently.

(Pause in proceedings.)

DR. PORTENOY: Thanks.

It's useful first to take a step back and to just point out to you what the obvious is, and that is that all clinicians who have to address problems of chronic pain have to deal with very complex medical and psychosocial and functional disorders that relate to each other in very complex ways.

The process of pain assessment usually involves an attempt to understand the pain in terms of tissue damage, neuropathic mechanisms, and psychological processes.

Then there's a higher order construct that you can call suffering or disability. Now, those words tend to be applied to different populations in different ways, but it represents a construct for trying to understand the overall impact of the pain in relation to the function of the individual, function and quality of life, which can be influenced by so many other factors like other symptoms, physical impairments, social isolation, family distress, role disruption, other medical co-morbidities and independent psychological and psychiatric disorders.

So the process of treating pain begins with an assessment that incorporates this complexity, and then usually requires the clinician to go through a process of attempting to create a multi-modality strategy that may include primary treatment for the pain etiology, if possible, but then also the application of a menu of approaches from a variety of symptomatic therapies.

Every treatment that can be used to treat chronic and acute pain can be subsumed under these

eight categories: the pharmacologic, rehabilitative, psychologic, anesthesiologic, surgical, neurostimulatory, complementary, and alternative medicine approaches, and lifestyle changes.

And the process of treating chronic pain patients which begins with this comprehensive assessment usually ends up with a strategy that involves more than just pharmacotherapy at least in the context of multi-disciplinary pain management programs.

The goal is typically both to improve the patient's comfort and also to enhance quality of life and functional capacity. In some cases, pharmacotherapy is emphasized as the mainstay approach. In other cases it tends to be de-emphasized in lieu of other approaches, like the rehabilitative and psychological approaches.

If pharmacotherapy is considered to be appropriate after a comprehensive medical management, the clinician has to position opioid analgesics among a very large number of other analgesics, and there has been an explosion of new drug development during the past 20 years which has really totally changed the armamentarium now available to treat acute and chronic pain.

When I first got into this field, we really only used a very small number of medications, including nonopioid and opioid medications. Now the numbers are in the hundreds.

These pharmacotherapies, therefore, can involved nay of a large number of opioid drugs, nonopioid analgesics, a very large and complex group of drugs called the so-called adjuvant analgesics, which are drugs that are on the market for some other indication other than pain, but can be analgesic in selected circumstances.

And then there are a large number of syndrome specific drugs, such as the drugs that are used for headache.

So if one focuses on opioid therapy, it's important, I think, to place that into the context of a broader number of therapeutic approaches that can be used to treat acute and chronic pain, and the context of the broader number of analgesic drugs that can be used to treat chronic and acute pain.

If one does that, we can then talk about consensus perspectives in relation to the specific use of opioid drugs.

Now, for a very long time there has been a consensus view that opioid drugs are the first line

treatment for severe acute pain and moderate to severe chronic cancer related pain. But there has at the same time been a large number of studies also performed during the past two decades that have suggested that despite this consensus perspective, the rule out there in clinical medicine tends to favor under treatment.

Research findings that have been accumulating in populations with acute pain, cancer and AIDS pain, and pain at the end of life tend to suggest that opioid drug use is contrary to published guidelines which encourage the first line use of these drugs in selected subpopulations with these disorders; that the patient outcomes achieved during opioid therapy are worse in general medical settings than they are when the opioid drugs are used by specialists; and that clinicians, in general, have limited knowledge about opioids and negative attitudes about opioids that tend to combine to contribute to under treatment.

There has been efforts made during the past five to ten years to try to understand the complexity of the problem of under treatment, and there has been some research as well that has tried to elaborate the specific types of under treatment and to

try to discern methodologies to potentially address some of these subtypes.

At the present time, there is a consensus understanding that under treatment is itself a complex phenomenon that may involve patient related factors, such as stoicism, fear of addiction, fear of medication side effects, desire to be considered a good patient, one who doesn't complain.

There are system factors, including fragmented care, lack of reimbursement for drugs, and then there are clinician related factors, including poor knowledge of pain management, poor knowledge of opioid pharmacology, inadequate knowledge of chemical dependency issues, and fear of regulatory oversight.

And so the problem of under treatment seems to be one that is quite real, supported by a number of studies, and the problem of under treatment itself can be deconstructed into a variety of different component parts, any one of which can be investigated and redressed at a clinical level.

And there have been efforts to redress under treatment. Guidelines and consensus statements from professional societies have become very common in the last ten years. New standards, such as the one you heard before by the Joint Commission on the

Accreditation of Health Care Organizations, and educational initiatives supported by academic programs, professional societies, and organizations and industry.

I will point out to you that during the past ten or 15 years, the educational programming of the pain professional societies has tended to be pro opioid in the sense of trying to expand the vision of pain specialists to include opioid drugs, and in the educational programs of which I've participated in too many too count, the problems related to chemical dependency have typically gotten short shrift.

The pain specialist community in the professionally guided educational programs has really paralleled the type of educational programming that has come out of industry.

So in the subpopulations with acute and chronic pain where there is a great consensus about the role of opioid therapy, there seems to be under treatment, and there seems to be a compelling and complicated problem.

What about opioid use for chronic non-cancer pain? Well, clearly we are in a period of rapidly evolving perspectives. Pain specialists have come full circle in their thinking about this. Dr.

Levy gave you his own personal story. I think all of the pain specialists in this room will tell you their own stories about coming to new realizations about the role and the positioning of these drugs vis-a-vis other therapies for pain.

And there has now in the last few years been a gradual diffusion of changes in the way pain management is considered on the part of primary care providers.

Pain specialists by and large 20 to 25 years ago had an early negative view of opioid drugs, and this, again, was endorsed by Dr. Levy, and that was typically because of the experience of multi-disciplinary pain management programs that appeared in numerous articles in the medical literature. These articles, all of which were written by good practitioners who were observing a selected subpopulation of patients who were referred to chronic pain programs usually at a university center; these articles suggested that opioids were associated with poor function, associated with substance use disorders and other psychiatric disorders, and associated with poor outcomes, particularly those related to function.

As a result, the guidelines the pain specialists followed two to three decades ago

generally excluded opioid drugs unless patients were in dire distress, all other approaches had failed, and the patients can be appropriately monitored.

But in the last couple of decades, there has been a seachange in the way pain specialists view opioid drugs, and this has been accompanied by an increase in use of this therapy among all the other approaches that have also been increasing in number during the same period of time.

Why have pain specialists come to feel more comfortable with this therapy, to use it much more? Well, there's been a slowly growing evidence base, including a small number of randomized control trials suggesting efficacy. This evidence base, however, still is largely confined to large surveys, anecdotal reports, and less, much less in the area of randomized controlled trials.

There's also a more sophisticated pharmacologic understanding, more reassurance from regulators in law enforcement that you just found out about. There's been an influence of the broad movement to improve acute pain management and cancer pain management. This is from the World Health Organization, from the Alliance of State Cancer Pain Initiatives, and many other organizations pushing to

try to improve cancer pain management and acute pain management.

There has been pressure from the media, the number of stories that highlight under treatment. I would guess if you added them up against the number of stories that highlighted the Oxycontin problem, it would still be far, far greater. The media has done, by and large, a good service to patients in medicine during the last ten years in highlighting the problem of under treatment.

And there also has been a strong and for many of us in the pain management field, a sense of a positive influence on the part of the pharmaceutical industry who contributed to educational programming for professionals that would otherwise not have occurred.

As a result of this, the pain specialists have gradually moved to a consensus view that opioids do play an important role in treatment of chronic pain, and we now have consensus statements that have been published jointly by the American Pain Society and the American Academy of Pain Medicine, the American Society of Addiction Medicine, the Canadian Pain Society, and other organizations and societies, all of which say the same thing, that opioids should

be used in the context of good medical practice as outlined previously. They should be positioned appropriately against that very large number of other therapies, many of which are non-pharmacologic in an effort to improve patient comfort and enhance the ability of patients to function.

That is now the consensus view on the part of pain specialists. So what are the implications of this view?

And here I'll move to a set of impressions that I have that are born from my conversations with a very large number of pain specialists over a very long time, and I put them here on the table, I think, for discussion and consideration, again, in an effort to contextualize what we're talking about here at this meeting.

The first is that pain specialists believe that opioids are significantly under used for chronic nonmalignant pain. And why is that? Because pain specialists believe that many of the barriers that are impeding expanded opioid use are illegitimate, like poor education, poor knowledge, system issues like poor funding for drugs and that sort of thing.

Because pain specialists recognize that there are biases in the published reports from the

multi-disciplinary pain programs, and so the literature is still moving toward a better element of balance, and because there are positive reports in the literature and personal experience with patients that suggest that these drugs are under used.

Secondly, pain specialists support the use of opioid therapy by primary care physicians. This is a very important point. Pain specialists believe that opioid drugs, opioid pharmacotherapy is within the purview of primary care, and that's because the barriers that would prevent it are viewed as illegitimate.

We have the belief that the treatment principles to optimize opioid pharmacotherapy are, in fact, simple, no more complicated than the treatment of many other more challenging, equally challenging medical disorders that primary care physicians treat.

We know that the pain epidemiology is such that even if you wanted to limit opioid prescribing just to specialists, it would be very difficult to do that with a very, very high prevalence of chronic pain, the United States estimated to be as high as 15 percent or more, and a relatively small number of pain specialists. It is just impossible for pain specialists to accept this task if you believe that

opioid therapy should be an option for some of these patients.

Pain specialists feel overwhelmed when all they do is write prescriptions and monitor opioid prescribing, and there's the influence of advocates, media, and industry trying to expand this to a larger number of physicians for the reasons outlined here.

But there's something else that's been happening, and this has only been happening during the past year or two in my estimation, and that is that pain specialists are beginning to perceive that there may be problems that have not received enough focused attention by the community of pain specialists, and these problems largely relate to the interface between pain and chemical dependency.

And this is now becoming acknowledged by pain specialists, for example, at the annual meetings to a much larger extent during the past few years than it has ever before. Many pain specialists have inadequate knowledge of addiction medicine principles, which are essential to the safe and effective treatment of patients.

I like to tell my trainees, for example that I went through medical school, I went through an internship, I went through three years of neurology

training, and I went through a fellowship in pain medicine and palliative care, and I never had a lecture on addiction medicine.

Generalists are adopting the therapy without adequate knowledge of pain management principles. This we already knew, but also without adequate knowledge of opioid pharmacology and addiction medicine principles and thereby perhaps placing patients at risk for the adverse effects of opioid drugs in this broad phenomenon of chemical dependency that wouldn't be there if the clinicians had better skills and training in addiction medicine principles.

There's also been a tacit reluctance on the part of supporters, including pain specialists, those in the media who have been portraying the problem of under treatment, patient advocates and industry to discuss the legitimate risk associated with opioid toxicity and abuse addiction because of the concern that if we opened up Pandora's box and talked about addiction and abuse, all of the progress that has been made during the past ten years would be lost.

This seems to be one of the most troubling aspects of the Oxycontin problem, the concern among

those who have a very strong and legitimate concern for patient care; that all of the discussion, and particularly the intense media attention, may act to actually reverse progress that has been made in destigmatizing opioid therapy, improving the ability of physicians to use it in an appropriate way, increasing the chilling effect, if you would, so that physicians don't prescribe and patients are more reluctant to take.

And because of that concern, in my estimation, there has been a bit of a tacit understanding that we won't talk about this too much. And now pain specialists, I think, are recognizing that this has been a problem. We do need to talk about it. We need to address it in a proactive way, and based on the science, and that's one of the reasons we're all here today.

So what's the evolving consensus of opioid therapy? Opioid drugs are still considered first line drugs for patients with severe or acute pain and moderate to severe pain related to cancer or AIDS or other life threatening illness. They are the mainstay approach for these patients, and the real issue out in the field is to train physicians to use it and reverse under treatment.

But in addition to that, pain specialists would now say that it would be appropriate to consider opioid therapy for all patients, for all patients, with moderate to severe non-cancer pain, but never to prescribe unless there has been a very recent judgment about the various influences on prescribing based on a comprehensive assessment.

What is conventional practice for this pain syndrome and this type of patient? Are opioids likely to work well for this condition the patient presents with? Are there reasonable alternatives to opioid therapy? Will the risk of side effects for opioid drugs be relatively high? And are drug related behaviors likely to be responsible?

All patients with moderate to severe pain could be considered for therapy, but therapy should never be offered to these patients until a comprehensive assessment is done and a recent judgment based on these sorts of questions is made on the part of the clinician.

So what does safe and effective therapy with opioid drugs require? It requires the knowledge and skill sufficient to assess pain and the relevant medical and psychiatric co-morbidities. It requires knowledge of conventional pain treatment sufficient to

appropriately position opioid therapy among other therapies. It requires knowledge of opioid pharmacotherapy, how to optimize the treatment once it is initiated. It requires knowledge and skills in addiction medicine sufficient to judge the risks, monitor treatment and handle problem cases when they occur. And it requires a commitment to documentation and appropriate infrastructure for following patients.

This is sort of the new view, in my estimation, of where pain specialists are in relation to trying to promote the concept of expanded opioid therapy. We want to promote it, but we want it promoted now with the understanding that it carries obligations and responsibilities on the part of clinicians who have to recognize the full panoply of risks associated with this therapy, including the risk of chemical dependency, and attest to having the knowledge and skills necessary to give the therapy safely and appropriately with knowledge of those risks.

Safe and effective therapy might also require a pain specialist to be available as consultants and pain specialists. Pain specialists have a particularly strong obligation now to be educated in principles of pain management and

addiction medicine.

So if that's where we are as a community of pain specialists, it may be worthwhile as a final effort to contextualize this discussion just to highlight what I would see as the critical issues for an ongoing review of opioid therapy for chronic pain.

And I would suggest to you that you can categorize the critical issues into three broad sets, what I have termed the perceived risk of sanctions, that is, the physician's concern that prescribing places him or her under risk of legal or regulatory scrutiny of perhaps sanction. How does one establish the effectiveness of this therapy? And how does one understand its safety implications?

First, the perceived risk of sanctions in my view is alive and well, notwithstanding the clear progress that has been made on the part of the regulatory community to try to address this fear.

About three years go I collaborated with the Medical Society in the State of New York to do a survey of 1,300 New York State physicians in order to evaluate their views of opioid prescribing, and among the very large number of data that we collected was the statistic that more than 50 percent of these physicians were moderately to very concerned about

regulatory scrutiny, and 25 to 50 percent admitted that they changed their prescribing practices solely because of concern about regulation.

At the same time, I became privy to the kinds of data that Dr. Levy pointed out to you, and I can tell you that New York State, in my view, is a very enlightened state.

Inappropriate investigations, I think would be extremely uncommon in New York, and yet this kind of fear is out there. So the perceived risk of sanctions is alive and well. It needs to be addressed as part of the issue of expanding appropriate opioid prescribing.

What about the issue of opioid effectiveness? It may be useful to think of opioid effectiveness in terms of three additional sets of issues. Are all pain syndromes responsive to opioids? Can opioids be used over the long term or does tolerance inevitably preclude long-term efficacy? And what must be done in order to achieve optimal therapy?

The concept of opioid responsiveness is now well established in the pain literature, but I would guess has not really leeched out yet into the general medical literature. There is an understanding

that pain in some populations is relatively highly responsive to opioid drugs, meaning to say that optimal therapy is capable of achieving a favorable balance between analgesia and side effects in a large proportion.

For example, many thousands of patients reported in surveys of cancer pain suggest that somewhere between 70 and 90 percent gain this favorable balance between analgesia and side effects.

There's also been numerous surveys of patients with non-cancer related pain, and these surveys suggest that this favorable balance between analgesia and side effects occurs with a lower prevalence, somewhere between 25 and 70 percent, not a very satisfying range, but that's what the literature would suggest.

There's a small number of relevant RCTs, suggesting that these drugs can be effective in neuropathic pain and those susceptive pain syndromes, but we really have very little data by which to understand the whole phenomenon of responsiveness, and most importantly, we have no data that allows us to predict which specific patient will not be responsive.

So we may say that certain populations of patients are relatively more responsive or less

responsive based on these data. We are incapable of saying that any characteristic of an individual patient or an individual's pain syndrome predicts opioid resistance. That at this point in time can't be said. It's a very important avenue for research.

So the conclusion for this is that opioid therapy probably can be effective for any kind of pain syndrome, but the data are very limited. Responsiveness varies across individuals and subpopulations, and responsiveness cannot be assessed unless therapy is optimized by individualization of the dose, which speaks to the problem of determining responsiveness even in the clinical setting.

And most importantly, we do not yet have predictors of responsiveness that are clinically useful.

What about the durability of the response? It's clear now that tolerance, which can be demonstrated in a matter of days in animal models is actually in human beings a very complex phenomenon. Most patients stabilize at a dose for a prolonged period of time, and in clinical practice the fear of tolerance is a greater problem than its effect on therapy. This is an issue I think which is emblematic of the limitations of clinical trials.

Clinical trials will allow us to do drug development and hopefully will meet standards set by the FDA. Clinical trials will be very -- it will be very difficult for clinical trials to assess the problem of tolerance. Studying tolerance in the clinical setting is extremely complex because we don't control the pain. The pain varies, and if we can't control the pain, it's very difficult to know if changes in the requirement for opioid drug is actually related to receptor or post receptor changes induced by the drug, meaning to say the physiology of tolerance or it's due to some changes in the pain induced by other processes such that patients need more medication because they hurt more.

So we can't really study tolerance, and we're going to have to look at survey data in order to try to understand the impact of tolerance on clinical practice, and I can tell you that based on a very large experience in the cancer population, worry about tolerance is much more of a concern than is tolerance itself as an issue in clinical practice.

And what about achieving optimal therapy? Obviously I don't have time to talk about the complexity involved in making a decision about which opioid to select for a specific patient. What's the

best method for individualizing the dose?

How aggressively should side effects be treated in an effort to open the therapeutic window and make sure that the balance between analgesia and side effects is favorable?

How does one manage the patient who is poorly responsive to a therapy?

Again, these clinical issues for which we now have nice consensus based guidelines in the literature are very difficult to investigate and end up in an evidence based labeling by the FDA. This is a great challenge.

If the FDA, for example, were to insist on an evidence base for making a selection of a specific drug for a specific kind of pain or a methodology for individualizing the dose, the numbers of studies that would have to be done and the size of the populations that would have to be studied would clearly stall progress in this area for many, many years.

This is not going to be solved without collecting the accumulated clinical experience and survey data to complement new RCTs.

It's also important to point out that in clinical practice the issues of import which I think should be in the label, although, again, difficult to

place in the label in any evidence based context, but the outcomes of import for opioid therapy are not only pain relief alone, but what kinds of side effects are occurring and what the impact of those side effects are, what the functional outcomes of the therapy in terms of both physical and psychosocial functioning, and whether or not the patient is engaging in responsible drug taking behaviors.

Clearly, anybody given an opioid drug could be maintained free if the goal is anesthesia, not analgesia, but our goal typically is analgesia with function, and so it is essential that these outcomes be a part of good clinical practice and how they end up in an evidence based label from the FDA is, again, a great challenge that we'll have fun talking about for the rest of today and tomorrow.

What about issues related to safety? I would suggest to you again that we could think of two broad categories, whether or not there's any major organ toxicity or other adverse effects and what the addiction liability is.

There's been a huge experience in both the addiction literature and the pain literature, suggesting that there is no major organ toxicity from opioid drugs, but clearly persistent side effects can

be a big problem.

The issue of adverse cognitive effects is now just beginning to get played out in studies. Most studies do suggest that cognitive functioning can normalize with chronic therapy in at least a large proportion of patients. Most pain specialists advocate that driving is okay when they're taking opioid drugs.

Again, very difficult clinical judgments have to be made, and how that relates to new drug development is a great challenge.

The important issue for the discussion today, I think, is the issue of addiction liability, and this is where our great responsibility is. In beginning to address the clinical needs of patients with pain in away that promotes appropriate opioid use, that optimizes the benefits of these drugs and minimizes their risk in terms of addiction liability.

It's important to recognize now that the definitions for addiction that have been in the psychiatric literature for a long time are widely considered by pain specialists to be problematic, and we now have a new consensus document recently published by the American Pain Society, the American Academy of Pain Medicine, and the American Society of

Addiction Medicine, all together which offers a new definition for addiction.

And it's also important to recognize that we have very, very few studies of addiction liability in pain patients. The studies seem to suggest that the occurrence of addiction in patients with no previous history of substance abuse during treatment of acute pain is very uncommon.

The development of addiction or abuse behaviors during the treatment of cancer pain in patients with no prior history of substance abuse is very uncommon, and the data would suggest that we really don't know what we're doing in chronic nonmalignant pain.

We all have to agree that disease is an addiction or that addiction is a disease. That's very important.

(Laugher.)

DR. PORTENOY: And that my speech therapy is not yet over.

We have to agree that addiction is a disease, a serious disease with genetic, pharmacologic, and psychosocial elements, and we all have to agree that we have to distinguish it from tolerance, physical dependence, and a concept common

in the pain community called pseudo addiction, which is a development of aberrant drug related behaviors driven by uncontrolled pain, which can be eliminated if pain were better relieved.

We all have to agree that addiction includes -- that the definition of addiction in the medical context is best if it includes constructs like loss of control, compulsive use, use nondescript harm and craving. That's the best way to consider addiction in a medical context. That's what the new definition from APX, AAPM and ASAM highlights.

And we all have to understand that because addiction is understood in terms of these behavioral phenomena, it is only diagnosed by the occurrence of aberrant drug related behavior.

The whole concept of aberrant drug related behavior about which I think you'll hear more in a lecture, I think, later is really, I think a very important trend, is a very important understanding for physicians, but one that has received almost no empirical investigation so far.

We know that some patients who are given opioid drugs develop behaviors that physicians view as problematic. Some of those behaviors are very minor ones, like taking an extra pill to help them sleep at

night. Some are more egregious, like grinding up a tablet and injecting it intravenously, doctor shopping, becoming inebriated and crashing a car.

And we know that this spectrum of behaviors can occur whenever we're using these drugs. These are all aberrant drug related behaviors. But clinicians also recognize that aberrant drug related behaviors may or may not reflect addictive disease. some patients with aberrant drug related behaviors will have this concept called pseudo addiction. Some will have other psychiatric disorders associated with impulsive drug taking behavior

Some will have an encephalopathy, a confusional state that drives them to take medications in the wrong way. Some will have family disturbances that drive aberrant behavior, and some will use these drugs aberrantly for the purpose of criminal intent.

And so part of what we need to do as clinicians is to understand the spectrum of aberrant drug related behaviors and also help clinicians understand how to diagnose those behaviors appropriately so they can be managed.

That I would love to see in the label. So aberrant drug related behaviors have to be monitored, diagnosed, managed, and the underlying disorder

driving the aberrant drug related behaviors have to be treated.

In some situations opioids have to be stopped in that context because it's the right thing to do. In other cases, opioids should be continued if the controls that can be created in prescribing are sufficient to allow the patient to regain control over opioid use.

These are subtleties and challenges in the clinical practice of opioid pharmacotherapy that have not really been portrayed in the educational programming by the professional societies, clearly not in the educational programming of industry during the past 20 years, and not in the labels and the consensus statements tha have been driving opioid use or promoting opioid use among clinicians.

These are the kinds of issues now that have to be brought out if we are going to have more appropriate opioid use.

So how can one then contextualize opioid therapy? In my own view, again, as a clinician and as an educator in this area for a long time, I view opioid pharmacotherapy as an approach with an extraordinary promise to help patients with chronic pain of all different types achieve a degree of

comfort and a level of function and an improved quality of life that would otherwise be impossible even with the best that medical practice has to offer.

These drugs have that promise, but there are also substantial risks. Opioid pharmacotherapy should be promoted and expanded among the primary care community, but it has to be done with the proviso that it carries clear obligations and responsibilities on the part of prescribers. Prescribers have to be able to assess and reassess, to give the drugs in a skillful way, to have some knowledge of addiction medicine principles so that aberrant drug related behavior can be picked up, appropriately dealt with and monitored over time.

And the physician has to be willing to document and communicate, and that means with all parties concerned, all the constituencies, those in the regulatory and law enforcement communities, pharmacies, patients and families and colleagues. That kind of documentation and communication is now fundamental with the therapy of this type.

Thank you for your attention.

(Applause.)

ACTING CHAIRMAN KATZ: Thank you very much, Dr. Portenoy for a wonderful synthesis of a very

complex topic, as always.

We are still ahead of schedule, although everyone is probably aching for that break that is going to happen soon. Would you be willing to take a few questions after a break? Maybe that would be --

DR. PORTENOY: Whatever you like.

ACTING CHAIRMAN KATZ: Okay. Why don't we go ahead and take a break right now until five minutes after 11. We'll start promptly then with Dr. Portenoy addressing any questions.

(Whereupon, the foregoing matter went off the record at 10:50 a.m. and went back on the record at 11:13 a.m.)

ACTING CHAIRMAN KATZ: Could everybody start taking their seats, please? Could people start taking their seats? Could everybody please take a seat? I'd like to get the rest of the morning session started.

Thank you for turning up my mic, whoever just did that.

Why don't we go ahead then and give Dr. Portenoy a few minutes to answer questions. We'll take about five or six minutes for questions for him. There are certainly many important issues that he touched on in his discussion, and I'm sure that there

will be many questions for people around the table for him.

So any questions from around this table for Dr. Portenoy? Dr. Holmboe, please.

DR. HOLMBOE: Hi, Eric Holmboe from Yale.

I wonder if you could speculate for a moment. You talked a lot about personal accountability for those who describe these things. One of the things though that often gets left out in this discussion is what is our accountability for the practice and quality of care of our peers, particularly when we see that they may not be practicing up to standards.

In my community that's a big issue, and it's often one that other physicians who knowingly see the deficiencies in the care being provided by one of their colleagues fails to act on that. I wonder if you might comment on how that would apply in this particular situation.

DR. PORTENOY: Well, I think it sort of goes without saying that it's a complex issue, and I would like to think that we would come to rely on systems rather than on individuals. I think to the extent that you place the onus on individual physicians to do those kinds of judgments, you're

going to see such scatter in terms of the quality of those judgments and what ends up happening that it's probably going to work to the worsening of the system overall.

If you're lucky enough to work in a hospital, especially a hospital in the New York area, you will probably be regaled with quality improve and quality assurance systems that essentially allow physicians to make reports to senior leadership and then for an investigation to follow that's quiet initially before any action that would be untoward occurs.

So I think the answer is, yeah, we certainly have obligations, if you see malfeasance or something that's particular dangerous for patients, but unless we get at that as a systems issue, I can't really see how it's going to really work out.

ACTING CHAIRMAN KATZ: Just a point of order for the folks around the table who are actually keeping a list of people who want to speak in order, and if you do want to ask a question, just raise your hand and you'll be put on the list here.

The next person is Jeff Bloom.

DR. BLOOM: Thank you.

I wanted to ask a question about it's

difficult enough for patients to get a prescription for an analgesic and for people with chronic pain, there's a pretty good document of literature that you need a baseline medicine to treat your chronic pain, but you also need a medicine for breakthrough pain as well to have adequate pain control, and that when people are inadequately treated, they tend to run into problems with their pain management.

What suggestions would you have to be able to better educate people about the need to have two medicines in order to properly control severe chronic pain in patients?

DR. PORTENOY: Right.

DR. BLOOM: And the fear that doctors have about writing, you know, with two prescriptions.

DR. PORTENOY: I think that's one of those questions that actually has multiple levels to it. At a clinical practice level, one of the goals is to try to train physicians to have the skills to know which patients do best, would do best potentially with a baseline drug and a breakthrough drug, which for any number of reasons would do fine with just one or the other, and if you expand the thinking about that a little bit, you're really talking more about polypharmacy with multiple controlled prescription

drugs.

And clearly among the community of pain specialists, there's an understanding that many patients will need multiple controlled prescription drugs. They'll need opioids or maybe two opioids. They may need a psychostimulant. They may need a benzodiazepine.

And so there's the issue of the increasing concern of regulatory oversight as one prescribes more and more -- one uses polypharmacy with multiple drugs, and then there's the issue of the labeling again. To what extent as one thinks in terms of what studies have to be done in order to establish the safety and efficacy of a drug does one think about needing to do interaction studies and combination studies?

If it is true, for example that it's now fairly common practice to combine an opioid with a psychostimulant, who's going to require those studies to be done? Who's going to pay for those studies to be done? Which psychostimulant, what dose?

Is that something we should put in the labeling of opioid drugs, that treatment of side effects is essential during therapy and these may include XYZ and, oh, by the way, psychostimulants, or is that something that shouldn't go in the label until

the studies, the interaction studies, are done?

So I think there's the issue of clinical medicine and there's the issue of regulation. The bottom line is the consensus among the community of pain specialists is that polypharmacy is clearly appropriate in the subgroup of patients with chronic pain and that that may involve more than one opioid and that may involve opioids plus non-opioid controlled drugs.

ACTING CHAIRMAN KATZ: Dr. Smiley.

DR. SMILEY: Just thanks for a great presentation, by the way, Dr. Portenoy.

DR. PORTENOY: Thank you.

DR. SMILEY: But I wanted to ask you. You had mentioned all of the knowledge that a pain specialist ought to have when dealing with chronic pain and prescribing these drugs, knowledge of your recognizing addictive behavior, knowing addiction medicine, pharmacokinetics, pharmacodynamics, and then you of necessity said that obviously these drugs need to be prescribed by general practitioners, family medicine, however we want to classify those physicians, and then implied that they needed to know the same things.

and while that's wonderful, and I agree

everyone should know everything, it's not that practical, and I'm not sure what the question is, but I wanted you to --

(Laughter.)

DR. SMILEY: -- I wanted you to expand. Yeah, I know. That's too bad, but I wanted you to expand on that a little bit.

DR. PORTENOY: Sure.

DR. SMILEY: What do you actually mean? What do you expect because, you know, there's talk of regulation of these sorts of drugs and who can prescribe them. What do you expect the general internist, the family practitioner to really know about these issues, you know, in opioid prescribing?

DR. PORTENOY: Right. That's a great non-question.

DR. SMILEY: Yeah, thanks.

(Laughter.)

DR. PORTENOY: That's a really good non-question.

You know, the older I get the more I am convinced that clinicians have to have some understanding about the parameters of generalist level knowledge and the parameters of specialist level knowledge, and that we have an obligation not to do

anything therapeutically unless we have some assurance that we have generalist level knowledge.

So, for example, I don't treat hypertension at all. I'm a neurologist and a pain specialist. I don't treat hypertension at all. I really feel that the changes in the field have been so dramatic since I did my internship that it would be doing a disservice to patients because I lack even basic generalist level knowledge of the treatment of hypertension.

And I think for some primary care physicians it would be totally appropriate to say, "I just have not gotten the time. I don't have the interest. I'm too worried about X, Y, and Z to acquire generalist level knowledge of opioid pharmacotherapy. So I don't do that."

I will refer you to another physician who will consider it, but there is a body of information and skills, I think, that could be viewed as generalist level knowledge for opioid pharmacotherapy. It includes the techniques to optimize the treatment.

How does one select a drug, individualize the dose, and treat side effects?

It includes the monitoring of outcomes, which includes pain relief, side effects, physical and

psychosocial functioning, and the occurrence of aberrant drug related behavior, and it includes knowing what to do when the outcomes are not going in the direction that you want them to go in.

And that might mean when to refer patients. If a patient is engaging in aberrant drug related behavior, you may say, "Well, I don't know what to do now. So I'm going to just write you scrip for the next week and refer you to the local addiction medicine specialist who's going to help me understand this, what these behaviors represent," or it may be that that person has enough skills to manage it.

But I really think that what we have to try to do as educators is to begin to define that body of knowledge and skills that can be reasonably called generalist level and then mandate that for prescribers, and if you don't have it, don't do it. Don't prescribe.

ACTING CHAIRMAN KATZ: Dr. Schuster.

DR. SCHUSTER: First of all, let me say that I'm very pleased with your presentation about the area of addiction. I also want to assure you that your experience in terms of your training a long time ago tragically has not changed that much today. I've been at four major universities, and we're lucky if we

can get two to three hours of curriculum time in the medical education for addictions.

I think -- and this is a statement, but I'd like your reaction to it -- I think we have to distinguish between two types of problems here, the naive doctor who is conned into prescribing opiate analgesics by an addict versus the individual who may have a predisposition to addiction or iatrogenic dependence or addiction.

And I think that we can train individuals to be more sensitive to the cues that someone is an addict, and that's fairly easy. I think we know very little about how to predict who is going to become addicted through their legitimate treatment with an analgesic, and I think this is an area that badly needs to have more research done.

DR. PORTENOY: My comment is I agree totally. We have tried to do some survey work on establishing the prevalence rates for various aberrant drug related behaviors. Steven Passik, who will be speaking later, and I did a small survey at Memorial Sloan Kettering Cancer Center of 60 patients with cancer related pain asking about a variety of aberrant behaviors.

We found out that more than half of those

patients had borrowed benzodiazepines from their family members, and so we began to ask not only what's the prevalence of these behaviors, but what's normative and what's aberrant.

And so we don't really have any clear understanding of what constitutes an aberrant behavior, particularly the word "aberrant" itself has a sociology to it. It suggests certain norms that we may not agree on, different -- we may not agree for them in terms of certain populations, certain different groups of prescribers.

So it assumes that we have norms that are sort of squishy at this point. It assumes that we know which behaviors would be outside of those norms, and we don't know the prevalence rates or how to monitor it.

So I think you're absolutely right. It's a huge problem.

Now, having said that, the fact is we can't wait for those studies to be done in order to improve opioid prescribing or the prescribing of any controlled prescription drug, and so you have to bring down to the level of primary care provider some very simple guidelines that help that person understand.

Some would advocate the use of a written

agreement in every case. I don't advocate that, but I do advocate an assessment of these behaviors at every visit, and I also advocate creating a structure for prescribing that it would be consistent with a perceived level of risk.

If you have a young man who admits to heavy marijuana use in college and now has a work injury with chronic low back pain, you might insist on relatively frequent visits, bring the pill bottles back. I need to have you use only one pharmacy, and os forth.

If you have an 80 year old cancer patient who has been a teetotaler her whole life, it might be, "Here, six months of drugs. See you later," or thereabouts. I'm not serious.

(Laughter.)

DR. PORTENOY: Any of you who are regulators, I'm just --

(Laughter.)

DR. PORTENOY: It's just hyperbole. I don't actually do that.

But you get my drift. My drift is that we need to do that, and I think, again, the issue of labeling for me and this issue of labeling in relation to educational programming, it has to evolve to

reflect that clinical reality and take those steps, to state certain things that we know to be true or we know are likely to be true, even if we don't yet have the clinical studies to do it in an evidence based kind of way.

ACTING CHAIRMAN KATZ: Dr. Foley.

DR. FOLEY: Russ, thanks again for your presentation.

In presenting it in this way, however, you have sort of bought into the belief that cancer pain is one category which has no scientific basis in a sense that's any different than -- cancer chronic pain is any different than chronic pain. It's a different population that has a different social and cultural and perhaps prognostic significance, but it has no science difference to it.

And we've created sort of a liberal perspective toward the cancer population because they carry that label, and we label drugs and develop them and way for chronic cancer pain, but there's no science here.

So would you want to perpetuate that or would you want to move it to a different agenda?

DR. PORTENOY: Yeah, that's really a great level, and I think over coffee you and I can move it

to that agenda.

I couldn't agree with you more, and in fact, some of the data coming out now from randomized controlled trials which are comparing opioids to non-opioid conventional treatments might have us evolve our perspective and begin to say that opioids might be the first line drug for the treatment of post hepatic neuralgia or other kinds of neuropathic pain if you look at the empirical data from randomized controlled trials.

And I agree totally with what you're saying, but, however, in an effort to historically contextualize what we're talking about today --

DR. FOLEY: Yes, yes.

DR. PORTENOY: -- I chose to buy into that because I think one of the things we're concerned about as an outcome of this meeting and other things happening at the regulatory level is that a backlash is possible, and that the movement to bring more appropriate opioids prescribed into primary care could have a major setback, which could ultimately even affect negatively what we're trying to do with cancer pain.

So one of the slides I said is that you might consider opioids for every patient with moderate

to severe pain, but you have to consider certain issues, and one issue is what is conventional practice, and so supporting the idea that opioid therapy is mainstay for cancer pain and acute pain, that's the conventional practice. We should buttress that and then bring the rest of our prescribing along in that same model, I would think.

ACTING CHAIRMAN KATZ: I'll take one more question, and actually it's Mitchell Max.

Let me just remind people around the table that when you're done speaking, turn off your microphone. There's some sort of feedback problem that occurs if you don't shut it off.

DR. MAX: Russ, I wanted to mention a couple of large NIH supported randomized trials that actually might suggest that opioids for neuropathic pain might be the first choice from the view of efficacy, and I can get those for my FDA colleagues if you want.

I mean, one is a study that we helped Sirinivasa Raja do at Hopkins with 73 patients where in a complete crossover morphine was compared to nortriptyline, maximum doses in post hepatic neuralgia, and morphine on most measures beat nortriptyline. Thirty-four percent of people had an

adequate response to morphine compared to 19 percent on nortriptyline, and both beat placebo.

And if you do the calculations, that comes down to there's about one patient in six or seven that got relief, clinically meaningful relief, from morphine, but got nothing from the nearest competitor. So on the efficacy side, that's the plus side.

And the other one that was presented only in abstract form at the American Pain Society, but will probably also be published in the next year or so is by Mike Rowbathan, UC-San Francisco, NIDA supported. He actually did look to the higher end of the dose range of opioids and neuropathic pain. It's one of the first dose response studies, and he compared low dose to high dose levorfanol (phonetic) over eight weeks, and the low dose was three milligrams a day, which is actually probably equivalent to about 90 milligrams of morphine, and he showed that the three times that or about 270 milligrams of morphine equivalent a day handily beat it.

So it raised the issue not only we haven't shown a dose response for any other above the usual levels of gabapentin or tricyclics. So maybe the opioid is just like we know in cancer pain, has a dose

response curve that keeps going up and up. Maybe even a higher dose of opioids are better, which raises more issues about what's the cost of providing this.

So if opioids -- and both of these studies showed there was no cognitive effects at all with careful testing. So if opioids are the best in advocacy, we certainly don't want to say the primary care doctors can't prescribe that, and we need to pay better attention to the risks, too.

DR. PORTENOY: I agree.

ACTING CHAIRMAN KATZ: Well, with that nice ending, I know there are a few more people who had questions, and I apologize for that. We'll need to keep to the schedule, but we do have some unstructured time for question and answer after the next presentation, and so I would encourage people to hold their questions just for a short period of time.

Now we'll have Gerald DalPan from the FDA speak about opiate analgesic trials and drug development plans.

MR. DalPAN: Okay. Well, thank you, Dr. Katz.

Good morning to the committee members and the guests.

We're certainly heard a lot this morning

about different aspects of opiate drug treatment, a wide range of issues, and I'd like to focus in on some of these issues now as we pose some discussion points for the committee.

And specifically I want to talk about something that Dr. Portenoy brought up, and that's drug trials to establish the efficacy of opiate agents.

Okay. We want to talk about two things in this regard. There will be the choice of the patient populations in the clinical trials, as well as the duration of clinical trials to support efficacy for chronic opiate treatment.

So the choice of patient population in clinical trials of opioid analgesics is a crucial element in the clinical development of these agents, and it's going to be the focus of part of our discussion later this morning.

Features of the patient population in clinical trials that require important consideration include, among others, the intensity of the underlying pain, the underlying disease that's the cause of the pain, the pathophysiologic mechanisms of the pain, and the duration of the treatment needed.

Because the clinical trial data form the

basis of the product's approved indication and labeling, the clinical trial data are an important source of information to health care providers and to patients. Inclusion of patient populations in clinical trials that are representative of the actual use of the product is, thus, important.

So to gain insight on the actual use of opioid analgesic use in the United States and on the temporal trends in prescription opiate use, we've obtained drug utilization data from two surveys, the National Prescription Audit Plus, or NPA Plus, and the National Disease and Therapeutic Index, or NDTI, both by IMS Health.

These data were analyzed by the Office of Drug Safety at FDA, and the purpose of these analyses was to quantify the changes in the number of prescriptions dispensed and the indications for which they were dispensed over the period 1996 through 2000.

The focus of the analysis was on out-patient usage of oral and transdermal formulations of opiate analgesics, and for this analysis we used ten commonly used opioid analgesics. We excluded cough and cold preparations, injectable formulations and rectal formulations.

NPA Plus is a cross-sectional survey of

dispensed prescriptions from pharmacies in the continental United States, and these include chain, independent, mass merchandisers, food stores, long-term care, and mail order pharmacies. Total prescriptions, both new and refill are projected nationally from this sample.

Now, here I apologize to the committee for your handouts. The two per page printing does not print imbedded tables, and the Executive Secretary, Ms. Topper, has told me she will be able to get you the full slides after the meeting.

This slide presents the estimated number of dispensed opioid prescriptions for the years 1996 and 2000, as well as the percent change in the number of dispensed prescriptions from 1996 to 2000. The numbers presented are in the thousands. Thus, in the year 2000 an estimated 163,023,000 prescriptions for opioids were dispensed, and during this period, there was a 27 percent increase in the number of dispensed opioid prescriptions.

NDTI is also a cross-sectional survey in the continental United States of visits to office space practitioners. Drug mentions or uses are captured, and these are linked to other information in the medical office visit record, including diagnosis,

and for the purpose of this analysis, only diagnosis was examined.

This slide here presents the number of opioid prescriptions in thousands for the top six diagnostic indication categories out of a total of 18 total large level categories, which is all we analyzed.

As in the NPA Plus data, cough and cold preparations are excluded, as are injectable and rectal formulations.

The two indication categories that accounted for the greatest number of opioid prescriptions were the first one, which is special conditions without sickness, which includes conditions such as post surgical conditions, and the second, which is diseases of musculoskeletal and connective tissue, which includes conditions such as back ache, low back pain, osteoarthritis, arthritis, and other joint pain.

Injury and poisoning, which includes conditions such as sprains and fractures, and another category defined as symptoms, sign, and ill defined conditions, which include conditions such as headache and abdominal generalized or chest pain, also account for a substantial number of prescriptions.

Other categories of interest are neoplasms, such as neoplasms of the lung, breast, colon, and prostate, and diseases of the nervous system and sense organs, such as migraines, otitis media, carpal tunnel syndrome, and neuropathy.

And with the exception of nervous system disease, which is relatively flat at a minus one percent change over the five year period, there were five year increases ranging from ten percent to 34 percent for the other five indication categories.

So this gave us an idea of how opiates are being used. I want to turn our attention now to what the label says about the indications for these drugs, and again, I think the committee members don't have this on their handouts, but what I have up here are a number of label indications for some currently marketed opioid analgesic products, and as the slide shows, most of these labeled indications are relatively broad, for example, something like for the relief of moderate to severe pain without any further specification.

And these indications generally then extend beyond the scope of the clinical trials that form the basis of the product's approval. In fact, for many of the older opiate analgesic agents,

clinical trial data are not included in the label, and with a few exceptions, most labels do not indicate whether the product is for long term management of chronic pain or for short term management of acute pain.

Some opioid analgesics brought to market more recently, however, do contain data from clinical trials, and these data can then potentially allow physicians and other health care providers to use that trial data to put the drug's indication into a clinical context and, thus, hopefully better informing physicians regarding the choice of agents for their patients.

And so in view of both this increasing number of prescriptions and the important role that these clinical trials have in the labeling of the product, we want to focus some of this morning's later discussion on the clinical trials that are used to establish effectiveness of opioid analgesics.

So on the next slide here, we've summarized some of the variety of patient populations that have been used in recent new drug applications for opioid analgesics, and patient populations here vary. So one way is to define entry criteria based on intensity of pain without regard to etiology.

For example, the development program for drug two includes a trial enrolling patients with chronic malignant or nonmalignant pain.

A second way is to put some restriction on the etiology. For example, the development of drug four includes a trial for cancer pain, but does not further specify the pain, such as bone pain.

And a third option is to include pain due to a specific condition. For example, the development of drug one has two trials, one for chronic low back pain, and one for osteoarthritis for the hip or knee. So you can see that some development plans use very narrowly focused patient populations. Others use broadly focused patient populations.

Now, the narrowly defined patient populations, such as patients with osteoarthritis or low back pain, the trials using these populations may afford a better chance to demonstrate a clinically beneficial effect to the drug by reducing the patient heterogeneity. The results of the trials, however, may have limited utility when deciding to treat patients without one of the conditions under study.

Do successful trials with chronic low back pain and osteoarthritis provide a sufficient rationale to use the drug to treat another type of chronic pain,

such as chronic bone pain due to metastatic cancer?

On the other hand, trials that enroll patients with a broad spectrum of pain indications may better reflect actual practice. In these situations though, patient heterogeneity may limit the ability to detect a true treatment effect of the study drug.

However, careful design and sample size considerations may partly overcome this problem. If the study drug is shown to be effective, it's not clear, however that the result would apply to all pain conditions included in the entry criteria or if there are some pain conditions that do not respond to the study drug.

Now, subgroup analysis may shed some light on that issue, but the relatively small number of patients included in these analyses can make interpretation of the data often difficult. If these studies are successful and the drug is approved, is there sufficient rationale to treat patients with a chronic musculoskeletal condition, such as chronic low back pain, even if chronic low back pain patients were not represented in the study?

So defining the appropriate patient population for entry into clinical trials of opioid analgesics is of importance to us as we consider

clinical trial design.

We turn our attention now to the duration of treatment in clinical trials. Because opiate analgesics are used to treat both acute and chronic pain, it's important that opioid drug products intended for the treatment of chronic pain or that have the potential for treatment of chronic pain be studied in such a setting.

While many trials of opioid analgesics have been performed to demonstrate efficacy in short-term studies, the clinical setting of chronic pain is often different from the clinical setting of acute pain, and clinical trials for chronic pain must account for these differences in order to provide meaningful information to patients and physicians.

So in light of that, we're posing two discussion questions here for the committee. First, we'd like you to discuss the target population for various opioid formulations and what factors you consider in making this determination.

And, second, in the context of clinical trials to support an indication for chronic pain, we'd ask you to discuss the need to assess sustained efficacy over the duration of the trial.

Thank you.

ACTING CHAIRMAN KATZ: Thank you, Dr. DalPan.

Now, there are a lot of issues to discuss here, and what I'm going to try to do with the help and support of the committee, which I'm sure that I'll have, is to focus the question in some clear way.

What I'd like to do, first of all, Mr. DalPan, is to ask if there are any specific questions from anybody around the table about the content that Dr. DalPan presented just now before we actually get to answering the questions.

(No response.)

ACTING CHAIRMAN KATZ: Well, that was easier than I thought.

What I'd like to do now is to proceed with addressing the questions, and what I'll do is I'll repose the questions that Dr. DalPan has asked and which are reflected in the briefing materials that everybody received. I will repose each question in what I think will be a semi-focused way, and I'll hope that everybody will help me by focusing on the issue at hand as much as these issues are all really interrelated.

And what I would ask the people on the committee to do in your response is to try to focus

primarily on the clinical issues that need to be reflected in the clinical trials rather than come up with a specific prescription, like, oh, you should do a cross-over trial for this or obviously the trial should be four months or something like that, because that's going to be less useful for the discussion.

So try to bring out the clinical issues that we need to understand better with our clinical trials will be of most use to us.

Let me begin as follows. I'd like the group to discuss the issue of what determines whether a patient with chronic non-cancer pain should receive opioids. It seems clear from the statements that we've heard from our speakers already that the use of opioids for long term in patients with cancer pain falls within the general consensus of therapy these days, as well as for severe acute pain.

But where many of the issues arise that need to be reflected in our clinical trials is in the use for chronic non-cancer pain.

So the first thing I'd like us to address is what determines in clinical practice whether a patient with chronic non-cancer pain is or is not appropriate for opioid therapy, and does that actually reflect who gets opioid therapy in clinical practice?

Dr. Portenoy, why don't you start since it leads directly from the slide that you showed us before?

The question: what determine which patient with chronic non-cancer pain is appropriate or not for long-term opioid therapy?

DR. PORTENOY: In clinical practice?

ACTING CHAIRMAN KATZ: In clinical practice.

DR. PORTENOY: Well, clearly part of the issue is the expressed severity of the pain. So patients who have moderate to severe pain might be considered candidates for trial of opioid therapy.

Other issues that play into the decision in the clinical arena is whether or not there's a reasonable expectation that an opioid drug is the best drug. A good example of that might be, for example, patients with trigeminal neuralgia. There are some patients with trigeminal neuralgia who say that opioids are helpful, but there's a large experience and lots of clinical trials to suggest that aborting that kind of pain syndrome might be better accomplished with an anti-convulsant drug with an opioid drug.

So the necessity of considering the type

of pain syndrome, the severity of the pain, and then these other factors that I talked about before, what is conventional practice with respect to that patient population and pain syndrome? What is the likelihood of adverse events given the patient's medical co-morbidities?

The decision to pursue opioid therapy, for example might be more difficult if the patient has severe chronic obstructive pulmonary disease than if the patient doesn't.

And then finally, what's the likelihood that the patient will be a responsible drug taker?

ACTING CHAIRMAN KATZ: Maybe you could just elaborate on that a little bit before we go on. Are there any specific types of patients or types of syndromes or populations that you feel a priori would generally not be appropriate for long-term opioid therapy in the nonmalignant pain arena?

DR. PORTENOY: Again, I think speaking -- this is very impressionistic, but I'm not comfortable with the concept of not appropriate. In other words, to frame the discussion in terms of contraindications, I don't think we have enough data or clinical experience to do that.

But we can frame the discussion in terms

of the skills of the providers and the characteristics of the population. For example, a pain specialist might be much more willing to begin an opioid therapy in a patient who has some history of substance abuse than a primary care provider may be willing to do because the pain specialist either by experience or by the infrastructure that the clinic provides him or her would be able to monitor that patient more effectively and pick up aberrant drug related behaviors and deal with them much better than a primary care provider would.

So a previous history of substance abuse, in the literature some guidelines would say those patients shouldn't get opioid drugs. That's clearly not an appropriate stance. Some patients with even active abuse should be considered for opioid therapy, but it has to be done in the context of a prescribing that accounts for that co-morbidity.

So you have to reframe the question a little bit. You say in the new world of primary care providers giving patients with low back pain and osteoarthritis of the shoulder and need opioid therapy on a long-term basis, are there subpopulations that would raise such concerns that the primary care provider should consider referring.

And I think, again, I'm not a primary care provider, and some of the people around the table would be able to address that better than I could, but I think you can begin to say that there may be predictors of more problematic clinical outcomes that would suggest that a patient shouldn't be started on therapy by a less skilled primary care provider, but instead should be referred to a specialist, and that might include active abuse. That might include abuse of a known addiction to an opioid. It might include social disruption, lack of family support. It might include very severe psychiatric disorders of certain types, access to disorders that are very problematic where impulsive drug taking seems to be a major issue. It may include all of those kinds of factors.

ACTING CHAIRMAN KATZ: So if I can distill out from what you're saying some take-home points, correct me if I'm misunderstanding. It sounds like what you're saying is that appropriate pharmacotherapy with opioids depends not only upon the patient and the drug, but also it depends upon the treatment setting and maybe even the patient's home setting.

DR. PORTENOY: Oh, yeah, I think that's absolutely true. Again, if you're not talking about the kinds of trials that have to be done in order to

establish safety and efficacy, but you're talking about what's going to happen when that drug hits the market, there's no question in my mind that you have to talk about the knowledge and skills of the provider community, and you have to talk about characteristics of the patient population and the pain syndrome as factors that might determine whether it's less or more appropriate to consider prescribing.

ACTING CHAIRMAN KATZ: Thank you.

Jeff Bloom, you're next.

DR. BLOOM: Thank you.

Unfortunately, the Oncology Nursing Society wasn't here to testify during the open public hearing, but I would refer the committee to their documents which I thought were excellent, and one of the points that they made that I think is a very similar point is that pain treatment decisions should be based on the nature of the pain, the pain intensity, and a response to treatment whether the cause of the pain has a malignant or nonmalignant origin.

And in that case, you would be capturing almost everybody instead of parsing people out into different subgroups, but we're actually getting into the root of, you know, how to treat pain in a broader

context, and we can bring this up in a different discussion because it perhaps is not the appropriate time for this now.

But we do have federal guidelines that were developed from Johns Hopkins, Dr. Bartlett's good, hard work, for the treatment of HIV and AIDS that even though they are treatment guidelines have become de facto the standard of care for almost everybody, for all the states, for all the state programs, and also for third party payers.

And given the wealth of information that Dr. Portenoy pointed out in terms of what we have in terms of good information about appropriate pain management and pain care, perhaps the time has come for HHS to consider convening the similar kind of thing as we've done with HIV and AIDS and come out with federal treatment guidelines for pain management so that it gives the flexibility of people to make choices, but it provides much better guidance based on good, sound information.

Because if we wait for studies to occur, people will go untreated forever, and if we waited for studies to be finished to treat people with AIDS, people with AIDS would be dying waiting for the studies to be finished.

And I think there's probably a lot of literature, and as Dr. Portenoy pointed out, there are fundamental, sound principles that are basic to pain management now.

ACTING CHAIRMAN KATZ: Thank you.

Dr. Foley, you were next.

DR. FOLEY: I think I'm a little bit confused of what we're talking about here. Are we talking about target populations in clinical trials or are we talking about target populations for treatment?

ACTING CHAIRMAN KATZ: We're talking about target populations for treatment which one would think ultimately will need to be reflected in the clinical trial process one way or another, but the first step is to help this division of the FDA understand how opioids are most appropriately used in clinical practice, and then from there try to figure out how the clinical trials ought to inform that ultimate practice.

DR. FOLEY: Well, then I would argue that we have insufficient research to know what patient populations would be appropriate for these therapies and that we have an enormous amount of bias and lack of knowledge and lack of education that is creating the sort of mythology about all of this in which we

think that that might be the case and isn't the case.

And so I have a great concern that we don't have data about patients who have a previous history of drug abuse, who develop a pain problem or develop cancer and what the risk is. We have little data about those with a history of alcoholism and then what their risk is. We have little data and a lot of anecdotes about an AIDS population who does very well with a previous history of drug abuse when they have an AIDS pain problem that they do not develop abuse.

So I think we don't have that kind of framing, and I'm afraid that we're going to fall into the lack of knowledge, and we're going to sort of go with common practice, and we've all agreed that the current practice is persistently under treatment and fear of prescribing.

So I'm not trying to make your job harder, but I do think that if we buy into these misconceptions, we're going to have to live with them, and we need to do something better than that.

ACTING CHAIRMAN KATZ: Dr. Portenoy, response?

DR. PORTENOY: I basically agree, although I think that it's important to understand the challenge also. If we in clinical practice make

decisions about opioid prescribing based on perceptions related to risk of addictive behaviors, risk of aberrant behaviors and we know that the clinical trials typically have substance abuse behaviors as an exclusion criterion, then you know that the labeling that will ultimately come from that either has to very overtly have to say that these patients were excluded so that the clinical practice issues that may relate to that population can't be addressed by these data or we have to think of another way of doing studies that would allow us to address the questions more directly so that the labels can be done.

So I basically agree with Kathy, but I think you have to -- I see where you're going and with support in the sense that we have clinical trial designs that have been used to get many of these drugs on the market. We have indications and labels that have been developed in the design, and then we have a clinical practice that's been galloping along seemingly unrelated to what those clinical trials have been.

And to bring them together we have to talk about what the consensus is.

ACTING CHAIRMAN KATZ: Let me just remind

folks to turn their mics off when they're done speaking again, and, Dr. Ashburn, you were next.

DR. ASHBURN: Thank you very much.

I had a couple of comments regarding your initial question and comment and then wanted to talk a little bit more about what Dr. Foley just mentioned.

First of all, the practice of medicine, as everyone who practices medicine knows, is partially evidence based. Those of us who do it every day recognize that it's less evidence based than we would like to admit.

We unfortunately make decisions based on anecdote, and sometimes we forget that the plural of anecdote is not data, and that frequently --

(Laughter.)

DR. ASHBURN: -- making decisions based on our own personal observations leads us to make decisions that may not be evidence based or truly data driven.

The other one that's important to know when you're talking about designing trials in patients with chronic pain, we've almost kind of gone towards that a little bit in this discussion. This is a focus on the use of pharmacologic agents in that physicians tend to always think about a drug interacting with the

receptor to block a no susceptor pathway that treats pain, and in fact, pain is a much more complex disorder. It is almost always more than just a disturbance of biological function within the body.

And pain care has to be done in the context of a biopsychosocial model of pain care. Pharmacologic management, including the use of opioids, can play an important role in the care, but also aggressive activating physical therapy changes in life styles, cognitive behavior therapy, addressing the psychosocial environment that those individuals live in and the impact that we've heard from our open public session of pain experience in individuals' lives is important to address, and simply giving opioids is unlikely to lead to long-term benefit from that.

Now, why is that important to recognize? Because it's important to recognize that designing these clinical trials is extremely difficult, and we have to eventually extrapolate looking at individuals that seem to have common themes and then identify whether or not the drug is safe and efficacious in those environments, and then as best we can, try to extrapolate that knowledge over to other areas.

But even limited areas like OA of the knee

and the hip, which may be mainly no susceptive versus chronic low back pain, which clearly can have a biopsychosocial component make doing those studies difficult.

And last, I'm conflicted a little bit about some of the things that Dr. Portenoy said. I was going to spell your name out for the regulators based on your other remark, but I wanted to mention a little bit about the role between specialists and primary care physicians with regard to the use of these medications.

When you get right down to it, the use of these medications is very similar to the use of the medications of different classes. One needs to do a history and physical. One needs to make a diagnosis, and then develop a treatment plan, implement that treatment plan, follow how the patient responds to that treatment plan, and then make adjustments as necessary.

It's an ongoing, fluid, active process, not a one time intervention or acute process. It's no different than when one is treating hypertension. As Dr. Portenoy mentioned, if a physician, whether they're a specialist or not, does not have the skill set necessary to make the diagnosis of hypertension

and treat it appropriately, then it ought not be part of their clinical practice.

It does not matter whether or not one is a specialist or whether one is a primary care physician. What matters is whether or not that individual has the skills necessary to treat that particular condition.

I have concerns about discussions or movements towards having a primary care or a pain center focus and that the recent events regarding concerns about diversion of Oxycontin caused a lot of primary care physicians to back away from prescribing potent opioids.

As a result, many specialists, including myself, were receiving ten to 15 referrals a day by patients who were desperate to get in to receive that care, and we simply cannot take care of all those individuals.

So we need to have some caution with regard to how we try to approach that issue.

ACTING CHAIRMAN KATZ: Dr. Connolly.

DR. CONNOLLY: Yes. I essentially want to -- who spoke about the oncology nursing society. We're talking very individually about individual physicians managing pain, but I think nursing and

nursing studies have shown that the management of pain is a team approach.

And Margot McCaffrey has been a nursing leader in pain management for several decades now, and she early on defined pain as pain is anything the patient says it is.

I agree very much with our last speaker in that there is the psychosocial piece. So it really is a team approach. So if we're going to set up a study and with a target population, we need to include those folks who have been very, very active in setting up guidelines and in studying pain management.

Pain resource nurses, advanced practice nurses, clinical pharm. D.s, psychologists and social workers.

ACTING CHAIRMAN KATZ: Mitchell?

DR. MAX: Regarding Dr. DalPan's two questions, he first asked which models should we study. Which are the patients for opioids?

And the academically correct answer is the ones with the right mechanism. The truth about that though is that even though a lot of us in the room have spent 20 years trying to find defined pain mechanisms in patients, we've really been groping and had very little success, and the RAD doctors are way

ahead of us.

And Clifford Woolf and I reviewed this in Anesthesiologist in July. We looked at all of the attempts to define pain mechanisms in people, and there are only two ways of getting at it. One is to take what you mentioned, people with objectively verifiable lesions and put them together and compare responses of different drugs or responses of different pain conditions, and occasionally there's been a hit there.

Like for instance, it looks like just from a few trials the gabapentin and son of gabapentin works in peripheral neuropathic pain, but doesn't work in OA and back pain. So there is some tissue difference.

So, you know, it seems to make sense to look at homogeneous groups with tissues overall, but there's a much stronger way to identify mechanism within any group. We all know that some patients respond to any drug and a lot don't, and there have been a number of groups who have gone back and done rechallenge enriched enrollment and found that small or medium size subgroups consistently respond within any group. So I think within any diagnostic group it may be a smaller number; it may be a larger number.

There are going to be some people who really respond to opioids.

So probably the best way to identify people that would be good for some types of further study would be to give them a short trial of opioids, identify opioid responders.

Then to your next question of should we do long studies, here, I mean, there are a lot of important questions in coming up with a risk balance ratio, and one issue is after six months or a year does the pain relief wear off and you're just hooked? I mean, what are the side effects?

And here there's absolutely no academically supported data, and these studies are very hard to do, and maybe you could do them if you took the enriched patients who really responded and gave them a low does or a high dose for this long, long time.

But I don't know if every drug company that wants to get a drug approved should have to do these precedent setting studies. This is just a weird anomaly that as Kathy Foley has shown in an IOM report that's just out, we've spent about half of a percent of the public budget on pain, and this is strange. Industry has been way out ahead, spending, you know,

probably ten or 20 percent of their budget on symptoms. So it's no surprise that marketing and industrial development is way ahead of the fundamental issue.

So I think perhaps there's some way of getting NIH -- they haven't before -- but getting monies for them to do in a few drugs, a few model drugs, what happens, what's tolerance at six months, a year? What are the side effects? And not have these repeated with every compound that comes along.

Certainly for every drug you need some sort of epidemiological survey of bad addiction and bad occurrences.

ACTING CHAIRMAN KATZ: Dr. Smiley? Dr. Horlocker? Dr. Roberts?

DR. ROBERTS: Thank you.

Let me begin just by asking the others around the U-shaped table: is there anyone else here who would consider him or herself a primary care clinician?

(Show of hands.)

DR. ROBERTS: So we have one. Okay. It's probably appropriate we're sitting across from each other.

(Laughter.)

DR. ROBERTS: Let me -- it's been interesting listening to this discussion. My sense is that most of us from around the table are from academic medical centers, and let us -- let me share with you kind of where we fit in the universe of health care in the United States.

There are about 820 million visits to doctors annually in the United States. A little more than half of those are to primary care physicians who comprise one out of four U.S. doctors. Now, many of you aren't even sure what a primary care doctor is. You're kind of struggling with what to call us, and indeed, we are multiple specialties that come to that kind of practice, family doctors, general internists, general pediatricians.

But the one out of four of us that are U.S. doctors doing this, taking care of more than one out of two visits wonder sometimes what the other three out of four docs do with their time.

(Laughter.)

DR. ROBERTS: Let me get a little more specific about pain. Dr. Portenoy was kind enough to share some estimates. He estimated that there are about 15 percent of Americans who suffer from some kind of chronic pain problem. So I would calculate

that to be about 42 million Americans.

The average American goes to their doctor about three times a year. That's all comers, all problems, all ages. You could probably speculate that these people are going to see their doctors more often than that understandably, but for rounding off purposes, let's say about 160 million visits a year to doctors for pain, chronic pain, and I'm not even talking about acute pain.

He was also kind enough to share there are about 4,000 pain specialists, and they probably average about 4,000 visits a year. That's 16 million visits out of 160 million for chronic pain. They're seeing about ten percent of the visits.

Who are the experts here?

(Laughter.)

DR. ROBERTS: Academic medical centers provide less than .1 percent of the health care in the United States if you look at numbers of visits. I know. It showed me, too, when I saw it. New England Journal, July, this year, past year.

So one of the things I would say to you is we're very quick to turn to our last bad case of referral and generalize from that to global statements about how good or bad a job people are doing out

there.

And what I would also share with you is the experience around guideline development often overlooks that problem. For instance, when HLBI came out with their first set of hypertension guidelines in the late 1960s, nobody followed them. Why? Because it was basically written by referral academic cardiologists/nephrologists for whom 25 percent of their patients had a secondary or curable cause of hypertension.

When they went out and did population based studies, it was less than three to five percent. So those of us that were not following those early guidelines to do angiograms on everybody were, in fact, doing the public a great service.

So one of the other things I'd ask you to reflect on is the challenge for me in the trenches is when I hear what the experts advise, whether it year's statement about opioid use versus 20 years ago when the experts thought they had it right by avoiding opioids, my challenge is to not only consider pharmacologic therapy, but all the other seven non-pharmacologic approaches to management of the problem, and to do it in the context of this person, his or her life, their family, their community.

And so while many of you will be very expert at the nuance of opioid prescribing, I am expert at this person, and we've been reminded this morning that this kind of therapy is very individualized.

So what to do with all of this? Well, one of my pieces of advice, answering the question before us about how to better understand this is do the research where the people are, and there are, indeed, a number of practice based research networks that are developing around the country that represent now about 120 million Americans being cared for through the primary care doctors' offices, and begin to do some studies particularly in the primary care setting. There are essentially -- and I have an expert in my department, a family doctor who is an expert on addiction and pain; there are no studies in this area.

And my fear is not that the plural of anecdote is data. The plural of anecdote unfortunately is policy.

(Laughter.)

ACTING CHAIRMAN KATZ: Dr. Schechter.

DR. SCHECHTER: Yeah, thanks.

I want to bring this discussion in a slightly different direction in terms of question

number two, in terms of chronic pain, and really speak specifically for a population that I'm familiar with, which is the pediatric population, and because we have an additional complexity in that population of a developing brain with pruning going on, nusenathegenesis (phonetic), prefrontal lobes.

If anybody has watched the PBS series on the brain about the teenage brain which they said was pretty complicated and understandable, and I think that that really speaks to a lot of the sorts of issues that we're dealing with right now.

So there is no data, and we're starting to use opioids frequently, especially in newborns who are on sedation for prolonged periods of time in institutions. There's really no data on that sort of long-term.

What happens to that population subsequently, there's certainly a number of people who have tried to address it, and there's a lot of theoretical models, but it brings us some concern because not only are we talking about chronic pain, and we do use opioids for chronic pain in children, but even on prolonged acute pain, if you will, whatever that terminology would be. We have real concerns about that.

Having said that, we feel the need to proceed and clinically treat who we see and provide human and compassionate care as we define it now, but that's an area of significant need.

The other thing I wanted to just address for just a second is the sort of primary care aspects of this. I've had a lot of concerns about the comparatmentalization of pain care over the past few years, and I think that that was necessary certainly for the development of the field for research, multi-disciplinary pain centers to evolve and provide new models and new research in this whole area.

But unfortunately it does centralize in a certain way pain to a subset -- management to a subset of patients who can see a pain specialist, and we've put a lot of our energies, for example, into broadening that so that there's a systemic approach to pain within institutions so that everyone -- it's considered that it's not merely if you happen to get a referral to the pain specialist, but for broader sorts of issues so that everybody who walks through the door, if you will, this is a consideration. It's not necessarily opioid driven, but certainly the whole issue of thinking about pain in all of its contacts.

And the final thing I wanted to mention in

terms of, again, what you had suggested is that seeing or our feeling about -- my feeling from the clinical side, again -- this is the consensus of the small number of pediatric pain specialists which I think parallels the adult chronic pain literature, which is that opioids need to be in the context of an overall treatment plan. It shouldn't be just a smorgasbord that you pick and choose which elements that you want, and if you only want the opioids, then that's fine.

We do think that there sort of needs to be a comprehensive matrix for which this is understood and appreciated and otherwise we're very anxious about treating.

ACTING CHAIRMAN KATZ: Thanks.

Dr. Rappaport.

DR. RAPPAPORT: I'd like to try to focus back on the first question a little bit. Everything that we've heard is very useful to us in evaluating clinical trial designs, but as Dr. Portenoy was saying, we have to look at the translation of the clinical practice into things like an inclusion and exclusion criteria in the trials and whether they're appropriate.

And we get concerned sometimes that if those aren't accurate, perhaps the clinical trials are

driving medical use rather than vice versa. So I would appreciate hearing from all of you ways that we can accurately translate this lack of information that, as Dr. Foley said, and the lack of data, as Dr. Max said, that's out there.

But there's sort of a clinical sense about who the right patient is. How do we translate that into inclusion and exclusion criteria and the right population for a clinical trial both in adult and pediatric patients?

ACTING CHAIRMAN KATZ: Yes, Dr. McNicholas, why don't we start with you?

DR. McNICHOLAS: Okay. I think that part of the problem here is you're asking for a definition of who the right patient is, and when it comes right down to it, the right patient to be considered for opioid treatment is the patient who hurts.

You may decide that the patient is not appropriate for opiates, but that's the person that you start thinking about this with. And then you start looking at why do they hurt. What else goes into it? How are they going to handle it? How are they going to handle the pain? How are they going to handle the medications?

And we don't have a lot of good

definitions for this. So I think that actually coming back to -- I'm sorry. Your name? Pardon me?

DR. McNICHOLAS: I can't even go by tie. They're dressed alike.

(Laughter.)

DR. McNICHOLAS: Not Dr. Portenoy.

PARTICIPANT: Glasses or no glasses?

DR. McNICHOLAS: No glasses.

DR. ROBERTS: Dr. Roberts.

DR. McNICHOLAS: Dr. Roberts.

There are millions of patients out there who come in with a pain complaint. Does every patient get opiates? No. Is every patient appropriate for opiates? No.

Does it go through the physician's mind? Yes, as to whether or not you're going to use it.

In some ways I'm not sure what the question is that the FDA wants us to answer here.

ACTING CHAIRMAN KATZ: Who do you include in your trial.

DR. McNICHOLAS: Patients who have pain; patients who hurt.

ACTING CHAIRMAN KATZ: Okay. So let's take that to the next step because that leads to further problems because would you then advocate in

most or all clinical trials for chronic pain incorporating a heterogeneous hodgepodge of different patients who have essentially the single entry criterion of pain, or would anybody advocate honing down that population further?

Let's hear a response from Dr. McNicholas and then we'll go on.

DR. McNICHOLAS: Okay. I think you do have to hone it down, but I think that the honing down comes once you have defined what the question is that you want answered.

Do you want a drug available for people who hurt or do you want a drug that you are looking for a specific indication?

For instance, osteoarthritis or low back pain or whatever the situation is, and then you may or may not start looking at the facets that go into treating that patient. For instance, the patient with low back pain, is there a physiologic reason for low back pain? What other treatments have they failed, et cetera? How have they managed their pain?

Because I see -- I get pain referrals. Frankly, I get a lot of the pain referrals when primary care docs go, "I don't know what I'm doing with this guy," and it's not just primary care docs.

I don't want to pick on Dr. Roberts or anybody else on that, but it's like I keep using more medication, and I'm not getting anywhere. And they still say that their back hurts.

Well, yeah, their back hurts, and the fact of the matter is their back is always going to hurt. Now, how are they managing the pain?

And they may or may not have had appropriate intervention, and that's the other thing, not only who do you pick for a trial, but what is the form of the trial? Does the trial mandate other interventions, physical rehabilitation, cognitive behavioral therapy, other coping mechanisms, et cetera? Those that people who treat pain appropriately look at all the time.

And so I think that you have to much more focus the question on what the trial wants to accomplish.

ACTING CHAIRMAN KATZ: The list got all messed up because we changed topics. So let me apologize for that. We're scratching out the whole list, and let's start fresh. Dr. Holmboe.

DR. HOLMBOE: I just want to raise a couple of points. The first would be when you're talking about the target population, we've been

spending a lot of time focusing on the skills of the physician.

I would also caution the FDA to also think about the skills of the patient and how do you prepare the patient to be skillful in taking the medication.

There are a number of issues that often get left out in these trials that aren't addressed, particularly the issues of health literacy, and also the issue of numeracy. So we're talking about, you know, a drug that has a risk-benefit ratio that may be difficult.

Part of the things we need to look at in these trials that really haven't been done very well before is where are the patients with regard to literacy and numeracy and how does that impact the use of these medications.

The second thing that really gets to Laura's point is that in a sense what you're really considering is a complex health intervention here, and that becomes very difficult because we like to be very reductionistic and like to say, "I just want to focus on this because I want to take everything out," and so most of our randomized controlled trials really focus on efficacy.

What we're really trying to get at here,

and I think what people are really struggling with is is it efficacy or is it effectiveness. They're different from an epidemiologic point of view.

I think what we're talking about was effectiveness out on the real world as Dr. Roberts got at. When you look at those conflicts and interventions, it's going to be very important in trials to define exactly what the intervention is.

And so I think that's the other challenge to think about when you're designing these trials.

My last point would be, just getting back to Dr. Roberts, is that there's also models that we can use with regard to taking research into the community, and it really comes from the substance abuse literature, bupamorphine being an example where a lot of work has been done in the out-patient setting in the community, and that may be a model to look at with regard to studying the use of opiates for chronic pain.

ACTING CHAIRMAN KATZ: Dr. Reidenburg is next.

DR. REIDENBURG: Yeah. I think that you raised a good point of efficacy versus effectiveness, and at least when I look at data in other areas of medicine, the first thing I want to see is efficacy.

Effectiveness includes many factors or influences totally independent of the drug's pharmacology.

I would say to address the question that the primary thing we need to know is efficacy. I want to know dose response in terms of adverse effects at doses that produce efficacy. Effectiveness is more a general medical problem that we have to deal with in context.

And I think that where clinical trials can give me clear data on efficacy and on the adverse effects that I have to pay for that efficacy, I'm happy to have this evidence.

ACTING CHAIRMAN KATZ: Dr. Max.

DR. MAX: To address Dr. Rappaport's question of inclusion or exclusion criteria for patients, I just read yesterday Paul Delamine is a Dutch researcher who's done a lot of opioid and non-malignant pain work, and he suggested -- he said, "Well, we had a lot of patients in our trials with neuropathic pain responding, but the ones that aren't good for opioids are the ones with idiopathic pain.

Now, I don't quite like that because it's kind of vague, and also about 70 or 80 percent of people with chronic back pain really have idiopathic pain. There's no clue till we look at Deyno's New

England Journal review, Deyno and Weinstein, a few months ago.

But you can actually get to something a little more refined. There's a marvelous issue supplement of the Annals of Internal Medicine in May 2001, I think, by Kurt Kroenke, K-r-o-e-n-k-e, on symptoms in primary care, and he and Spitzer have taken the prime -- it's a general medical diagnosis study; taken 1,000 patients and devised a new diagnosis for primary care called multi-somatiform disorder that's much easier to get into than the classic somatiform disorder.

Nine percent of people who walk into a general primary care office have it, and there are people with three or more unexplained symptoms, and they respond in study after study differently from many other patients, and they have a very high rate of affective disorders lifetime.

At this conference some of the -- many of the patients with fibromyalgia and interstitial cystitis and so on respond. So this may be an interesting distinction that has been very well validated to study because there are many different loadings.

I think we've already heard from some

multi -- from people with multiple unexplained symptoms that get response to opioids, but that would be a good literature to look at.

ACTING CHAIRMAN KATZ: I'd like to pursue Dr. Reidenburg's efficacy versus effectiveness distinction. Many people around the table have already stated that proper pain management often requires a multi-disciplinary approach, consideration of family factors, treatment settings, et cetera, which would, I think, fall more into what you're calling effectiveness.

Whereas efficacy is when we look for more of a pure pharmacological response and a more homogeneous population in trying to control as much as possible for these factors that are extrinsic to the pharmacological properties of the drug.

Do people feel that efficacy trials are enough in a clinical development program or do we also need effectiveness trials in a clinical development program with an opioid?

Dr. Foley?

DR. FOLEY: I would argue for efficacy studies first, and I would argue for efficacy studies in various disease models where the questions were unresolved, and attempting to make the study as clean

as possible by focusing on specific populations.

So the kinds of models and studies that, in fact, Mitchell has done, among others, is using a model such as post herpetic neuralgia, which could be a mixed somatic and neuropathic model, but is a rather profoundly neuropathic model.

We're looking at peripheral neuropathy or looking at osteoarthritis. The minute you move to the more sort of general, diffuse chronic pain syndromes or you move to fibromyalgia or more complicated studies like that, one could argue that what you would like to build into that efficacy study is a much more sophisticated understanding of the quality of life and the psychological make-ups of that population.

But by looking at each of those, it would at least advance the field forward for what were the role of opioids in large populations of patients with fibromyalgia that the primary care physicians are seeing of osteoarthritis, and one could do it joint by joint and disease by disease of certain types of neuropathic pain.

And I would argue that putting those trials together in that kind of way would help move us forward using the extraordinary data that currently exists on studying opioids and the methodologies that

have been put together over a long, long history that one chooses; that the opioid is based on the intensity of pain, and this comes out of wide clinical trials that compared low doses and high doses of various opioids for mild, moderate and severe pain and developed a methodology around that construct.

So there is an FDA sort of analgesic trial design looking at issues of intensity and looking at various potencies of drugs that is one piece and then looking at selected populations.

And I would then argue that if you wanted to ask very difficult patient questions is to look at the role of opioids in an HIV population with peripheral neuropathy who had a history of drug abuse. And again, we have an IOM report that argued very strongly for supporting the kind of research in the drug addiction population to be able to better understand what their ability to and to compare their perspective on efficacy in that selected population with other general populations.

ACTING CHAIRMAN KATZ: Dr. Kweder.

DR. KWEDER: I want to step in here because I think you've laid out, Dr. Foley, exactly where our conundrum is, and one of the things that Dr. DalPan said was that historically when we have

approved opioids for marketing, the labeled indication is very broad, and there are many different kinds of studies that are often very focused efficacy trials that underlie those labeled indications.

And so part of our struggle is is that okay and how much do we need to be requiring prior to marketing in order to establish an evidence base for such a broad indication?

ACTING CHAIRMAN KATZ: Comments on that specific question? Dr. Smiley.

DR. SMILEY: Well, speaking not as a pain specialist, but also unfortunately not as a primary care physician -- somewhere in between, closer to the pain specialist, I guess -- it seems to me that one of the things that the FDA is asking us for is some kind of consensus among the physicians on the committee or the people on the committee.

And it does seem that there's a pretty broad consensus that opioids work for a broad variety of patients, broad variety of types of pain, and it does seem reasonable that in general the indications ought to be broad or the approval, the labeling ought to be broad.

I'm saying what a lot of people have said, and this microphone is behaving funny, but I'm doing

it because I think part of what you want is to see if there is a consensus. So I'd be happy to be contradicted by Dr. Foley or Dr. Portenoy or someone who knows a little bit more about pain than I do.

But it does seem that in general most pain syndromes are responsive to opioids that work, to doses that work in other studies, with some exceptions that, you know, we've heard some examples of and we all kind of know about.

But I would think that the indications ought to be relatively broad and that there's evidence that that's a reasonable way to go.

Now, what one then does to try to improve medical practice or even improve labeling is a little unclear, and some of that may be some comparison of relative efficacies of different drugs and different syndromes and seeing whether there are more similarities than differences in that. I would defer to people who study that as opposed to the things I look at.

ACTING CHAIRMAN KATZ: Holding aside the issue for the moment of what clinical trials should be done, is there consensus that people feel that labeling itself should be broad, in general that that should be the ultimate target, is to have a broad

label for something broad, chronic pain in general, chronic pain of certain severity?

Answers to that question? Dr. Max.

DR. MAX: Yeah.

ACTING CHAIRMAN KATZ: Dr. Portenoy?

DR. PORTENOY: Yeah, I think one of the very critical elements here is whether we're talking about pure mu agonist drugs usually in a new delivery kind of system or whether we're talking about novel drug agents, either some sort of a mixed opioid, non-opioid mechanism, or a non-opioid mechanism.

And I think if you have a drug that is a pure mu agonist kind of drug in a new kind of delivery system, then it would be very important for the clinical development scheme to answer the questions that are going to be appropriate, going to be important to clinicians, you know, the dose response, the relative potency with other known agonist drugs, the titratability of the drug.

And I think that long-term trials to look at tolerance are not appropriate. I think forcing a drug company to expand their study populations into those that include active abusers because the field is moving into that, the clinical field is moving in that direction, but other drugs of the same class have

never required those studies before. It doesn't seem appropriate.

And I think a broad label is very appropriate. At the same time, I would think that FDA should begin to encourage in all of these clinical trials industry to do more astute measurement of covariates because I think we're in the process of trying to understand the importance of covariates, including medical co-morbidity, psychiatric co-morbidities, including substance use disorders, as potential predictors of response.

And in some of the Phase IV survey data, the post marketing surveillance data that are so important to clinical practice, if we have good, astute, ongoing measurements of covariates, that's what clinical practice is based on largely.

As Mike Ashburn said, we like to think we're evidence based. I don't know how much of his practice is evidence based, but mine isn't much evidence based. And so if you show me a survey of 1,000 patients and I can see that the covariates were measured with validated instruments and a sophisticated and systematic way, that's influential, and I think that's appropriate for a pure mu agonist drug.

At the same time, I think for a pure mu agonist drug it's totally appropriate to have a mixed population because these are opioids, after all. You know, I mean, they've been around for a while. We basically know they're pain killers, and we know that they can work with any kind of pain.

So forcing a mechanism based study when the clinical identification of mechanisms is nonvalidated doesn't make any sense to me.

On the other hand, if you have a new chemical entity coming down the pipeline and there's a desire for drug development, not only to have this pragmatic focus, but also to be explanatory, I think it's very appropriate to say, "Do a study in neuropathic pain, a well defined neuropathic pain condition. Do a study in OA, which is a widely accepted nociceptive pain."

But you know, as my colleagues will tell you, the basic science models suggest that much of what's happening at the dorsal form looks the same if it's joint pathology or if it's nerve pathology.

So recognizing that the clinical entities are constructs and they're nonvalidated, it still can be informative to do those studies with a new chemical entity, but with an opioid, a pure mu agonist opioid,

I don't see the sense. I think we have a big history, and the history basically tells us now we want better long-term surveillance data with systematic measurements of covariates, and we want broad labeling, broad indications based on efficacy trials that help us understand the weighted dose of those agents, you know, the relative potency and other critical issues like that.

ACTING CHAIRMAN KATZ: To make sure that I understand what you're saying going forward, it sounds like you're suggesting that a fairly traditional efficacy program should be sufficient to achieve broad labeling, and that should be the goal of the development program, but that there should be, following approval, post marketing studies of various types to identify covariate subpopulations and to further inform the clinical utility of the drug.

Are you suggesting that those be required as part of the approval process? And if so, how does one go about the process of determining which sorts of studies should be required and then, in turn, how those will back influence the labeling of the drug once they're done?

DR. PORTENOY: You know, without knowing all of the regulatory details, I would be in favor of

having FDA take the stand that those sorts of systematic, prospective surveys of the pure mu agonist drugs in relatively large populations carefully followed for a prolonged period of time should be required.

Now, they may be required in Phase IV. The drug may get on the market, and then these could be studies that are subsequently required, but I think that we're at a point now where there's enough concern about what should be in those labels and enough concern that well designed, controlled randomized trials are not going to provide the critical effectiveness data that would allow the labels to be written; that the FDA could now say going forward this new drug with this new delivery system, we want to see 2,000 patients followed for X number of months using validated measures of substance use, of psychiatric co-morbidities, of medical co-morbidities, and maybe get some population pharmacokinetic data so that we can begin to do some modeling of various effects versus pharmacokinetics, and hopefully that information over time can begin to inform the core guideline piece of the label so that a primary care provider opening up the next oxycodone delivery system will see some instructions there that make clinical

sense.

ACTING CHAIRMAN KATZ: Let's have specific comments on Dr. Portenoy's proposal that we allow opioid drugs to be approved by a relatively straightforward efficacy program and then require post marketing trials to further identify covariates, populations, clinical utility, and these various effectiveness issues.

Dr. Horlocker.

DR. HORLOCKER: I'd agree with the broad based labeling for opioids because I think that that's the only way you're going to really be able to study the populations.

Subsequent post marketing surveys though are going to have to focus mostly on safety issues unless you want to proceed as Dr. Foley recommended, that we truly define a very clear-cut population to study, and then you're going to need thousands of patients in each of these population groups, which is going to be just an outstanding number of patients and money.

So I'm not sure exactly how the drug companies could fund something like this if we're talking about thousands of thousands of patients over time in each different population, and that will have

to be reconciled in some way.

But if they focus mostly on safety issues with long-term use, I think that that could be easily done with a homogeneous or heterogeneous group of patients.

ACTING CHAIRMAN KATZ: Other comments on this specific issue? Yes, please.

DR. PORTENOY: Just a very quick reply. I think that I agree with that, and that's the conventional thinking. But there are so many things that we don't know about long-term therapy in the primary care community, like, for example, of 1,000 patients that my friend to the left puts on opioid medications, how many will still be taking them in three, four years. I don't even know that.

You know, how many times will the patient require dose escalation over a period of three to four years? I don't know that in this kind of community of patients, you know?

So I think that there are questions that relate to efficacy that can be informed by a survey, although the statements about efficacy will be very limited.

ACTING CHAIRMAN KATZ: Dr. Ashburn.

DR. ASHBURN: I just have one quick

observation. I agree absolutely with the concept that Dr. Portenoy has laid out with regard to indications and with regard to the safety and efficacy studies that should be necessary to get a fairly broad indication for opioids.

I have some concerns with regard to a suggestion of requiring pharmaceutical companies to bear society's weight in doing large population based, long-term studies to answer the key questions that we need.

And I just wanted to put out that I can see somebody making a credible argument. This is a societal issue, and these are studies that appropriately should be investigator initiated studies sponsored by NIH with an increased emphasis through NIH funding for these sort of long-term studies to look at outcomes rather than something that is dovetailed on top of requiring a pharmaceutical company to sponsor these projects.

As you know, short-term efficacy studies go for what, $1,000 a patient? If you're looking at, you know, these sorts of studies, you're looking at much more cost. You're proposing studies that will cost two to $4 million easy, and whether or not that's a barrier to entry for other drug delivery systems

that may actually add to our armamentarium and improve the quality of care is something that was probably worth debating.

ACTING CHAIRMAN KATZ: Well, I know better than to mess with the lunch break. So even though this is obviously a very important discussion, we will have more time to pick up on these themes.

Just to recapitulate, it sounds like there's a general feeling that a fairly traditional efficacy program is appropriate for a broad approval, but that there should be some sort of post marketing, more affected in the style program required, although exactly how that would be funded and how extensive it needs to be is still under a great deal of discussion.

We'll regroup here at exactly 1:30; is that right? At exactly 1:30.

For the people at the head table, there is a room reserved in the restaurant. Please head right there, and we'll see everybody else at 1:30.

(Whereupon, at 12:38 p.m., the meeting was recessed for lunch, to reconvene at 1:30 p.m., the same day.)

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

(1:37 p.m.)

ACTING CHAIRMAN KATZ: Could everybody take their seats, please?

Let's go ahead and start the afternoon session then. If everybody could take their seats and bring their conversations to a close, we'll move forward.

What I'd like to do now, we've got an afternoon session on pediatric issues planned. What I would like to do, however, since I think we were on the verge of hitting on some very critical issues from the morning, I'd like to take just ten minutes out of the afternoon session, the first ten minutes, and try to focus hard on two specific questions that are left over from the morning, and then we'll launch into the afternoon session on pediatrics.

So apologies to the pediatric folks. The first question that I'd like to get into is that it seemed like there was a feeling that there are a broad range of -- that while we can relatively straightforwardly determine in a somewhat traditional program how to determine that an opioid is really an opioid. There still are some important questions about effectiveness in a real life situation, about

long-term safety that we don't understand very well with regard to the whole class of opioid analgesics.

And so I'd like to focus a question on what people think are their major issues from an effectiveness point of view or from a safety point of view about opioids that would need to be addressed in such a program that addressed either a specific drug or the whole class of drugs.

And, Dr. McLeskey, you were last left over from the morning. So why don't we start with you?

DR. McLESKEY: Well, thank you very much.

I was going to just make some comments because I was very pleased to hear the commentary especially at the end of the last discussion. I believe it would be industry's perception that we concur with most of what was said right there at the end.

For example, I think we would endorse the concept of a broader label claim rather than a narrower label claim. It would provide more incentive for development and the like.

And then I'd also like to highlight what Mitchell Max said earlier in the session where some of these large, precedent setting studies, long-term studies and the like he felt like potentially would be

better directed by the NIH rather than by industry, and I believe industry probably would endorse that concept as well.

(Laughter.)

DR. McLESKEY: And interestingly, that was also echoed by Mike Ashburn when he suggested that efficacy trials might be relatively limited in scope and cost compared to some of the longer term follow-up trials that might become complicated and rather expensive.

So I know I speak for industry when I say that we all would like to cooperate with the FDA, and we want to contribute to medical advances, and we want to contribute to advances in medical understanding of patient management and the like, but I would just ask that when you reach your conclusions that potentially some restraint is used when the requirements or the suggestion for Phase IV trials, post marketing Phase IV trials are discussed in order that those trials not become such a hurdle that they then actually turn into something that stifles innovation.

DR. MAX: Could I respond to that?

Thanks, but I'd like to clarify what I said. I agree. I agree that I think it would be unfortunate if every company that wanted to market a

mu opioid was saddled with doing a $20 million two year effectiveness study. It would really be a bar to quick moving little companies on the market.

On the other hand, you can't just say, "NIH, do this."

And here I speak -- while I work at NIH, I have no authority or expertise of the governing areas. I'm just one clinician investigator. So it's just a personal view.

We've been calling for NIH to do more in this for many years. I was a co-author of an institute of medicine report commissioned by NIDA about five years ago, what research they should do, and we had a chapter saying they should do these studies, and I'm not aware that there are any current studies going on.

The NIH mantra seems to be we only fund. Don't earmark us. We only do the best investigator initiated research. Some of the people at this table have submitted proposals to do just these studies and gotten rejected, and then they say, "Well, they aren't trained investigators."

So my proposal actually is I would ask my friends from industry to try to think of some alternative, some way that industry can provide the

money, say, to let the peer review system get the smartest young people trained and do a few studies rather than a lot because I can't believe NIH is going to come up with it, though I'm not authorized to speak for them.

ACTING CHAIRMAN KATZ: Industry perspective on that suggestion?

DR. McLESKEY: No.

(Laughter.)

ACTING CHAIRMAN KATZ: Again, to focus, what are the major issues that need to be addressed in effectiveness and safety trials in the real world? Dr. Reidenburg?

DR. REIDENBURG: Yeah. I continue to have a problem with effectiveness, and the reason is we know that --

ACTING CHAIRMAN KATZ: Your suggestion.

DR. REIDENBURG: -- our present clinical diagnostic structure isn't predictive of response, and that some people respond and some not for most of the various diagnostic categories.

At this point the science hasn't advanced enough to know how to stratify people a priori into responders and nonresponders, but then this is true of every other illness I treat.

With hypertension, I know a lot of drugs lower blood pressure, but I can't predict which patients will respond to it. So I think the problem of effectiveness in clinical trials is really something that we need more development of a technology before we can mandate rational studies.

ACTING CHAIRMAN KATZ: So predictors of response.

Dr. McNicholas and then Dr. Horlocker.

DR. McNICHOLAS: Yeah, I just want to -- I absolutely agree with Dr. Reidenburg on this, that effectiveness versus efficacy is a very difficult issue, and what you can expect of the drug versus what you can expect of a system, and the system varies for individual patients and individual areas, et cetera, is a very different question.

So I think that you can ask drug companies to do safety. You can ask them to do longer term studies on monitoring patients over the long term, whether they've had to do a long-term study or not in order to get approval. But I think you have to look at what you can reasonably expect from the medication versus what you can expect from a system when the system is very variable.

ACTING CHAIRMAN KATZ: So it sounds like

what you're saying is that the outcome of long-term opiate therapy, depending upon aspects of the treatment setting is an important clinical issue.

DR. McNICHOLAS: Absolutely.

ACTING CHAIRMAN KATZ: Okay. Dr. Horlocker.

DR. HORLOCKER: I'd like to reiterate some of those same ideas. As I said before the break, I think once we get a broad based labeling, it's going to be up to the academicians and the clinicians to perform the studies that determine the actual effectiveness within the model. How many other multi-modal approaches do you add with the opioid to determine what's the best, what's the optimal way of making a patient comfortable?

On the other hand, I think that industry could be responsible for performing the safety studies, and the safety variables that I would recommend studying are those that are the serious or life threatening.

I don't think you have to look at how many people are constipated or have pruritus, but things such as respiratory depression, the aberrant drug behavior, those sorts of things that really would require an intervention on either the regulatory

societies or physician would be the ones that I think would be most appropriate to evaluate from a safety standpoint.

ACTING CHAIRMAN KATZ: So it sounds like what you're saying is that addiction or whatever word you'd like to use for whichever construct you're interested in is one of the long-term safety issues of opioid that needs to be looked at.

Other critical clinical issues with regard to long-term opioid outcomes? Yes.

DR. SCHREINER: Partly as a lead-in, I just wanted to focus attention that for pediatrics, that we need trials in adults of acute pain. Most of the kids who get opiates have acute pain and not chronic pain, and I haven't heard anything mentioned this morning about studying these drugs in acute pain states.

We often in kids are extrapolating data from adults to children at least in terms of planning, and so if we're going to have a rational use of these drugs in children for acute pain, we should know how they're used for acute pain for adults.

At least 60 percent of the children at my hospital who come for day surgery and go home, I mean, come in for surgery and go home the same day, and

usually those that are admitted, the primary reason they're in the hospital is their pain can't be managed with an oral opiate.

So as soon as they can be managed on oral medications, they go home, and typically they only need a drug for three to five days, in some cases up to two weeks, but I think that we should not forget that.

And I believe that one of the presentations Dr. DalPan's slide showed, the number one use for these drugs was surgical pain. So everybody is focused on the chronic patients, but let's not forget a really big use, especially in the population that I see.

ACTING CHAIRMAN KATZ: Does anybody feel that there are specific patient subpopulations that are critical to study long term outcomes in, for example, patients with histories of substance abuse or patients with histories of co-morbid psychopathology?

Yes.

DR. FRIEDMAN: I think an important populations to study long-term effects is the populations of children who use opiates and other analgesics long term for sickle cell anemia. I think this is a population that, again, it's mostly used in

the acute setting for acute vaso-occlusive crises. The use of analgesics starts in childhood, but extends all the way through adulthood. So this isn't an adult or a pediatric issue. It's an issue for all age groups.

The other thing is we know that from the pediatric studies that children with sickle cell disease have long-term cognitive effects of their illness. How long-term use of opiates impact on that is really not clear.

We also know that they are at risk for cerebral vascular abnormalities, including stroke, and again, how multiple medications used over time affects those risks and how adjuvant medications may affect the risk of vascular injury is really poorly understood.

So if there's one group that we can think of as a paradigm for acute pain, chronic pain, and pain over a lifetime, it's a group of patients with sickle cell anemia, which is not an insignificant population in the United States.

ACTING CHAIRMAN KATZ: Sure. Dr. Rappaport.

DR. RAPPAPORT: You're all aware that when we approve a drug it's based on a risk to benefit

analysis, and one of the risks is the risk of problems with the wrong patient population being treated with the drug. So I'm trying to move it back in that direction again.

My question is, and one of the things that we're trying to focus on, is: do the more general indications in a more general patient population in a trial end up driving the way the drugs are used in the community rather than vice versa?

I've asked that before, but it's important to think about because what's written, what comes out of a trial, what's in that protocol and then what comes out in the study results are what end up informing the label, and the label is what's used to inform the advertising and marketing and the way the drugs are used.

I wonder if we could focus on that for just a minute before we move on to the next section.

ACTING CHAIRMAN KATZ: Dr. Schechter.

DR. SCHECHTER: Yeah, I think that's a very interesting and important point. On one hand I totally support the notion of very broad labeling and broad indications because I think that will -- individuals are so unique and special, and it's hard to sort of configure all of the possible situations.

But I would like to offer an analogy, again, as a pediatrician, thinking about something that's similar, and I'd suggest the marketing of stimulants as a possible analogy because those have sort of -- even though the indications are limited theoretically, they're very open to enormous interpretation.

And there's enormous variability in the way that even if one goes by the DSM criteria or whatever, people with varying different degrees of the same sort of problem get put on stimulants or not, and merely allowing those into the community, I think, has been at least in part responsible for some of the increase in use of stimulants, and I would suggest at least some percentage of that is probably inappropriate.

So on one level I support it, but on another level I'm cognizant that there may really be problems, and of course, it becomes an individual clinical issue, and then it's probably contingent on the academic and practicing community to use those drugs appropriately.

So I don't want to constrain their use, but on another level I'm aware that just putting a drug out there without very specific indications might

be problematic.

ACTING CHAIRMAN KATZ: Okay. So, again, on focusing the issue of whether there's any specific population that would be better or inappropriate to study, Dr. Portenoy, you had a comment?

DR. PORTENOY: Yeah, just to respond to Dr. Rappaport.

I think the way that I model it in my head is that you're in a situation now of sort of an oscillation between what's happening in drug development and what's happening in conventional medical practice.

I don't think it's true that having a broad indication drives clinical medicine, that drives conventional medical practice. We've had labels that have had broad indications for a long time, but the reason we're having this meeting now in 2002 is because we had a phenomenon occur with Oxycontin which went into the primary care community in a major way during a short period of time and then became associated with an epidemic or pockets of epidemic abuse which has driven the sudden concern.

If it was that the broad labels drove conventional medical practice, it wouldn't have been that drug at this time. It probably would have been

another drug many years ago.

But now that we're in a situation where a spotlight is being shown on the role of opioid therapy in the primary care management of chronic nonmalignant pain, it's appropriate for the agency to say, "Well, what happens now if we release a drug into this marketplace?" Because this marketplace, the U.S. in 2002 was a different place than the U.S. in 1965, and so if we're going to release a drug at this time, what do we need to have in terms of labeling and in terms of data that would help stem the problems that we've identified as occurring with Oxycontin and with other drugs?

And I think when you look at it in that perspective, I don't know. It seems a little bit less concerning for me about the specific indication. If your indication was chronic low back pain because that's what was studied, and the drug is a pure mu agonist drug and the company marketed it and it was a good drug, it would be out there just like Oxycontin even though the label says just back pain. It would be used for all sorts of things.

What drives conventional medical practice is not just the FDA labels. So I think that's -- you know, in other words, I'd ask you to sort of reframe

your question a little bit. What data are necessary now to put new things into the current environment in a way that would allow some confirmation of safety and efficacy and also a label that reflects the new realities of what we have learned with expanding use during the past few years?

ACTING CHAIRMAN KATZ: I think what we ought to do is move into the pediatric session. We've already stolen 20 minutes from the pediatricians, and that's not very nice.

So why don't we go ahead then and begin with Dr. Rappaport who will introduce this afternoon's session on opiate analgesic use in pediatric patients?

DR. RAPPAPORT: In November of 1997, components of Section 505(a) of the FDA Modernization Act provided the agency with the ability to request that pediatric studies be submitted for an approved drug product or for drug product under development.

In return, a few studies were performed according to the points outlined in the written request. An additional six months of marketing exclusivity will be granted to the holder of the drug's application.

Effective in April of 1999, the pediatric rule provide the agency with the ability to require an

application, an applicant for a drug product approval to conduct an assessment of the product for use in pediatric patients, including, if appropriate, developing a new formulation deemed to be needed for use in a targeted pediatric population.

While the impact of the aforementioned regulations on the evaluation of a drug development plan has proven to be time consuming and complex, we're beginning to see the fruits of our labor as drugs previously devoid of data for pediatric populations are being scrutinized in trials of pharmacokinetic activity, clinical safety and dosing and effectiveness.

Each time we at the agency are asked to evaluate a pediatric development plan, we must take into consideration the value of the data that this plan will provide, the risks associated with the experimental use of the product in children, the appropriateness of the treatment for the target population, and the fact that a fair and equal burden must be placed on all sponsors.

A clear set of guidelines from the physicians who treat pediatric patients with pain would be very useful to us.

In considering the discussion points we

presented to you this afternoon, continue to keep in mind the regulatory framework that provides for the availability of pediatric exclusivity, as well as the requirements of the pediatric rule, as Dr. Rodriguez will describe them to you later.

Remember that the product labeling can only provide prescribers with information on the appropriate use of the drug if clinically sound data is obtained from appropriately designed trials in the target population.

Consider the conundrum of a drug for which the agency granted six months of marketing exclusivity based on the completion of clinical trials as outlined in a pediatric written request only to find upon review of the data a serious new safety concern resulting in nonapproval of a pediatric indication. That company still maintains six months of exclusivity for all of its indications.

ACTING CHAIRMAN KATZ: Dr. Debra Friedman now will give us a talk on pediatric use of analgesics.

DR. FRIEDMAN: Good afternoon. I would like to thank the committee and the FDA for inviting me to come speak with you this afternoon.

When I was asked to talk about issues

regarding analgesic use in pediatrics in a 20 minute presentation, the task was rather daunting. So what I decided to do was present some overall issues without a lot of details and then use some of the examples of analgesic use in pediatrics as a mechanism to perhaps stimulate more discussion later.

So the first thing we think about when we think about analgesics in pediatrics or, of course, in adults is utilization. Several things go into utilization. The first is thoughts and beliefs. Thoughts and beliefs of who? Thoughts and beliefs of society. Do children really have pain? If so, should children be treated with opioids for their pain or should we try to avoid that because these are kids?

Thoughts and beliefs of physicians are very similar to those thoughts and beliefs of the general population. Again, there's some thought in the general medical community that neonates don't have pain because because they can't tell us they're having pain in ways that we're used to in adults or even in older children.

There are also beliefs that children shouldn't be treated with opioids because of concerns of long-term effects, addiction and other concerns.

Thoughts and beliefs of parents. A lot of

parents are very resistant to giving their children opioids. They're afraid their children are going to become drug addicts when they become teenagers.

And thoughts and beliefs of the children. The children want you to believe that they are having pain, and they want to believe that the medicine you're giving them is going to make that pain go away.

The next issue affecting utilization is the availability of agents, not only which agents are available, but how they're available, and I'll go into that a little bit more later.

The third issue is supportive care. This is especially important in pediatrics because you're treating a growing child. So you need to think about all the other issues that are going on, and when we talked this morning about efficacy versus effectiveness, I can't think of a better setting than pediatrics to think about that. What else is going on in the child's life, and what other kind of support systems did they have in place as they tried to fight this pain?

And the last thing to think about is clinical setting. Of course, pain is very different in a child who's going to receive an analgesic for a few days post operatively versus a child who's going

to receive analgesics for months on end during acute cancer treatment versus children who are going to receive analgesics at end of life versus a child, for example, with sickle cell anemia who will use analgesics on and off perhaps their whole lifetime.

In terms of administration, there are several things to consider. What preparations are available in children? And what preparations are appropriate for what age children? The route that the medication is given; the dose; are there established doses for these medicines in children?

What are the other conflicting health issues that children may have that may affect the choice of which medication to administer? And other external issues in their environments.

When I think about evaluating a child's pain, I think about it in who, what, where, and when. Who evaluates the pain management?

This morning several panelists discussed the importance of a pain management team. We also discussed the importance of the involvement of primary care physicians in pain management. But with children, you also have to think about the children themselves and their parents.

So when you think about who manages their

pain, well, the pain management team, whoever that is in terms of physicians and nurses are important. I would argue that other people are important, such as people in their atmosphere, teachers, other support personnel, social workers, clergy, et cetera. Those people are all very important.

But also we need to ask the kids in some way how are we managing their pain, and we need to ask their parents how are we managing their pain. And we may get different answers when we look at the kids and ask them versus asking the parents versus what we think as health care providers, and that's a real challenge in pediatrics, and I don't have a simple answer.

What is evaluated? Well, you would think, "Now, that's a stupid question. It's the pain, of course." But let's say you're looking at a child who has oral mucositis from high dose methotrexate. He's on cancer therapy. So you think, "Okay. What hurts?"

Well, their mouth hurts or their throat hurts because they've got mucositis. Well, I would argue that when you're looking at children and especially young children, you're treating the whole child. So you need to ask not only, "How is the pain in your mouths?" but, "how are you feeling?" and

that's something that's probably also very important in adult medicine.

Where is the pain evaluated? Again, it's very important to think about whether the child is in an in-patient setting, an out-patient setting or home because everything else that's going on in those settings may affect pain management, again, the concept of efficacy of the drug versus effectiveness because of the environments.

And then when is the pain management evaluated? Going back to several themes we heard this morning, we don't want to give kids a prescription for pain medication and see them in a few weeks.

Similarly, we don't want to make follow-up visits arduous for parents and for children and over evaluate them because we're frightened because we're giving these medications to children. So we need to think about logical time frames in which to evaluate our care.

We also need to think -- when you think about pediatrics, we need to think out of the box of just what are we doing with drugs and we need to think about overall patient and family concerns.

We talked a little bit about physicians' thoughts and beliefs. We need to believe that

children hurt. We need to remember that especially for the younger children pain is scary and unsettling,a nd I would argue that even for teenagers pain is very scary and, in fact, for some teenagers it's more unsettling because they're trying to be grown-ups. They're trying to be big guys and big girls. They don't want to cry. They don't want to let on that they're in pain because they think pain is for babies, and they'd be less likely to tell you that they're hurting.

You need to listen to the verbal and nonverbal cues that parents and children are giving us. You need to consult with other experts who help manage the children, and we have to remember foremost that children are not just little adults.

We need to provide communication and education. We need to initiate the use of analgesics early in the pain process. It makes no sense to assume children have pain and let them tough it out for a while for fear of giving them medication that may have adverse effects.

We need not fear addiction. We talked a lot this morning about pain medications being used inappropriately. We talked a lot about the concept of tolerance and addiction. Certainly children, like

anyone else, can misuse drugs. Certainly other members of the household can misuse their children's drugs. And there is certainly a risk of addiction.

But this needs to be studied in the same way it's studied in the adult population, and it shouldn't be a reason not to use analgesics in children.

We need to give parents and children respect, appreciate their areas of expertise, capability, and strength, and we need to involve both children and family in these decisions.

There are numerous agencies that have set standards and policies, and I'm not going to go through any of these. this is just a sample of some of the many agencies that are involved in standards and policies regarding analgesic use. And we need to think about are there appropriate standards in both adults and children.

So we're talking a lot about analgesics. So I thought we should step back and say what is pain. There are lots and lots of definitions out in the literature for pain. I especially like this one when I think about pediatrics. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in

terms of such damage.

And important terms in this definition are sensory and emotional experience, actual or potential tissue damage.

Someone brought up the point this morning that pain is what anyone says it is. If someone says they hurt, they hurt, and I think this definition really encompasses that thought.

In terms of pain assessment in children, we need to evaluate the various components of pain, and we need to think about matching the intervention to the individual situation.

We discussed a lot again this morning about whether we need to design trials for specific situations. Since pediatrics is a subsection of the population and a small subsection of the population, if you then divide children into little subcompartments for studies, you would never ever have enough kids for any one study. But you need to think about what's the situation of the child and try to match the intervention.

We also need to think about the domains of pain in children: affective. How do the children feel? Behavioral. How are the kids acting? Cognitive. What are they thinking? Sensory. Again,

what do they feel in a truly sensory sort of way? And physiologic. What kind of signs can we see on an exam?

Routes of analgesic in children are important to consider. In terms of oral medications, taste is very important. If you have children where they're not going to be able to swallow a pill and you're going to give them liquid medication, kids are not going to take something that they think tastes "yucky." It's plain and simple.

So what we need to do is think about medications that are palatable. We also need to think about the preparation, and we need to be really ingenious in thinking about preparations that are going to be appropriate for children.

Young children certainly can't swallow big pills. They will take liquid, but if you had dosing where they're going to need to take large quantities of liquid, even if it tastes good, they're not going to want to take all of that, and especially if they've got other medical conditions going on. A lot of sweet tasking, sugary kind of liquid that's thick and flavored may make them quite nauseated.

We need to think about onset of action. A lot of talk was this morning about Oxycontin. We do

use Oxycontin in pediatrics. We obviously don't use it in very young children because the dose is inappropriate, but we do need long acting medications in children. It's an important, important area that's lacking.

But we also need to think about if kids can't swallow capsules and that's the way we have these long acting medications. What other kinds of oral preparations can we come up with that will have long onset of actions?

Similarly we may need some medication that is very short onset of action. Some things like transmucosal films and sublingual tablets, although it's very hard to explain to a child to put something under their tongue.

Bioavailability needs to be thought of as well as other physiologic conditions. You notice that I have intramuscular right next to painful administration, and I did that very deliberately. Intramuscular medication should not be thought of as pain medications in children. It makes no sense to a child for them to come to you and say, "I hurt," and you're going to go and give them a needle to make it stop hurting. No child is going to buy that, and they're not going to tell you they hurt anymore, as

well as, of course, the issue of wide fluctuations in absorption from muscle.

Intravenous medications are very important in children. We need more studies in terms of the use of continuous or intermittent medications. They are safe if done appropriately. They provide comfort, but we need to think about dosing, and if we need special dilutions.

Transmucosal medications, what I think about is the Fentanyl lollipop. There are real issues of safety. What happens? Can the kid choke like they can choke on any other lollipop? Can they fall asleep with it in their mouths?

I think there's a big risk of confusing medication with candy. When we think about the issue of opiates in kids, we worry about will other kids in the house look at this, think it's candy, and take it. Well, I would argue that that's not a reason not to pursue opiates and other analgesics in pediatrics because kids can take their parents' analgesics as well as they can take their siblings' analgesics.

However, if you make it look like a lollipop, you are asking for trouble. So you need to think about do we really want to make things for children in preparations that look like candy. And we

need to think about appropriate monitoring and safety around that.

Subcutaneous continuous infusions are rarely used because the need for local anesthetic. Transdermal medications are important, and we need more research in that system because often the patches are too big in terms of a starting dose for young children, and regional anesthesia is used in certain settings as well.

Dosing issues. this is one of the most important areas where we need research in kids because kids are not little adults. So what we often do is if there's not pediatric dosing that's been tested and available, we extrapolate down from the adult dose. So we say, okay, an average male is 70 kilos, and we give him this much. And this is kid is 20 kilos. So we're going to give them this much.

We know that's not the appropriate way to do it, but we don't have a lot of data for a lot of drugs in terms of dosing.

The other thing is we need to give kids enough medication so that they stop hurting, just like we do with adults. So we shouldn't be guided by fears that if we give them higher doses they're going to become addicted.

We need established guidelines as a starting point, and we need to escalate doses with the goal of comfort with tolerable side effects, and we need to think about the pharmacokinetics of drugs.

In terms of pediatrics, we don't have a huge repertoire of medications. The most common medications we use to treat very mild pain are acetaminophen and ibuprofen. There are other nonsteroidals that are also used.

For moderate pain we have, you know, things like codeine and hydrocodone, oxycodone, ketorolac, and for severe pain we have morphine, hydromorphone fentanyl, methadone. There are many, many other medications that we use for pain, but these are the most common ones.

And these are the same ones that we use in adults. So we need studies to really look at these medications for children appropriately.

We also use a lot of adjunctive medications, and I think these medications are important, and for some kinds of pain they're going to help the pain, but we also have to be careful not to use adjunctive medications to treat pain when we're not using analgesics.

So if children have pain and fever, they

should receive anti-pruretics. If they have pain and they're anxious, they should receive analgesics and anxiolytics, but it makes no sense to give a child an anti-anxiety medicine and not treat their pain.

Similarly, if you give children enough sedatives, they'll sleep through their pain, but that shouldn't be the goal. The goal should be to treat the pain, and then if they need sedation for some reason, then provide sedation.

We need to, of course, use anti-pyretics and anti-anetics if kids have itching or nausea and vomiting related to their narcotics.

Similarly, laxatives if they're constipated. Antidepressants, we're using antidepressants in pediatrics like it's being used in adults for certain types of chronic, nonmalignant pain, and we need more research in that area.

We're starting to use anti-convulsants for neuropathic pain, such as gabapentin from vincristine related neurotoxicity, and anti-spasmodics as well, but again, we need to think about are we using these as adjuncts or are we using them as substitutes.

In terms of deciding what medication, the World Health Organization has its pain letter that everybody is very familiar with, and I think that

people start with a non-opioid and then up to an opioid from mild to moderate, and again, this broad labeling that we talked about this morning.

And then if the pain is persisting, an opioid for moderate or severe pain, and I think we need to rethink this paradigm with all respect to the very brilliant people who developed it because perhaps what happens is often in pediatrics we start at this bottom level, and we don't go up fast enough because we don't pick up on all of the cues that the kids are giving us that they're having pain.

I'm going to skip these for time. Common uses of opioids in children. We use it in mechanically ventilated neonates, infants and children. We use it for procedural pain. We use it in the setting of acute trauma or illness, including surgery. We use it for sickle cell vaso-occlusive crises, for burns, for cancer pain.

Several studies have looked at the use of pain medications in specific, in specific areas of pediatrics, and I think looking at some of these studies brings up some big issues in pediatrics.

So looking in the intensive care unit, well, fentanyl may increase intracranial pressure and increase chest wall rigidity and, therefore, some

intensivists are less likely to use it, although it's a very good analgesic.

Morphine may cause some venodilitation, again, may preclude some of its use. There are concerns over respiratory depression which may limit dosing. If a child is admitted to the intensive care unit and has a borderline respiratory status, there are some intensivists who will be less likely to use an opioid analgesic which may cause respiratory depression, or they may feel uncomfortable with pushing the dose to achieve good analgesia because we're going to tip the kid over the edge and the kid is going to end up requiring intubation.

Kids who are in intensive care units are very ill, like are adults, and they have altered hepatic or renal function which impairs the ability to give certain analgesics, and pain may be more difficult to assess especially if children are sedated, and time may not be taken to assess pain management.

In the emergency department several studies have looked at the comparison of pediatric and adult centers, and several things have come out of this that I think are very important to remember. Doctors are less likely to order analgesics for

children. Children are less likely to receive analgesics even when ordered.

Children are more likely to receive non-narcotic agents. Administration of analgesics are delayed and often under dosed. Home medications and instructions are inadequate, and people don't ask what the home situation is like to make sure that they're sending kids, especially with opiates, home to safe situations.

And importantly, on the positive side, adverse effects of procedural analgesia with appropriate monitoring are rare.

In terms of sickle cell crises, we usually use combinations of opioid and nonsteroidal agents, and this can be very effective. Infusional, continuous and bolus infusions are used. We need to remember the avoidance of meperidine in this situation. As a metabolite, it's epileptogenic, and if you had a sickle cell patient who then starts having seizures, then you're saying, "Okay. Is this kid having seizures because we just gave him meperidine or is this kid having seizures because they're having a CDA related to their sickle cell disease?"

But, again, this is outside of big

pediatric hematology-oncology centers, and outside of academic centers where you have pain specialists who treat children. This may not be well known, and this can cause more complications for children. So we need more education.

We need a good way to transition from transfusional to oral or transdermal approaches. We need not to delay in starting analgesics for children with sickle cell disease who are in pain.

There's need for observational units in hospitals so kids don't get admitted when they don't need to be, and we need to think about and to try to overcome the confusion between tolerance, physical dependence and addiction. Again, some of these children have received narcotics for many, many years, having credible narcotic tolerances, but are not addicted and are not drug seeking kids.

In terms of cancer pain, pain may be chronic and require combinations of agent types and administration, and we need to learn to be creative. Many sets of guidelines exist, but uniformity within and among centers is lacking.

Under medication is still a common issue, especially, especially towards the end of life, and this is a particularly bad period for children.

Nobody likes to think about a child dying. People don't recognize pain at the end of life. Parents often are barriers to providing good pain relief to their children at the end of life, which people would think makes no sense, but lots of parents equate giving children opiates with giving up on them and, therefore, say, "No, they don't really need that morphine."

Physiologic conditions, of course, dictate choice of agent, mode of administration, and dosing, and we need a transition from hospital to home setting.

Congressional provision declares that this decade is the decade of pain control and research. There are several things that have been said out at the National Pain Care Policy Act of 2001. So we now even have some government support behind us.

Of course, we need to take the lead as scientists and work together with government agencies to try to design appropriate research for pediatrics. We need to think about the epidemiology of pain and utilization practices in children.

Of course, we need studies that focus on pharmacokinetics and pharmacodynamics, but not at the exclusion of other issues. We know very little about

mechanisms of pain and mechanisms of actions. All new agents should include pediatric patients. Older agents still need pediatric trials.

We know that morphine works in kids, but we don't really have great ideas about dosing, and we still don't have big studies that talk about clearance, et cetera. We need broader dosage forms and routes of administration. We need an adequate supply of drugs.

There's nothing more frustrating than to be treating a child with chronic cancer pain. You've got them stabilized on a hydromorphone drip, and then you find out, oh, there's a national shortage of this, and our pharmacy only has one dose left, and you've got to switch them over to morphine, and that happens a lot.

We need combinations of different drug classes. We need combinations of pharmacologic and nonpharmacologic management, and we need to destigmatize patients, families, and doctors with respect to opioids for pain relief.

I think this is a job for all of us in this room today, the health care providers, the children, and the adolescents, the parents, the greater community, the pharmaceutical industry, the

Federal Drug Administration, the NIH, as well as other granting agencies.

Thank you very much for the opportunity to speak with you this afternoon.

ACTING CHAIRMAN KATZ: Well, thanks, Dr, Friedman, for a very nice overview. Why don't you stay there for one second?

First of all, I've seen a lot of people fanning themselves and looking like they're about to keel over. So we are turning down the temperature in the room to try to cool it off a little bit and hopefully revive some of you who didn't tolerate the heat very well.

Why don't we take one or two questions from Dr. Friedman? And then we'll move on to the next talk.

Are there any questions about the information that Dr. Friedman just presented?

(No response.)

ACTING CHAIRMAN KATZ: All right. Thank you very much then. That's great. I'm sure more questions will come up.

I'd like to introduce now Dr. Bill Rodriguez from the pediatric team at the FDA, who will now be speaking to us in more detail about pediatric

exclusivity and the pediatric rule.

And I hope, Dr. Rodriguez, you can give a more complete introduction since we didn't get to hear about you during the introductions this morning.

DR. RODRIGUEZ: Dr. Katz, Dr. Rappaport, Dr. Kweder, members of the Advisory Committee, colleagues, pediatricians, it is for me a pleasure to be here to share with you very exciting information that has to do with essentially how we're going to probably accomplish some of the things we're talking from the pediatric point of view.

I'm going to share with you some of the exclusivity initiative, some of the rule, and then an area that we just moved in on the 4th of January, the Best Pharmaceuticals for Children Act.

So essentially those three things are pretty much collaborative in terms of our working and in our studies of the pediatric population.

No pain involved, a relaxing atmosphere.

(Laughter.)

DR. RODRIGUEZ: This paper, Clinical Pharmacology, 1992, by Gilman and co-workers -- thank you. that took care of the first obstacle -- show that there was inadequate information regarding pediatric use in about three fourths of prescription

medications.

It's a little bit interesting that we all have been using medicines in pediatrics and doing back and forth what is called extrapolation at best, and if we could go back to the 1900s, early, but decided that would be boring at this moment so I decided to take something after the '50s, and it's actually in 1979 we have directives, level of requirements in the federal regulations asking that for indication approving adults, there must be some special evidence derived from adequate and well controlled studies, and then that there should be some information about the pediatric use.

Safety and efficacy in the pediatric population, not established. That's what we've got. Very interesting.

In '94, we have an attempt at taking care of, well, maybe we don't have to do all of those studies in pediatrics. We can use those situations where the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric population we're going to be able to extrapolate and, therefore, limit the number of studies that need to be done in the pediatric population and essentially do PK or safety data and

say we have gained this information and we'll have it on board.

It sounds very good on paper, but if you take a look at the number of new molecular entities and the number of pediatric studies that were done for these new molecular entities by '97, you say, "My gosh, you know, we had approximately between 15 and 25 percent, depending on which numbers you take." Not very good.

So we have the first attempt at solving what is called the inadequacies of the studies for the pediatric population, and it is the Food and Drug Administration Modernization Act, which was signed 11/21/97, and is sunset this year.

We have the pediatric rule that we'll hear more about it, and then we'll hear some new attempt to not only extend FADAMA, but to close the holes that FADAMA had in terms of some of the stuff that Dr. Rappaport mentioned earlier. If we come upon something that is not very -- I mean that is scary or whatever, what do we have in hands to make sure that everybody knows about it and out kids don't continue to be exposed to a medication that may have some problems or at least that the physician and the family knows what those problems are.

We have in FADAMA the market exclusivity. I call it the carrot, and essentially the Secretary would make a written request through the Food and Drug Administration to the holder of an approved application, and if there was a pattern of exclusivity of a level, then six months of exclusivity could be added.

But that assumed that the person to whom the written request or the owner actually fulfilled the requirements of the written requirement. It didn't have to leave to a label, but you had to fulfill what we thought was needed. That was probably a little hole that has been taken care of.

What did that result on? That result in sponsors actually proposing 293 trials and talking about different medications. That's far in excess of what we had before.

FDA issued 237 and as of 1/1/02, 56 of these have been submitted with pediatric studies. That, again, is in excess of what we have submitted from '92 to '97, and of those, 49 were granted exclusivity.

In other words, not everybody got exclusivity, and in fact, let me tell you that there are some that didn't get the exclusivity, but we got

stuff for the label. So it's actually a very important point to keep in mind.

And 28 of these have new label. So essentially we have done more since this initiative started than we have done, say, from '92 through '97, and what type of studies have been done?

Well, approximately one third have efficacy and safety or have a PK on safety or PK on pharmacodynamics, safety. So essentially we use whatever was available that looked reasonable, was used, and a total of 561 studies were done for 237 products.

Now, a very important point. Of those 28, what have we learned? And we have in there that approximately not only do we need to extend the agency safety profile for a team, not only did we come up into one where the kinetics showed that there was even in excess of the levels that are expected in the adult and that they would expect also from the extrapolation, but there was no effect whatsoever in the pediatric population. A very important point to keep in mind.

And the label now says not effective in spite of the pharmacokinetics and everything. So that's something that people should be aware of.

Nine have had significant dosing for changes for risk: midazolam, propofol. Somebody mentioned fentanyl over here earlier. If you give that little lollipop with propofol, you can have massive drops in the pulse of the patient. So that's one thing.

Propofol, there is some question of in a non -- where causality had not been determined yet, where there was nine percent mortality noted in the pediatric ICU compared to the control, not in the anesthesia. That has to be proven.

And we have seen sevoflurane, fluvoxamine, gabapentin, and provolac. Fluvoxamine, some of the kids, eight to 11, for example, girls, were getting overdosed. Some of the adolescents were getting under dosed.

What do you see in the PDR? We don't know why it isn't working well in the adolescents. Well, actually they probably needed more where the children needed less.

Gabapentin, children under five years of age may need a higher amount of it because their metabolism is two to three times faster than the pediatric population.

And we can go down the line all the way

over. So these are medications where we have found out we were using them, and we were using them inappropriately, many of them in pediatrics.

Now, let's move to the rule. It was published in 12/2/98, but we could not require things until December of 2001, and it required that for certain new marketed products -- I mean packaged drugs and biological -- that the company or the owner or the person submitting the application had to put down the intentions of doing studies in the pediatric population.

When would this turn on? This was actually discussed with the agency if it was a matter of something that would be used for life or death during the first phase discussions. Otherwise during the second phase discussion.

At that time the plans for completion of studies or whether there will be a deferral or whether there will be a waiver. So it's not that we were trying to hold the adult population hostage. It was a matter that we wanted this to be known in the kids.

And it was actually for conditions for which the company was looking for application adults. For example, if you're trying to study pneumonia in adults, then do pneumonia in kids, and that's what the

agency was requesting.

Now, there could be a referral if the companies were ready to submit the information for the adult and the pediatric studies were not ready, for example, or we needed more studies in the adults of effectiveness and safety before we accepted the pediatric condition.

Now, the studies were waived if the use did not meet the criteria for a minimum therapeutic benefit and substantial use, both. This is an area that is confused many times by industry, by the way. It has to be "and," in other words, both.

The applicant may have all the best will in the world, and the studies may be impossible. For example, there are patients disseminated all over creation, and in other words, not enough in a place to do it. So, in other words, the agency is not trying to be obtuse. It's trying to be very practical with what's been done.

And other produces are safe or effective in pediatrics or it could be a condition, for example that does not affect the pediatric: BPH, for example, cancer of the breast, in other words, and there is a list in the literature going into that, or you heard that we could require a formulation.

Now, the company may have gotten the best pharmacologists in the world and been unable to develop the formulation, and the pharmacology. They say, well, we have to work with whatever we have available. We're not going to hold you hostage because you try your best in all honesty.

But more importantly, the adult was not delayed, and it actually promoted the early consideration of pediatric use and drug development plans. What's happened with these other, with what is called the stick?

Well, we're doing analysis once a year, and in 6/01 -- you remember 499. The products were approved from there, but we do not require anything until December. Products approved in 499, 41 with pediatric studies; 170 are deferred; 241 waived. Remember that we could not require anything before December, and 12 of these were granted exclusivity; 288 as of 6/01 have submitted thus far.

So we're making progress from the biased point of a pediatrician. How does it differ? Why does the whole thing differ between final rule and FADAMA?

In the final rule the stick studies are required. However, the evaluation for the pediatric

information, only the drug product and indication currently being produced are to be submitted. While in FADAMA, we could send an urgent request, but the company will say, "We aren't going to do it," and that was it.

And evaluations are needed for pediatric information on the active moiety. So essentially it could be a number of things that we thought would fulfill public health benefit, and the incentive only exists when there is exclusivity or patent protection.

Now, here we are at this stage in HANSCOM, the Best Pharmaceuticals for Children Act signed into law, 104-92. What did it do?

First of all, extend pediatric exclusivity. Congress recognized that we were making some progress there.

And another thing that was done was that pediatric stuff may have to be handled like six months, six months prior to review. In other words, they have to be given priority and move.

And the sponsors are required to submit with the IND a statement about intent to study pediatric populations. So essentially it sort of supports the rule and promotes the FADAMA experience.

But it did more than that. The NIH in

closed session with the FDA and other official experts is going to develop and prioritize the publish of off patent drugs. Remember in the previous experience the drugs were on patents. Now it's off patent drugs. There are a lot of those around, as we all know. Some of them are used for the pain. That's right.

And so that needs to be studied in the pediatric population. So FDA -- NIH promotes it. FDA does it, and FDA issues a written request to innovator and generics. In other words, this written request to innovators and generic, if it is declined by the innovator or the holder of the generic, then we turn that written request to NIH for development of a request for proposal.

So essentially now it's in the hands of NIH, and even if the innovator or the holder of generic, they will be given appropriate time, et cetera. There will be a guidance. It will be promoted, et cetera. This is just a general thing, looking at something that was approved this month. So things may change a little bit.

Then the NIH now provides it to like a grant, like a -- yeah, like a grant. And when that information is finished, the study is reported to the NIH and the FDA, and it becomes public domain. So, in

other words, it doesn't matter what we find. You all will find it. Okay?

And within 180 days it will also be published in the Federal Register. So essentially it's going to be open windows for everything that we find. Okay?

As far as labeling is concerned, for both approvable and approved application at the time of action, if the labeling remains the only issue, it is referred then to the Pediatric Advisory Subcommittee, and the Pediatric Advisory Subcommittee then takes a look, and if they approve on that, then -- and, by the way, some is published on the Web at that time, and we have a dispute resolution process that effectuates the level in change, and if there is not agreement with the approved drug holder, then what happens is that FDA could really misbrand the drug.

What else has happened too? There's also going to be an Office of Pediatric Therapeutics set up within the Commissioner's Office. The Pediatric Oncology Subcommittee has been restructured. There is going to be a Pediatric Advisory Pharmacology Advisory Committee to advise the FDA Commissioner so that we will have the most scientific and the most approach, so that there will be no criticisms that you people at

the FDA are doing this and you're not aware of what's going on.

On the outside, yes, there will be people who will be from the outside to helping on that, and more importantly, there's been a requirement concerning tracking ethnicity and race for written agreement. Okay?

There is also a request from the Institute of Medicine to develop a review of federal regulations and report of research relating to children addressing issues such as assent, minimal risk, and compensation, the most ethical approach to anything that we do.

And importantly, a foundation for the National Institute of Health to receive written requests for products which has patent life. So, in other words, if we have products that you all think are important, that we have information for public health benefit and they have patent life and the sponsors decline to honor the written request, we can actually -- the Commissioner can actually return it to the foundation at the National Institutes of Health and say, "Okay. This group, academic group in the community is going to do the work, and this will result in the formation that we need to be able to study that."

So essentially we're going to have the off patent with the NIH RFPs, and by the way, there are approximately $200 million a year assigned to the NIH for that, and this foundation which already exists at the NIH which will take care of the written request for products that still have patent life.

Also, for safety, all adverse events, not just the rapid (phonetic) indications, will be reported for one year after exclusivity is granted to the new Office of Pediatric Therapeutics, and the report will be reviewed by the Pediatric Advisory Subcommittee and any recommendations for action obtained.

In other words, we're going to make sure that any questions of adverse event become -- see the light of day, become part of the level it may be, become part of the docket, become part of the Federal Register.

If you want to find more about it, which I just barely skimmed the whole thing, www.fda.gov/cder/pediatrics or you can call, for the people who may not feel like spending the time in front of the computer, (301) 594-PEDS. There, you see.

And essentially I have enjoyed the time

with you all, and one of the reasons why I'm doing this, because these are my grandchildren, and I just want to make sure that they get the safest, most efficient medication if they need it.

Thank you.

ACTING CHAIRMAN KATZ: Thank you very much, Dr. Rodriguez. Why don't you, if you could, stay up there for one minute?

We have time for a couple of questions for Dr. Rodriguez and his presentation if anybody has any.

(No response.)

ACTING CHAIRMAN KATZ: Thank you very much. I appreciate it.

DR. SCHUSTER: Bill.

ACTING CHAIRMAN KATZ: Oh.

DR. SCHUSTER: I keep seeing the number of studies in newspapers and in your presentation, you know, 400 and some odd, and 560. Those are the number of studies requested. They're not the number of studies that have been performed.

DR. RODRIGUEZ: No, no, no. I have in there how many have been turned in.

DR. SCHUSTER: I understand that.

DR. RODRIGUEZ: Yeah.

DR. SCHUSTER: So there are 59 drugs that

have been turned in, and it's a little over two studies per application, but we don't know how many of those other requests are actually being translated into action.

DR. RODRIGUEZ: Okay. We do have internally that information, and I can tell you that approximately four fifths of those are in the process of working. In fact, we're just trying to -- we're bracing ourselves for the onslaught that is going to be coming in because each time these things come in, there has to be a -- the division has to work on it.

We have an exclusivity board. They have to work on it, and essentially it's a major, time consuming process. But we're looking forward, and you know, the people in the divisions are very helpful.

Thank you.

ACTING CHAIRMAN KATZ: Thank you, Dr. Rodriguez.

Why don't we then move on to Dr. Rappaport again who will be speaking with us about pediatric opiate analgesic trials and development plans and will be giving us some case vignettes.

And right after that we'll be taking a break.

DR. RAPPAPORT: Thank you.

After the break there's going to be a quiz for the committee members on the difference between the pediatric rule and pediatric exclusivity.

(Laughter.)

DR. RAPPAPORT: It took those of us who work with this every single day the full five years before the bill came up for reauthorization before we understood it.

This afternoon, as Dr. Katz said, I'm going to present three brief vignettes of drug product development plans that raise specific issues in relation to pediatric patients. While these are only three out of hundreds of development plans that now must find ways to be responsive to the pediatric rule, these three do cover a broad range of issues that we frequently encounter.

Of course, due to the proprietary nature of drug products that we review, these drug development plans are hypothetical. However, these hypothetical products consist of a compilation of features drawn from very real drug products that are under development.

Drug number one is a novel, long acting, modified release, oral preparation opiate. The sponsors propose studying this new formulation in a

single, multiple dose pharmacokinetic study in pediatric patients over the age of seven years. While the protocol for this study indicates that efficacy will be assessed along with safety as secondary objectives, the study would clearly not be considered adequate to establish efficacy by design.

And the sponsor's rationale for not performing an adequate and well controlled study consists of the following points.

First of all, efficacy for opiate analgesics can be extrapolated from adults to pediatric patients.

And, secondly, the endpoints normally used to assess effectiveness in adults are unreliable in children.

The sponsors also requested a waiver for pediatric patients under seven years of age. Their rationale for this request consists of the following points.

Substantial use of this product has not been demonstrated in the younger pediatric population.

The second one is recruitment would be difficult.

And the third is that the currently available doses would be too high for the younger

pediatric patients.

We already have some answers to these questions from the previous talks. In your discussion this afternoon, please consider what evidence is available to support or refute the sponsor's contention that efficacy of opiate analgesics can be extrapolated from adult to pediatric patients.

We're aware of the difficulties inherent in the assessment of pain in pre-verbal pediatric patients. However, how reliable are the currently available tools for measuring pain or pain relief in the very young child?

Also, please include in your discussion the issues of recruitment of pediatric patients for analgesic trials. What factors are inhibiting the ability to recruit these patients?

While we have not seen this as a major impediment to the drug development programs that we're currently evaluating, it is important to us to know if there is a problem and why that problem exists and if there's something that we can do about it.

Finally, include in your discussion the development of new formulations. What formulation and routes of administration that are currently not available might be useful in the pediatric population?

Dr. Friedman talked a lot about that, and we'd certainly like to hear from everybody else on that issue.

Some sponsors have actually argued that it would be inappropriate for the agency to require a sponsor to develop a new formulation for pediatric patients under the pediatric rule due to the lack of data to support that the formulation would be of any value in the marketplace.

While we believe that it's often difficult to know the value of a new drug product until it's been used and studied in a particular patient population, the rationale that a sponsor would not be marketing this new formulation is not one that we can consider in the setting of public health risk-benefit assessments.

However, we do recognize that the realities of the marketplace play a role in drug development.

The second drug that I want to tell you about is a new delivery system for chronic malignant pain patients. This is a drug delivery system that provides pain relief for pain lasting greater than 24 hours.

A previously improved injectable opiate

project is held in a reservoir that adheres to the skin, and a continuous subcutaneous infusion is administered from the reservoir via a 25 gauge needle. Bolus doses may also be administered by the patient by pressing a small button on the device. Appropriate lock-out mechanisms are built in.

The sponsor has requested a waiver for pediatric patients under 12 years of age, and they've done so because they believe that it would be an unsafe product in younger children.

In addition, they argued that patient controlled analgesia in the younger pediatric patients is inappropriate and that the boluses would be too large.

This, of course, brings up the possibility of requiring the sponsor to reformulate this device so that the product would be available for younger patients.

What are the appropriate age groups for continuous infusion devices for patient controlled analgesia, for needle delivery devices, and for devices that are applied to the skin for prolonged periods of time and for other innovative devices?

In discussing these delivery systems, please address the larger issue that we at the agency

are grappling with on a regular basis, and that is: what are the needs of the pediatric patient population for high tech delivery devices? Would it be more appropriate to require those resources to be spent on new formulations of old opiate drugs that can be delivered by more traditional routes of administration?

In particular, for the infant and neonatal patient populations, what are the specific needs that are not currently being met? And what are the existing impediments to meeting those needs?

The third and last item I'm going to tell you about is the new fixed dose opiate-acetaminophen combination drug product. Sponsor has requested a waiver for all pediatric patients, arguing the combination drug products are inappropriate for this patient population.

They also report that their IRBs don't feel that analgesic trials are ethical in children, especially placebo controlled trials.

As physicians in training, we were all taught that combination drug products are, in general, not the best idea. Not being able to adjust the individual components might lead to significant and unnecessary toxicities.

However, these products do appear to improve compliance, and they're widely used in reality. Pediatric patients are likely to be more vulnerable to the toxicities, however.

We'd appreciate your considering the value of these combination analgesic drug products and the pediatric armamentarium. While we always require that an appropriate rescue medication paradigm be written into any pediatric pain trial protocol, are there some settings in which this is not an appropriate strategy?

We'd like you to discuss the ethical considerations that exist when performing pain studies in children.

These are the currently available drug delivery systems for analgesics. I can't tell you about the new formulations in the pipeline today, but I can tell you that there are some very novel and innovative products out there, and that some of them have potential to advance the science of drug delivery.

Some of them also have the potential to endanger patients and family members in very novel and innovative ways. As you address the following discussion points this afternoon, please remember to keep in mind the important legal and regulatory

framework described to you today, and please feel free to ask questions of those of us from the agency.

I'm going to read the question to you, and then Dr. Katz will introduce each one individually.

The first discussion point, as we prefer to call it, is the following. However, I'd just like to say that these were written to provide the basis for a sort of broad discussion of the issues relating to pediatric analgesic use and development.

That being said, there are a number of very specific questions we're trying to get at here, and so we may interrupt and try to focus your conversation in certain directions, and many of those questions are things that I included in this talk and that Dr. Friedman discussed in her talk as well.

This first question: the FDA is aware that there are still significant unmet needs in pediatric pain management. In the context of the agency's new mandate to require studies of drugs in children, discuss these unmet pharmacotherapeutic needs in current pediatric pain management and how they might be met with regard to opioid drug products.

Include discussion of the significance of barriers to opiate analgesic trials in children and what strategies might be used to overcome those

barriers.

The second discussion point for today this afternoon, many different opioid formulations, delivery methods and drug device combinations are currently on the market or may be available in the future. Discuss the age appropriateness and limitations of these various methods of administration, as well as any other that may be particularly useful or particularly hazardous in the treatment of pediatric pain patients.

And the third discussion point for this afternoon, it's been historically accepted that mechanisms of action of opioid analgesics are sufficiently similar between adults and children so that large controlled studies to demonstrate efficacy have not been required for a pediatric indication. Instead pediatric trials have been largely focused on investigating safety, pharmacokinetics and appropriate dosing regimens.

Discuss the shortfalls, if any, to this approach, and also include discussion of approaches to dose finding and the evaluation of pain in the very young patients.

And the last discussion point for this afternoon's session is as new opiate analgesic

products become available for home use in younger patients, there may be a risk of accidental ingestion by family members or deliberate abuse and diversion of these medications.

Discuss the strategies for risk communication and risk management that should be considered at the time of pediatric opioid drug approval.

ACTING CHAIRMAN KATZ: Thank you, Dr. Rappaport.

What we'll do now is we'll take a break, and reconvene back here at ten minutes after three, when we'll start to address these questions.

(Whereupon, the foregoing matter went off the record at 2:55 p.m. and went back on the record at 3:16 p.m.)

ACTING CHAIRMAN KATZ: Could we get started again? Could we take our seats, please?

What we'll do now is begin the discussion phase for the pediatric component of our program. Let me begin by just asking if anybody around the table has any questions for Dr. Rappaport about the last presentation or for any of the other speakers.

Dr. Horlocker.

DR. HORLOCKER: I would just like a

clarification of a pediatric waiver. If a company requests a waiver and it's granted, what are the medical legal implications for the use of this drug or device in pediatric patients? Specifically, are clinicians really going to be held medically responsible and basically not use these drugs or devices in children, or alternatively, will it be considered more of an off-label use and things will go on with business as usual?

DR. RODRIGUEZ: To the best of my knowledge, that's more into our council group, but I would, off the record, consider it like an off label use if you just do open. But I think by knowing that it was waived, I think the main one you should know is why that it was waived before you use it.

ACTING CHAIRMAN KATZ: Yes, Dr. McNicholas.

DR. McNICHOLAS: A follow-up on that, please.

So if they request a waiver it does not have anything in the label like this drug is not recommended for children under the age of?

DR. RAPPAPORT: There's usually that type of language. In recently approved products there's going to be that language in there if there's no

studies to base an approval on.

ACTING CHAIRMAN KATZ: Does that answer the question?

DR. McNICHOLAS: It does, but essentially in industry then there would be no real reason to try to get these labels on the drugs because as long as it doesn't specifically state in a black box that you cannot use this for pediatric patients, things will proceed as an off label indication.

ACTING CHAIRMAN KATZ: Dr. Smiley --

DR. RODRIGUEZ: When you give a -- when we go for a waiver, you actually put a -- in other words, you have the reason why. It's either because the disease does not exist in the pediatric population or it's unlikely to be in the pediatric population.

I was in a place where we said that, and there was actually one instance of something in the pediatric population. I can't recall which one it was, but anyway, that information should be available and could be available, I assume, from the FDA if you really want to find out why something cannot be -- you know, was not done.

ACTING CHAIRMAN KATZ: Dr. --

DR. KWEDER: I would just like to add to that that this is why, you know, the granting of

waivers for pediatric studies -- this is why the questions that Dr. Rappaport has laid out for the committee are extremely important to use. You know, the decision is in our hands whether or not to grant a waiver, and oftentimes the arguments that companies come to us with can be very persuasive about, gee, why there really isn't going to be any public health benefit to studying this drug in children. That's why we're taking some of these issues to you, because you're the experts.

What is meaningful? What are the needs out there?

And sometimes the needs are great in a small population, but that's important, and we need to hear that.

DR. SMILEY: I guess in a minute we're going to get to the whole analgesic issue specifically. We're right now on the general pediatric questions.

I guess my question was: is there any thought to actually putting in the label the reason the waiver was given?

I mean, that would seem to kind of make people much more straightforward about why they're asking the FDA for a waiver. They're asking for a

waiver because this isn't a serious problem in pediatrics or because we already know the drug works. Then the last line or wherever it would go in the label would say studies have not been done because of these reasons that have been accepted by the FDA or questioned.

Again, this is a more regulatory question, but it seems to me that would be a more effective way of keeping the reasons appropriate than just saying, "Well, if you really want to know why studies weren't done, Doctor, you could have called the FDA and asked."

DR. KWEDER: Actually information on who was granted waivers, deferrals, and requests is not necessarily that easy to get. As to whether or not to put it in a label, that's a very different discussion, but point well taken.

ACTING CHAIRMAN KATZ: Dr. Schechter.

DR. SCHECHTER: Yeah, I guess I have a misunderstanding about what the exclusivity or these sort of rules are about because it was my understanding that the reason the whole movement was towards promotion of pediatric drugs is that, in fact, this was a small population that were therapeutic orphans, in effect because no one wanted to do

research on them because it wasn't financially as viable.

So the issue that there's not substantial use as indication for a waiver seems contradictory to me, or at least it doesn't make sense in terms of what the pediatric community requires. There are often small cadres of kids who very much need these sorts of medications, but you wouldn't call that substantial use.

ACTING CHAIRMAN KATZ: Dr. Rodriguez, maybe you could address that.

DR. RODRIGUEZ: I think we're using the term "therapeutic orphans" very broadly here. Essentially the use of that name was namely because they were not being studied, period. That people took and took the way you're going at this moment, saying because of size, et cetera. And, in fact, we say that it has been used on more than 50,000 people, for example, and it has substantial public health benefit.

So that also takes care of even a smaller population where it might be the thing that's keeping them alive, for example. Then those things have to be addressed before a waiver is granted.

So essentially, you know, we've come a long way from the 1960s, therapeutic orphan first --

the discussion to the more present, which takes into consideration your concerns.

ACTING CHAIRMAN KATZ: With that, why don't we move into question number one, which I think all of you probably have, but I'll reiterate.

What are the unmet pharmacotherapeutic needs in pediatric pain management, and how might they be met by opioid products?

We already heard some suggestions which we could certainly amplify or have more comments on. Those were preparations that are more palatable for children; things that don't taste "yucky," if I am quoting you correctly; long acting opioid preparations, studies of continuous IV opioid infusions in children; transdermal preparations; studies of old drugs that might still be useful. Those are some of the ideas what were mentioned for potential unmet needs.

We certainly don't need to rehash every one, but are there any other comments about unmet clinical needs or unmet ways that opioids could help address that?

DR. SCHREINER: I think that when I've seen issues about formulation, people are often talking about taking pills and making liquids, and I

would just say in the extended release formulations, that we should be requiring companies to make lower dose pills, that often the obstacle is the smallest dose available for adults, is inappropriate for children below the age of about eight, nine, or ten, and some of those drugs would be of benefit to kids at younger ages.

So we shouldn't just be thinking about -- it may not be possible to make an extended released liquid formulation for whatever reason, but it certainly would be possible to make a lower dose pill or lower doses.

ACTING CHAIRMAN KATZ: Other clinical areas of pediatric pain management where there are unmet needs? Dr. Foley.

DR. FOLEY: In a recent report from the National Cancer Policy Board, a particular chapter of that report which is called "Improving Palliative Care for Cancer," there's a section devoted to the needs of pediatric patients and the needs for the development of symptom control agents.

And in the research chapter written by Charlie Cleeland accompanying that same report there is a discussion that relates, again, to sort of the research barriers, and there appears to be a pretty

significant barrier within the cancer structure for symptom research in pediatrics because of a lack of an infrastructure, a lack of a work force, and that in the current cooperative groups for clinical trials, clinical trials for an active agent for cancer get paid about $2,000 and for a symptom relief trial get $400, and there's sort of no easy access to the available agents out there that are currently off patent. There's no way for the NCI to buy those drugs.

So they were identified as a series of very significant barriers that were limiting symptom research, pain particularly, among other things, in this population, and they, I think, would be important for the committee to look at that report and use those because they're evidence based barriers for which the National Cancer Policy Board thought that there was need to look at this.

ACTING CHAIRMAN KATZ: So the need for an infrastructure to conduct pediatric clinical trials and --

DR. FOLEY: Right, and to pay the researchers to do this, et cetera. So that that is one of the major barriers that limits this kind of work, and since many of the drugs are currently off

patent even, there's no source of funding for the NCI to buy those drugs and then to put them into a clinical trial.

And since cancer pain in the pediatric population has been a group that has been a driving force in trying to look at what agents would be available, the lack of that whole infrastructure to address this by the experts that could address this is significant.

ACTING CHAIRMAN KATZ: Thank you.

So pediatric cancer pain being the clinical niche and the lack of infrastructure being the barrier.

Other clinical areas? Dr. Friedman.

DR. FRIEDMAN: To follow up on Dr. Foley's point, the Children's Oncology Group is the large cooperative children's cancer group. It's formed by the merger of the four previous cooperative groups: the Pediatric Oncology Group, the Children's Cancer Group, the Revdomyer (phonetic) Sarcoma Study Group, and the Wilms (phonetic) Tumor Study group.

So now there is a single cooperative group that manages all trials for cancer in children in the United States and North America, with about 250 participating hospitals.

It's important to note that children participate in cooperative group trials for cancer at a much, much higher rate than do adults. When cooperative group trials are open, approximately 90 percent of children are treated on cooperative group trials as opposed to about ten to 20 percent of adults with cancer.

Therefore, if this infrastructure could be used for children with cancer, one could argue that similar pediatric groups, pediatric nephrology, pediatric pulmonary groups could be brought together and consortia of pediatrics subspecialists could be brought together so that multi-institution trials could be undertaken in a very efficient manner, as opposed to individual institutions.

In addition, cooperative group trials would give much better results than any single institution might give because you're not limited by sample size, selection bias, and other similar manners.

ACTING CHAIRMAN KATZ: So there's a consortium, but we still have a reimbursement issue for the symptom oriented trials. Does anyone have any thoughts about how that could be addressed?

(No response.)

ACTING CHAIRMAN KATZ: Well, that question was a loser, wasn't it?

(Laughter.)

ACTING CHAIRMAN KATZ: Dr. Foley?

DR. FOLEY: Yeah, I'm glad to. There's a recommendation that has been put before NCI that basically says that these should be supported, which would fit very nicely with trying to support the FDA to -- that has worked hard to sort of push forward these studies in the current legal setting in which these should occur so that there's a need for funding that needs to be put forth and prioritized both in developing the work force, in creating the infrastructure, and producing the incentives to do this.

And I think that the work that you just have outlined as sort of the receptivity to do this and the support for doing this and moving this forward is the way of, I think, an FDA/NCI approach.

And there is currently another IOM committee looking at how can we increase rapid development and translation of these drugs into the patient population with cancer, and I think that this is an opportunity that there's clearly an emphasis being placed on Phase I and Phase II trials in

pediatrics, and I think that it would be important if this group would recommend that they want to encourage the NIH to support these kinds of studies.

ACTING CHAIRMAN KATZ: Dr. Portenoy?

DR. PORTENOY: I would ask the pediatricians to comment on what's the consensus view about the proportion of children with chronic nonmalignant pain syndromes or not cancer related pain syndromes that might be candidates for opioid therapy.

When a program like my own, which is focused on adults, gets a pediatric referral, it's usually a child who has been through a lot and has a very severe chronic pain syndrome, and we tend to use opioid drugs in that population like we do in adults.

These are children with reflex sympathetic dystrophy, with chronic pain related to sickle cell anemia, chronic pain related to an inflammatory arthropathy. So they usually have some relatively serious systemic illness, and the question is: to what extent is that common practice now among pediatricians, or might there be some speculation about what proportion of those populations?

And then, of course, there's the population of children with chronic headaches and chronic abdominal pain of unknown cause, and

fibromyalgia syndromes, and all of these chronic pain syndromes that aren't associated with potentially progressive systemic illnesses.

And so what's the consensus view in the pediatric world for those populations?

DR. SCHECHTER: Well, I can't really speak for the whole community, but in general, we share the same sort of approaches that you do. I think there's very little debate about children with documented organic illness, inflammatory bowel syndrome, a variety of other sorts of things where there's no cancer certainly; sickle cell disease where there's no question that those children receive opioids, and the same sorts of drugs as sort of our adult colleagues would prescribe.

I think with RSD or complex regional pain syndrome, I think there has been a slightly different approach in pediatrics which tends to be more conservative, not necessarily withholding opioids, but much less aggressive regarding regional anesthesia, in general. And it's not the first thing that we do and it's significantly down the road with those kinds of problems.

I think there is within that community, as well as in this sort of fibromyalgia community, there

is a reluctance I would suggest to use opioids in some aspects, but I think it probably parallels the similar debates within the adult community about whether to start with -- at what level we use analgesics.

So I'd say it probably is reasonably similar in terms of approach and philosophy to what the adult community is doing. I wonder if my pediatric colleagues would support that.

DR. SCHREINER: I think that in a study that we helped run, which was about 120 patients with chronic pain, and chronic was defined as a need for potent analgesic anticipated to be somewhere between seven and 30 days, 80 percent of the patients had either postop. or traumatic injuries. Less than ten percent were oncology, and then there were about a similar percentage, five or six percent that were rheumatologic or hematologic problems.

So most of them are going to -- even when you're looking at dosing for a week to a month, the majority of the kids are going to be traumatic or surgical, and of those 120 patients, only 80 actually needed therapy for seven days. So a third of the group dropped out because they were off potent medications sooner.

ACTING CHAIRMAN KATZ: Dr. Tobin.

DR. TOBIN: Yeah, I think our experience is the same, and the thing I have concern about is that should a child have recurrent pain, that we don't have data on PK and PD after long-term recurrent exposure, and that's certainly my experience with sickle cell children who come in for recurrent treatment.

But with the more recent advance of dealing more effectively with procedural related pain, particularly lumbar puncture, bone marrow aspiration, and multiple recurrent procedures in children, we have no PK or PD data about the fact that we are recurrently anesthetizing these children once a week, once every two weeks over a six to 12 week period of time as our oncologists are advancing their therapy, they require us to put the child in a receptive mode for that therapy, and I'm very impressed at their tolerance in the increasing doses that are well out of the labeling range just in order to get the child unconscious, not necessarily immobile.

So I think we need that PK/PD data for recurrent, persistent, procedural or pathologic pain due to their disease, such as sickle cell pain.

ACTING CHAIRMAN KATZ: Anything else on the wish list for opioid development? Dr. Schechter?

DR. SCHECHTER: The other, along those same lines, again, the neonatal population has been one in which there's been a dramatic increase. In Dr. Anon's (phonetic) work, the no pain trial, which results will be out shortly, would suggest that kids, newborns or preterms who are ventilated in the nursery for prolonged periods of time, if they are ventilated without adequate sedation or analgesia have a much higher incidence of a variety of sort of noxious events and intraventricular bleeds.

So the tendency with that data having come out at least preliminarily, there has been a dramatic shift towards aggressive sedation in the neonatal period. There is very little data on the long-term effects of that for babies, and it would be very, very helpful to have that even though that has become a state of the art in most settings.

DR. TOBIN: I'd like to follow up on that. We have seen such incredible tolerance in these tiny infants that it was well beyond anyone's expectations, and I can't believe that there would be any sponsor in industry who'd be willing to do a trial on a novel agent in an infant population under two kilograms; that this really ought to be one of those small groups of patients who demand some of that money out of the

NIH or at least be considered competitive for some of those funds because we need this data in order to take care of those children more appropriately.

ACTING CHAIRMAN KATZ: So there are clearly specific subpopulations of pediatric patients in which more data is needed, and that's one of the wishes that it seems like everybody is expressing.

Anything else by way of specific formulations, specific delivery systems that are needed in a subgroup or general group of pediatric patients?

(No response.)

ACTING CHAIRMAN KATZ: All right. We'll go on to question number two then.

Question number two is discuss the significance of barriers to opioid analgesic trials in children, ethical, safety, scientific, practical, et cetera, and what strategies might be used to overcome the barriers.

So perhaps somebody with experience in this area could lay out a list of what the major barriers are. Any takers?

I don't know anything about pediatrics. I'm relying on you guys to pinch hit for me here.

DR. TOBIN: I'll start, and I hope this

just opens up a few questions.

We are currently involved in a number of clinical trials involving analgesic and other new agents in children under age 12. The first thing I'd like to echo is what Dr. Friedman said. It's actually quite surprising the number of families that are willing to enroll their child in an experimental study, and that has been greatly to our favor.

So instead of the large number of patients who decline, we actually have a higher than 25 percent, usually closer to 60 percent who will say yes.

The second is that I still in my own mind question whether a child really has a lot of capability of giving assent, and although we require it down to age six or seven, I'm still not sure that children six to nine really understand anything about risk if there is greater than minimal risk

Probably the third issue is that the IRBs are getting more savvy about requiring why you are not going to study children, if you are not going to study children. So that has been an advantage for children to be included in studies, and those are not necessarily sponsor initiated studies, but just any study that we wish to do.

A couple of other questions are listed here about fixed dose combinations, inappropriate in this setting. They may or may not be. I think that some fixed dose combinations are appropriate, but not necessarily.

And just as importantly, I think we've matured as a group of clinical investigators, that what used to be the placebo controlled randomized trial is no longer the gold standard. It is one of many standards.

More the randomized controlled trial, which means that no one will be necessarily diverted only to a placebo group and have insufficient rescue medication. That is considered an inappropriate design in some studies right now.

So children will either have a high versus low dose with rescue or a current standard of care versus a new formulation, but the placebo controlled trial has not outlived its usefulness, but it clearly has now become equal with other appropriate ways of randomizing the control.

ACTING CHAIRMAN KATZ: Still as someone who does not do pediatric trials, all my friends who do still tell me that it's very difficult to get them done, and I'm still not sure that I've heard really.

There have been some actually positive things why some of the rumors that I might have thought make it difficult are actually not true, the high rate of consent, et cetera. Am I missing what the barriers still are to getting these pediatric trials finished?

Yes.

DR. SCHREINER: I personally believe we should be doing placebo controlled trials, but with rescue as the primary outcome variable, not pain scores. Children given access to rescue, like if you did a six to 16 year old population and they had a PCA for rescue, they will titrate themselves to the same pain score, and it's not zero. They don't titrate themselves down to zero. They make that tradeoff between the benefits of more pain relief versus the side effects.

I believe that kids six and up can do that, and there are also in some centers, like Hopkins, which do nurse controlled and parent controlled analgesia where they are operating the button.

So I think one of the things we get with placebo controlled trials is we get, you know, the equivalency of those oral drugs to intravenous

morphine, which is really what people have the most experience with, and I think that's what we should be doing, as long as there's access to rescue.

I think there are some barriers for the chronic dosing studies, particularly the long release studies, because children when they're on oral medications go home. Nobody wants to bring a child in pain back to the hospital, and the biggest reason why people do not consent to chronic dosing studies is they don't want to come back until the child is no longer in pain.

So we have to think about do we really need blood work if there is no evidence in a large number of adults of any toxicity to deliver a kidney. Do we really need blood work from these kids? Can we not wait until three weeks or four weeks when the kids come back to assess for adverse events?

And I think the requirement for steady state PK for drugs that have shown no evidence in adults of either accumulation or inducement of enzymes so that they might have other drugs is a big impediment because bringing a kid who's had scoliosis surgery back seven days after surgery so you can do steady state PK is a nonwinner from the family's perspective, and these children just simply do not

stay in the hospital on these medications.

So that is a very common reason why people come in.

ACTING CHAIRMAN KATZ: So that sounds like a legitimate barrier. On the one hand we have folks demanding PK/PD studies, but on the other hand, that is difficult for patients to comply with.

DR. SCHREINER: I think that for patients that are in the hospital, for hospitalized populations, for intravenous drugs, which is what you're talking about, Joe, for that chronic use, that's a different story, and I'm all for that we should be doing single dose PK studies.

But if you can predict the steady state levels in adults, then certainly if we exclude the neonates, the six month olds, perhaps, and look at the older kids, we can predict from single dose PK, standard PK, the steady state levels. Then I think that that is -- it has two problems. one is if we're going to use rescue medication, you'd like to use the same moiety. so if you're using MS-contin, you'd like to use immediate release morphine as the rescue.

Well, if you're going to do steady state PK, now you have to give them some other drug for rescue, and so then you don't know how much of that

drug they need in that 12 or 24 hour period. So it lessons -- for me it detracts rather than adds from the information we get, and it makes it harder to enroll and more expensive to do, and I don't think it adds anything.

ACTING CHAIRMAN KATZ: Other barriers? Dr. Reidenburg?

DR. REIDENBURG: Yeah. I'd like to pick up on that and add that really what we need to focus on are the areas of ignorance that give us trouble, that if we had the information, we'd change our practice, and that for the kind of studies like you're talking about, dosing to effect, I doubt very much that in these patients steady state PK is going to give you information that will change what you're doing with the patients because you're setting your dose in accordance to response.

And I can say this for a number of things that we've mentioned, that studies won't change the pharmacology of anything. They'll just describe it a little more precisely, and that if we focus on the specific areas of ignorance where the information -- where we're troubled when we treat the patients and this information will help us, then we can focus a whole lot better on what we need for the limited

resources in terms of patient availability as well as money.

ACTING CHAIRMAN KATZ: So it sounds like several people are saying that the requirement for steady state PK levels in these studies is not necessary from a clinical or from a scientific point of view.

So where is this barrier coming from? Is this industry perceiving a regulatory requirement for this? Is this an actual regulatory requirement for this information?

DR. SCHREINER: I'm seeing it in the written requests. So I assume that within the FDA that someone perceives this as a requirement.

ACTING CHAIRMAN KATZ: Dr. Rappaport, Dr. Rodriguez, any thoughts about that?

DR. RAPPAPORT: Would you repeat what it is that we would see as a requirement?

DR. SCHREINER: Steady state PK for --

DR. RAPPAPORT: That's not a standard requirement. It may be sometimes something that we have asked for. It depends on the situation though, on the particular drug and the particular written request.

ACTING CHAIRMAN KATZ: Dr. Tobin?

DR. TOBIN: I just want to get into this conversation. I think this has to do between regulatory and the sponsor, and what do they want to define as the primary endpoint.

If the sponsor really isn't as interested in efficacy and they think PK is the faster, quicker way to get the study done, that's what they're going to offer, and that's what's going to be given back by the FDA.

And as we've talked among the group of pediatric individuals, efficacy is certainly a harder, a less quantitative endpoint, although our conclusions are just what Mark said. Children titrate themselves to some level that they're comfortable with even though it's not zero, but demonstrating safety, efficacy, or enhanced or an improved new product over an old product, you're not going to see very easily in these studies.

So I think that's where the written request for PK data frequently comes from.

DR. RAPPAPORT: That's probably the situation, yes.

ACTING CHAIRMAN KATZ: So it sounds like the recommendation is that perhaps a more creative dialogue between the sponsor and the FDA could

potentially obviate the need for steady state PK in some of these studies that might decrease a barrier to getting the study done.

DR. RAPPAPORT: Well, the purpose of getting the steady state PK would be to look at dosing over time obviously and needs for any changes. So if we don't have clinical information from efficacy studies, generally we feel that we need one or the other.

ACTING CHAIRMAN KATZ: Yes, Dr. Smiley.

DR. SMILEY: Yeah, but in the case of opioids, we were talking about this before. It's one of those drugs where the pharmacokinetics are much less important than the effect because the difference between -- I mean, we're talking about differences between kids and adults -- the difference between any two adults at the end of this table on average is probably not that much different than the difference between the average kid and the average adult.

So actually the average kid and average adult are probably very similar. So that the actual pharmacokinetics, the actual drug levels are much less predictive than just the clinical response, and the difference is orders of magnitude have been described probably based more on genetics than the age of the

individual.

So I think it's a drug class where the pharmacokinetic data even if you get it and you say, well, it's the same or different between kids and adults, tells you almost nothing about clinical response.

DR. RAPPAPORT: We hear the comments. Thank you.

DR. SCHREINER: And I think we should be looking at dose response in terms of efficacy. I think it's possible to do and we should do it.

ACTING CHAIRMAN KATZ: Dr. Holmboe.

DR. HOLMBOE: The other thing I would point out is that this really is a trial design issue. What I'm hearing is that you're expecting the kids to come to you. What I would argue is that for a lot of this data, you can go to them and get it, and this really becomes a patient centered issue.

You may be putting up certain hurdles for the patient that you can remove very easily by going to where they are. If they're at home, then drawing things like blood can be easily done. I do that all the time with my geriatric patients. I don't expect them to come to the hospital every time I need to have blood drawn because that would be cruel and unusual

punishment for somebody who's in a walker.

The same principles, I think, would hold for a child.

ACTING CHAIRMAN KATZ: Other barriers to getting pediatric analgesic trials done? Dr. Schechter.

DR. SCHECHTER: Just a few things. I think what Dr. Friedman suggested before is a seminal issue in all of this, which is the sort of lack of a patient pool at any given location, and we had talked as a pediatric pain community frequently about developing collaborative groups modeled on this sort of COG group, but not necessarily linked with cancer per se because there are a lot of broader pediatric pain issues, and five, eight, ten centers together could instantly present to industry the capability of having a population that the accrual rate that would be much better.

In most of the studies that I've been involved with, it's been hard to recruit patients because there's been a couple of sites and studies go on for long periods of time. There's recruitment issues, but if one had an automatic base that one could feed into or withdraw from a group of centers that were comfortable with us, I think that would

help.

The second issue that I just wanted to raise has to do with the issue of effectiveness, if you will, or assessment more critically, and I think that that has been the perceived barrier for a while because of people's feeling that children were harder to assess in certain ways, and they certainly are, and unfortunately the data continues to suggest that there are new assessments. Every other place has a new tool with a new acronym coming out all the time, which has been in a certain way a problem in this literature because I don't think there will be a gold standard, but there are certainly many instruments at this point, and most people in the pediatric pain measurement area suggest we don't need more tools necessarily at this point.

But I wonder whether there's a sense of inaccuracy that's out there or vagueness, and then people are sort of reluctant to get involved in this because of some of the measurement issues, which I think are probably not really relevant specifically. There are certainly enough tools there that are widely agreed upon and that at least can give you pain/no pain or some gradations within that.

And the final other issue had to do with

the fact that so much of the pediatric pain is postoperative pain, and there's a huge percent of kids that are going to have day case surgeries, and kids are coming home. And there's some Finnish data and a number of other studies that have suggested a large number of children have continued to have pain at home. Yet they're inadequately treated because of a variety of reasons, their parents' reluctance, a whole host of other sorts of reasons, inadequate prescribing.

And I think that that's another problem that we have, is that the kids aren't in the hospital in the way that they used to be. So it's harder to get that particular pool, which is a very vast and very, I would suggest, under treated pool.

ACTING CHAIRMAN KATZ: Yes, Dr. Roberts.

DR. ROBERTS: And to deal with this issue of sort of reaching out to the kids as Eric and Mark have talked about, there are networks out there. The American Academy of Pediatrics has pros, the pediatric research in the office setting network, practicing pediatricians who are going to be taking care of the vast majority of kids who are postop. It's not going to be at the cancer center or with the pediatric nephrologist.

Family docs and pediatricians take care of about the same proportion of kids. So using both kinds of networks I think would be very helpful at getting past some of these barriers about where to get at them.

ACTING CHAIRMAN KATZ: Is there a reason that you would point to why those network that are already in place have not been used more aggressively for conducting clinical trials of analgesics?

DR. ROBERTS: There's several reasons. The first is that it's a relatively recent phenomenon. They've only been recently developed in the last eight to ten years. so there's kind of a critical mass and momentum issue, and the second is because they're attempting to look at the entire scope of things that affect children's health if we're talking about kids from, you know, growth and development through common infectious disease, through whatever. Pain is just one of a myriad number of issues they're looking at.

But I'm suggesting that for sponsors and the FDA as they look around at places to sort of get at kids in real world settings, this is a good potential pathway.

ACTING CHAIRMAN KATZ: Dr. Rodriguez?

DR. RODRIGUEZ: The pediatric pharmacology research units that you're all aware of, 13 centers across the United States have actually done quite a bit of work in evaluating not only new modalities of therapy, but even more interestingly the mechanisms, in fact, are evolving into various things.

In fact, some of the things that I flashed there like propofol, et cetera, they have participated in those studies. The infrastructure is supported by the NIH, is a competitive process. These people are, you know, top of the notch, and essentially you know, they're up to 13. I don't know how many more they're going to do, but I'm sure that they will refund it because this is a competitive process, but something like that is very similar to what we talk about with the oncology.

We have a representative to the oncology that participates, Steve Hirschfield, very closely, and in fact, I go to their meetings, and some of this stuff that we're talking about, streamlining and efficiency, comes very rarely.

And I agree. They've done more than the adults do in terms of the studies and in terms of participation.

ACTING CHAIRMAN KATZ: Yes, Dr. Roberts.

DR. ROBERTS: Just one other comment that Dr. Rodriguez reminded me of. You had asked the question about why these kind of networks, practice based networks haven't been used more, and besides their newness, you have two other issues, I think. One is the methodology issues are a little more complex in the out patient setting because the ability to control the environment is so much less.

You know, in a sense you go from a lab bench with rats in a cage to an academic medical center, which is sort of humans in a cage, to the office setting which is, you know, the rats are all loose running around.

So that's a challenge, and we're still figuring that one out, how to control for those multiple confounders.

But the second, which Dr. Rodriguez mentioned, is the issue of infrastructure. If you have a center, say, a university that maybe has 30 kids with a condition of interest, it takes one level of sort of infrastructure support to study them.

Now imagine you've got 30 practices, each with one kid with the condition of interest. That's a very different order of magnitude in terms of maintaining the support, and the support for those

infrastructures have really not been there.

And so one of the things that the FDA could help with the sponsors, with NIH is to begin to help provide that kind of ongoing support so that you can develop, you know -- in the marketing world it would be distribution systems sort of get the word out. You use a very different model than in a centralized approach.

ACTING CHAIRMAN KATZ: Dr. McLeskey.

DR. McLESKEY: Well, in follow-up to that specific comment, I'm not a statistician, but our statisticians tell me that when we move from a single site to multiple sites, as you've mentioned, probably because of the variability to which you've alluded, the n goes up quite a bit in order to maintain the same power.

So that is one of the hurdles that we come upon in this multi-center type of an approach.

ACTING CHAIRMAN KATZ: Any other industry perspectives and barriers to conducting trials in the pediatric population?

DR. TOBIN: Can I make a suggestion?

ACTING CHAIRMAN KATZ: Yes, please, Dr. Tobin.

DR. McLESKEY: Other than those that have

been mentioned so far?

Sorry, Joe.

DR. TOBIN: Charlie, I want to address this to you and Dr. Rappaport.

In almost all of the studies that a sponsor comes to us with, one of the exclusions are the child may not be involved in another study within 30 days prior or 30 days after.

If I'm in an academic center with a bunch of children in an oncology trial, they're excluded then from the opioid trial.

Now, my question becomes then: is this exclusion something that sponsors are requesting because they want to have more clarity in their data and not have adverse events suggested due to their product? Is it because there is sufficient product interaction, or is it a regulatory decision? And how do you both perceive that?

ACTING CHAIRMAN KATZ: It's not a regulatory decision.

DR. McLESKEY: Well, Joe, that's a complicated issue. For example, you've already mentioned that in some of the opioid studies, you would eliminate from the group patients who had a history of substance abuse for potentially obvious

reasons.

You might want to eliminate children in this case who have been involved with other studies because you don't want your product to be accused of causing some kind of organ toxicity that might be as a result of a drug interaction or some kind of a hangover effect from a previous study.

So I think all of us strive to achieve a direct product focus and try to limit as many variables as possible, and I suspect that's the reason behind it.

ACTING CHAIRMAN KATZ: Dr. Friedman.

DR. FRIEDMAN: To follow up on that point, I think that's a valuable point, but I think it is clearly a barrier. The other thing is that if you -- and I'm using the oncology setting because obviously that's the one I'm most familiar with. We have many children who are at the end of life who have relapsed from their cancer, have been treated on multiple protocols. Sometimes the parents or the children elect to participate in a Phase I study of an experimental agent. Often they're not eligible for the same reason, because they've already been on the previous study or they've had so many studies.

So in that case, we often use

chemotherapeutic agents in a palliative setting to try to at least get some -- in some ways to use it as a symptom control to try to make the end of life easier for those children and their parents.

So you may have children who in the same physiologic situation with respect to organ toxicity, you may have children who have the same risks for toxicity, but haven't officially enrolled on another trial and, therefore, may have the same risks with respect to the opioids in terms of the opioid being associated with an adverse effect as children who have been on trials in that period of time.

So that just has to be remembered, and perhaps there needs just to be some sort of controlling for other medications as opposed to precluding those children from study.

ACTING CHAIRMAN KATZ: Thank you.

That was a useful discussion on the barriers. I'm going to move on to the next question, which is -- I'll read it quickly and then focus on what seems to be the salient issue.

Many different opioid formulations, delivery methods, and drug device combinations are currently available on the market or may be available in the future. Discuss the age appropriateness and

limitations of these various methods of administration, as well as any others that may be useful or particularly hazardous in pediatrics.

Are there particular delivery systems that have found a useful niche in pediatric pain management that should be encouraged?

And so perhaps our pediatric colleagues could address whether their particular delivery systems that are either especially useful or potentially useful or potentially inappropriate in any particular pediatric populations.

DR. FRIEDMAN: I addressed some of this in my comments obviously earlier this afternoon. I think when we think about delivery systems in pediatrics we obviously want to think about delivery systems that are noninvasive because of the issue of trying to deal with children.

One of the little vignettes that Dr. Rappaport gave us was that of a subcutaneous delivery system. That's an issue in pediatrics because even the tiniest needle may be considered invasive for kids, but the other issues that he brought up are very important, such as should the needle get dislodged and the child is no longer receiving the medication that they want to receive if it's a 24 hour.

An older child can clearly do that, and with small subcutaneous systems, I think that that's not -- it shouldn't be excluded. However, kids still have a big barrier when they see a needle, even the smallest, thinnest possible needle.

But I think for teenagers who may not have indwelling catheters and want to use that kind of system, smaller, tinier needles, such as one that I was shown during the break, are really very valuable. I think they will be less valuable for the other children.

We do use subcutaneous systems in children for some medicines. For example, children who have iron overload are treated with desferol (phonetic), which is a subcutaneous infusion that goes over several hours. The compliance rate is terrible because kids have to stick themselves each day with a subcutaneous needle to get their desferol, and we have children, older teenagers, who actually prefer to be iron overloaded than to give themselves the desferol which will chelate them.

So I think that's subcutaneous. We need better longer acting agents, and I agree with what was said earlier. They don't necessarily need to be liquids. I mean if they can be in a tiny capsule,

that you could have a young child swallow. Certainly long acting liquids would be ideal.

It would be nice to have more options that don't require either the need for an intravenous or a subcutaneous device. Intravenous devices we use a lot in oncology. Most of our patients have indwelling catheters, but I would argue for the rest of the pediatric world that's probably not the case. So we're probably a spoiled subsection.

So we really need to think about it. Patches are a wonderful idea, but the problem is most patches don't have a small enough dose for kids, and what people are doing out in the community is they're taking, you know, the bigger size patch, putting something underneath the patch on half the patch and thinking that they're getting half the dose.

People are doing all kinds of things to try to get around this, and the answer needs to obviously be more formulations.

So I think even young kids, even kids who are four and five years old can swallow a small pill. We do that. In leukemia therapy, we have pills that kids need to swallow that they don't come in liquid medications, and the kids don't like them crushed because then they taste the pill. So what we do is we

take, you know, little, tiny corticosteroid pills and we put them in tiny little gel caps, and I can get a three year old to swallow a tiny little gel cap to get that medication in.

So I think if we have smaller doses for the long acting medications and tinier capsules or even pills, that will help in addition to liquid medications.

And the other thing is to think about novel ways of giving medications, such as these films that somebody just puts in their mouth. I mean, they're doing them now with after coffee mints. They have little films that they were giving out at the recent meetings. So that's another way, and you know, that's an easy thing to give to kids.

I do worry about things like lollipops, as I talked about, and we need to think about issues of choking in children and think about whether, you know, whatever it is, that it's not a choking risk in a child.

ACTING CHAIRMAN KATZ: Dr. Schuster.

DR. SCHUSTER: Actually you began to answer the question I was going to ask. We're reluctant about the fentanyl lollipop, and in addition to choking you seem to have some other objections.

And I wondered have there actually been significant numbers or cases of them being diverted to other children who have suffered adverse events because of it? What has been the experience?

ACTING CHAIRMAN KATZ: Dr. Ashburn, do you have an answer for that?

DR. ASHBURN: No, but I'll make one up.

(Laughter.)

ACTING CHAIRMAN KATZ: Works for me.

DR. ASHBURN: For those of you who don't know, I participated in many of the initial trials on oral transmucosal fentanyl citrate. We don't use the "L" word. The pediatric product actually has been withdrawn from the market which actually I'm disappointed with, even though I did not agree that the product was a very good drug to be used for preoperative sedation.

The lower dosage forms, removing the lower dosage forms from the market for their ability to be used for breakthrough cancer pain and for procedure related pain is probably a step backward based on the discussion that we're having here today.

To my knowledge, I know of no -- although I don't track the data, I know of no reports that the drug is necessarily ramp with diversion with regard to

diverting it to other areas. The FDA worked with the company, did a lot of work with the company, to develop a risk management plan and packaging in order to work very hard to avoid diversion of either the pediatric dose indication or the adult dosing form, and the product does seem to have a niche for breakthrough pain, particularly for individuals who are having cancer.

One thing though I wanted to talk about was that there's -- and this kind of goes to what we're going to talk tomorrow on, and I just want to bring the subject up -- is the concern of potential benefit with potential risk, and if you get right down to it, that's some of the things -- we haven't really talked about that in the sense that when we talk about a waiver or a film with a fairly rapid transdermal delivery or transmucosal delivery system, that's going to lend itself quite nicely to diversion.

I mean if you have a film and theoretically you can load the film up. If you have a wafer, then you're going to be able to crush the wafer and deliver it transmucosally through the nasal mucosa. And it will be interesting in hearing from the FDA, from other individuals. How do you balance that risk?

The unmet need of pediatric pain and adult pain versus the potential for diversion for illegal illicit use of the product.

ACTING CHAIRMAN KATZ: Dr. Schechter.

Is your mic on?

DR. SCHECHTER: We actually did the clinical studies of transmucosal fentanyl for procedure pain in kids with cancer for bone marrow aspirations, and I really respectfully totally disagree with the notion that it has a significant potential for diversion for a bunch of reasons. Number one, it's a hospital administered medication, at least the way it was formulated initially.

So to give kids that prior procedure who are coming in for a laceration repair when one doesn't have to start a line, it's not going to be sitting at home in your medicine cabinet.

Number two, the way it was formulated and sort of sucking on the lollipop, there are fast suckers and slow suckers. If you bite the medication, if you bite the lollipop, basically it's no longer -- it's not metabolized in the stomach. So it sort of loses efficacy.

The other thing is the onset is not a rush in any sort of way. So a lot of the things that would

make it attractive for diversion and for other situations have been dealt with. But I think it comes to the fundamental issue of do we make medication palatable and attractive to children.

Is it a message, "This is an opiate. It tastes horrible," automatically suggesting, well, we don't want -- number one, it gives you one sort of message and number two, related to that, maybe a sibling who might want a candy or something and mistake it for a candy, but in general, I think that that's a mistake and a misdirected notion, and I really think our goal is, you know, the spoonful of sugar makes the medicine go down, and I do think almost every medical formulation is palatable, and I think to suggest that an opioid shouldn't be in some way, assuming there are obviously adequate safeguards and precautions and it's used appropriately, I think it's as a disservice and goes in the wrong direction.

ACTING CHAIRMAN KATZ: Dr. Rappaport, did you have a comment? No?

Well, it does sound like everyone is saying that one does need to pay attention to formulating medications that can be used in the pediatric population while at the same time paying careful attention to the potential for inappropriate,

dangerous use or at least liability, and that just needs to be fleshed out with each individual application.

Dr. Friedman, did you have a comment?

DR. FRIEDMAN: I think that my comment about the transmucosal fentanyl were taken a little out of context. I was not proposing that I think that it has a significantly higher diversion potential than other drugs. And as I said before, I think any kid can go to the medicine cabinet and take their parents' drugs, as well as their siblings' drugs, and those were not meant to be sent home.

I just meant that I didn't want people to think that, oh, we have this formulation now and we have to stop thinking about new and different formulations available, and I think we just need to be careful and take some thought about I know we need to make opioids palatable, and I said that myself, but I think we need to be careful about confusing medication with candy because that really does -- I mean, kids get overdosed with iron on a regular basis in this country because iron tablets look like M&Ms to them. So they get confused with candy. So it happens with other medications as well.

So I think we just need to be careful if

we're going to propose something and make it so much like candy that it may be confusing to children themselves and may lead to other problems.

So I just didn't want people to think, oh, we have this great formulation that's the be all and end all of everything. But to my knowledge, I agree that there have not been increased incidences of diversion or other problems with that approach.

ACTING CHAIRMAN KATZ: Just before we take leave of the formulation issue, I want to make sure that we haven't ignored the neonates. Is there a formulation, a wish list with regard to neonatal pain management? Anybody who deals with neonates want to make sure we haven't forgotten them?

Yes, Dr. Tobin.

DR. TOBIN: That's an important point because this is probably the group at risk for the greatest number of procedural painful things I can imagine happen to them in a short hospitalization of 90 or 120 days, and that's the 24 week old gestation infant to the time when they're finally discharged.

Unfortunately my comment isn't directly at opioids. We need some other appropriate anesthetic analgesic topical agent before we're going to lance this infant's heel anywhere from 100 to 500 times

during that four month window in the hospital. So it's not just opioids, but we have to think about that as a very, very different physiologic organism.

We already know that morphine is very differently metabolized in those infants. We know that their threshold for apnea is significantly different, and that's unrelated to opioids; that their blood-brain barrier may be different. There's some discussion about that right now, whether or not that's, indeed, true, and we know the pharmacokinetics of drugs in that infant age range are hugely different because their volume and distribution is different, and there's immaturity in their organ systems.

So not specifically for any kind of out patient drug development, but for in patient drug development, yes, there's still a great need in that age group.

ACTING CHAIRMAN KATZ: Thank you.

Let's move on to question four, which again I'll quickly read through and try to focus on the salient issues.

It has been historically accepted that the mechanisms of action of opioid analgesics are similar between adults and children; that large controlled studies demonstrating efficacy of the nature conducted

in adults have not been required for a pediatric indication. Instead pediatric trials have been largely focused on investigating safety pharmacokinetics and appropriate dosing in children.

Discuss the shortfalls, if any, to this approach in the ways it has been used to guide and inform the clinical use of opiate analgesics in pediatric patients.

So let me just focus that with the first part of that question. Is it true that if an opioid analgesic is demonstrated to be efficacious in an adult that we can assume it's also efficacious in a pediatric population?

I guess that's not a yes or no question. Dr. Tobin?

DR. TOBIN: I'll start. As far as the mechanism, I think that most of us who have done any type of developmental pharmacology at the bench would agree that the mu opioid receptor is expressed even in that preterm animal, and in mu opioid receptors that are seen in humans at autopsy as well.

Is that the only mechanism by which mu opioid agents are going to work? And with the other isoform receptor expressions that change with development, I'm not sure that we can assume that that

is the only mechanism by which these drugs work because they're not as specific as we once thought they all were.

Secondly, there is a significant development of kappa opioid drugs now for peripheral analgesic action, peripheral meaning outside the blood-brain barrier. We have no idea whether or not those drugs will be efficacious in this group because we don't know if this group expresses kappa opioid receptors.

So there is an insufficient amount of data to conclude to my opinion that the only mechanism by which these drugs work in these small infants is via the mu opioid receptor.

ACTING CHAIRMAN KATZ: Are you specifically referring just to small infants, or are you generalizing your comments to the entire pediatric population?

DR. TOBIN: Well, I've got to go further than just the infant range. Dr. Woolf's work and many other basic scientists are now beginning to show us that there are developmental changes in sodium channel expression and many other important neurotransmitter systems that occur with neurodevelopment through to early childhood and then change again possibly with

the advance of new chronic pain syndromes.

So I don't think I'm saying just infants. I'm saying probably at least through early childhood.

ACTING CHAIRMAN KATZ: Are you saying then that in older pediatric age groups you are comfortable that demonstration of efficacy in adults can be used as a proxy for efficacy in these older kids?

DR. TOBIN: I'd have to say that clinically those are trials I am doing. So at least down to about age five or six I'm pretty comfortable that the great majority of action is via the traditional mechanisms.

I just don't know how low I can go, age two, age one, six months or whatever.

ACTING CHAIRMAN KATZ: So that's the comment on the table. Any agreements or disagreements? Dr. Friedman.

DR. FRIEDMAN: I certainly concur with that. So I think that we know that these drugs are efficacious, but two things. One, we know that the older drugs that are on the market are efficacious, but I think that we still don't have a good handle on how to best dose these medications either on a short-term basis, but especially on a long-term basis for kids, either neonates, who are going to be getting

these drugs for months and months on end, children with cancer, children with sickle cell who are going to be getting them on and off.

And I think that those are issues that we can't just extrapolate from the adult literature.

We had a long conversation earlier about our pharmacokinetics and pharmacodynamics, the only end points, and I think the answer is, no, that we need to look at efficacy, and certainly as new agents come down the road, if the mechanism of action is not clearly the same as the mechanism of action as our older agents, I think we need to do efficacy trials in children the same way we do efficacy trials in adults.

ACTING CHAIRMAN KATZ: Dr. Schechter, did you want to weigh in on that?

DR. SCHECHTER: No, I completely support that, but an example of that, for example, would be tramadol (phonetic) or something like that, where we really don't know anything about how it works in children. A lot of us are using it in chronic pain situations, but you know, I think, again, we can't just extrapolate from the adult literature on that.

ACTING CHAIRMAN KATZ: So what do both of you think about Dr. Tobin's assertion that down to about the age of five, six, somewhere thereabouts, we

can assume that if efficacy is demonstrated in an adult population, then there will also be efficacy in a pediatric population, granted that we need to do more dose finding and that sort of work? Do you agree or disagree?

DR. SCHECHTER: I'm reasonably comfortable with that, but I think when you're talking about dose finding, then you're talking about efficacy. You're talking about measuring a dose response, and to me that that's what we need.

I would just like to state that I have a particular problem with requests and as a member of an IRB with protocols that are 100 patient safety studies. Part of what an IRB is required to do is look at the scientific merit of the study, and it is considered unethical to approve a study that cannot answer a question.

Safety is not a question. Safety is a byproduct of all the information about the drug from other trials, and so I think that a lot of IRBs have problems with this notion of safety, and if the FDA is going to require safety studies, then they ought to come along with the question instead of like "Jeopardy," you know.

(Laughter.)

DR. SCHECHTER: Your trial should be in the form of a question.

ACTING CHAIRMAN KATZ: That does lead us to the second part of this question number four, which is are there specific ways that safety data ought to be sought in pediatric analgesic trials, especially if it's not being done the way you like right now.

Comments about safety in pediatric trials? Do you want to continue on the vein that you were on?

DR. SCHREINER: Well, I mean, safety is always assessed compared to something else. So if we have an open label trial and everybody is on the same dose, what does it mean? I mean, the drug could be better than all other alternatives and we wouldn't know it. So I think that we have to think about what we're asking for when we're asking for safety.

I think that the agency may know what they want, but it is not crystal clear to the pharmaceutical companies, and I say that as a member of an IRB who sees a lot of these protocols.

DR. RAPPAPORT: Well, actually I hadn't heard that from any of the pharmaceutical companies before, but, I mean, the discussion of safety, the discussion of how we evaluate safety and how we come up with the instances that we're using in the label

is, I think, a little bit of out of the realm of this particular meeting, but I mean, as Dr. Rodriguez and I were just discussing, we look at the entire profile of safety from a large patient population for multiple trials when we look at a new application. We're not just looking at a single trial to see whether there was a particular event that won.

DR. SCHREINER: No, but a lot of the written requests -- and it's not just this division -- are for a PK study and a 100 patient safety study. So the company has put together something that is a 100 patient safety study, but what does that mean? They collect adverse events.

And so the members of IRBs who are looking at these have a lot of trouble. What are you looking for? If the drug isn't safe, what are you looking for?

And I think that it's almost from my perspective as a clinician not very useful information. I think we can ask better questions and that we should be looking for dose response. We should look at the range of doses that are necessary.

There are other things that we could be looking at other than just saying, oh, a 100 patient safety study.

ACTING CHAIRMAN KATZ: Why don't you continue with that thought? What do you think ought to be looked for from a safety perspective in pediatric analgesic trials?

DR. SCHREINER: Well, opioids are titrated to effect, and so what we really need to know is where do we start. What's the minimum dose that provides anybody any analgesic benefit?

And then is there some plateau above which there's no further effect, you know, a mixed agonist/antagonist, or can the doses keep going up and up and up?

Eighty percent of the children have acute pain, and actually their pain because they're post surgical pain, the kids in the trial, their pain is going down with time. So you know, they're using less narcotic. It's another problem with doing steady state PK.

Are we going to demand that they take the drug every four hours even if they don't have pain just so we can do the steady state PK?

ACTING CHAIRMAN KATZ: So those are all efficacy and PK issues. What about safety? Are there specific safety issues in pediatric trials that ought to be considered? I haven't heard any yet.

DR. SCHREINER: I think we are all concerned about respiratory depression and we're concerned about the typical side effects of opioids, and aside from the very youngest patients, I don't think -- we're not -- I don't think there are additional concerns.

I think kids tolerate a lot of these drugs a lot better than the elderly do.

DR. TOBIN: I think being in the anesthetic community, we have to understand that when sponsors do provide drugs that they don't always know what the safety issues are going to be either. One, in particular, that wasn't discussed before this committee was the development and clinical introduction of the drug rapicuronium, and it actually did not have a problematic safety profile in the adult patients or in the trials.

And once again, as a practitioner who takes the drug, not immediately, but relatively quickly will take the drug to use in children, we found a very dangerous problem that resulted in pretty significant clinical detriment to those patients, and the drug has since been withdrawn.

So I just use that as a bit of a preamble to the statement I don't always know what I'm looking

for with safety. I know the usual profile of opioids, but how do I know that the next opioid that is an ester related drug is not going to have bronchospasm associated with it or worsening chest wall rigidity or a metabolite that's going to cause the seizure profile worse that meperidine nor meperidine right now?

I don't know what I'm always looking for. I think we do have to do what Mark suggests: find out the actual minimal efficacious doses and go forward from there, but not be hiding our results. As a community we need to have post marketing surveillance through the FDA so that if we do find a safety profile problem, we acknowledge that and get it out as quickly as possible.

DR. HOLMBOE: I think that there are two different types of safety issues here. One is in the acute use of the opioids, and the other is the long-term, chronic, intermittent.

And in the short term, you have the cancer patients that are either undergoing treatment and recovery from their cancer or recover from their surgery and no longer need opioids. So in those patients you're more likely to see the things that we always worry about as an anesthesiologist, the respiratory depression, the bad side effects.

On the other hand, as Dr. Friedman brought up, the patients that have sickle cell anemia or sickle cell disease that are going to have chronic intermittent use of these, there may be changes in cognitive function, and so we really need to look at what the patients that are on these medications long term may have different safety issues than those that are on them in the short term, and so we probably need to do two different types of surveillance.

ACTING CHAIRMAN KATZ: So long-term neuropsychological changes in children on chronic or recurrent opioid therapy is a specific safety issue that you would like to see addressed in children.

Any other specific safety issues that we would like to see addressed in children or should we move on to the next question?

(No response.)

ACTING CHAIRMAN KATZ: Let's move on then.

Question five, discuss approaches to dose finding and the evaluation of pain in the very young.

I think Dr. Schechter already very clearly stated that there are adequate assessment scales available for young children, if I didn't misunderstand you. So we're left with the first half of that question, which is approaches to dose

findings.

Does anybody have any thoughts about good or bad ways to accomplish dose finding in the very young patient? Has anyone seen examples of how not to do it? Maybe that would be the place to start. It's always easier to criticize.

Dr. Portenoy.

DR. PORTENOY: I just woke up. Can I go back to the safety issue again?

ACTING CHAIRMAN KATZ: That was yesterday's session.

(Laughter.)

DR. PORTENOY: I was just ruminating about some of the issues that are coming up in the adult use of opioid drugs and areas in which we are sure that we need more data, areas, for example, like sexual dysfunction, the abuse liability of drugs, and the issue of cognitive impairment.

And some of those issues I haven't heard discussed, but it may be worthwhile at least to put them on the table. For example, the issue of hypoprolactinemic, hypogonadism or non-hypoprolactinemic, hypogonadism, which is probably a fairly common. These two abnormalities are fairly common in adult use of opioid drugs, and here we have

a population of children that may be intermittently bolused or on more chronic therapy approaching puberty. Is that an issue or not an issue?

And I wondered if any of the pediatricians would address that.

There are data from some interesting animal models suggesting that bolus administration of opioid drugs, particularly in young animals may alter the ability to or may alter the outcomes in relation to self-administration of opioids secondarily.

In other words, there is some data that would suggest that intermittent, high intensity administration of opioids may predispose to a craving syndrome as opposed to continuous administration in young animals.

And this concept of giving neonates in an ICU repeated bolus injections of opioids for procedure pain, is anybody in the pediatric community looking, thinking about that in terms of the possibility that we may actually be creating the substrate for a subsequent craving syndrome that could be disposed to addictive disease?

And then the issue of a cognitive impairment that was mentioned. I mean, obviously a constant concern in adults, particularly with the

recognition that some cognitive impairment is not apparent to the person who is experiencing it and can only be picked up with very good neuropsych testing, it's the same sort of issue we see in all centrally acting drugs, like anti-compulsives and anti-depressants as well.

But the issue in children, I would think, would be looking at school performance and other kinds of outcomes that are not -- that we don't look at in adults. You know, in adults we're all worried about driving, but in children I would wonder about learning and state dependent learning, and has anybody been looking at those issues?

ACTING CHAIRMAN KATZ: Endocrine complications, long-term cognitive function.

Dr. Schechter.

DR. SCHECHTER: Well, of course, one of the problems is that most children who are on chronic opioids have a concomitant illness that's significant. So, for example, the sickle cell population is predisposed to growth failure, but that's sort of independent presumably of aggressive opioid treatment because we've only started aggressive opioid in young kids recently, and that's been a longstanding problem with secondary -- in almost everyone you can consider,

and again the sickle cell population also is prone to -- and now with the transcutaneous Doppler we're finding small strokes in those kids that we didn't realize were there before.

So clearly that is an issue, but that's in so many of the conditions that it's almost hard to factor that out. As regards to the sort of craving, we all worry about that a fair amount or we're starting to worry about that.

I mean, first we were starting to get people to use these medications, but now that we're using them, there is some significant concerns about that. There is data on the inadequate use of those medications, and the NICU in particular and the sort of changes in the central nervous system that are at least pretty chronic, at least as long as they've been followed out for years.

So on one hand, we risk that. On the other hand, we sort of know what's going to happen if we continuously perform procedures on kids without adequate treatment. But I do think that that's very much worthy and a very important area to study and look at as we start to do this.

DR. PORTENOY: Just to clarify, you're talking about the data that suggested inadequate

management in the NICU may predispose to more pain with --

DR. SCHECHTER: Yes, right.

DR. PORTENOY: -- injury later on.

DR. RODRIGUEZ: Right.

DR. PORTENOY: Right, yeah.

ACTING CHAIRMAN KATZ: Dr. Rappaport, did you have any other -- you or your group have any other specific issues with regard to the dose finding question in the very young that you wanted to have covered before we move on?

DR. RAPPAPORT: I guess if there are no other thoughts on the issue of metrics here, I mean, that's really a problem. If we have to do dose finding for the very young children, for the neonates and the infants, we're going to need to do essentially efficacy studies. It's the only way to do it, and the metrics aren't really very good.

Is there any other comment in that area?

ACTING CHAIRMAN KATZ: Dr. Schechter, did you want to readdress that point about whether the -- I don't mind putting you on the spot -- with the metrics in evaluation of neonatal analgesic responses are psychometrically sounds or not?

DR. SCHECHTER: Well, there are a number

of them, as everyone is aware, and each day, you know, in the Journal of Pain and Symptom Management or a Clinical Journal of Pain there's another one or two that pops out. I'd say that some of them have better properties than others. None of them seem to be perfect at this time.

There have been some significant psychometric investigations of at least some of them, and I would certainly say that it's not at the level of what one would identify in an adult reporting their discomfort and looking at the other sorts of measures. It certainly is not at that level.

But the ability using facial recognition and a variety of other things and comparing that to pain is reasonably good. It's just hard to know what the gold standard is when you're comparing it. It's sort of construct validity, but having said that, I think most people in this field who have looked at this for a long time -- it's probably been ten or 15 years of investigation -- are reasonably comfortable, people like Bonnie Stevens and Patrick McGrath, and that sort of scale developers are reasonably comfortable that they have instruments that can at least tell a little bit of pain/no pain, maybe not in significant gradations, but certainly at some course

level they certainly can identify discomfort.

ACTING CHAIRMAN KATZ: Dr. Roberts?

DR. ROBERTS: Well, I wouldn't hold my breath waiting for them to point to the smiley face or the "frownie" face, but you know, a lot of the pain studies in newborns actually occur in the context of circumcision with dorsal penile blocks. People were measuring catechol levels and cortisol levels, and I guess you could insist on that. That seems a bit overdone.

You know, maybe with a kid in the NICU that's got indwelling lines in where it wouldn't be perhaps that hard to get another cc or two to check some of that, it's a helpful way to go, but I don't know that I'd require it.

I think some of the other psychometric tests that Dr. Schechter spoke to seem to me reasonably convincing, and that's probably as good as it's going to get.

ACTING CHAIRMAN KATZ: Any further details about the issues of psychometric testing?

We have one more question to address today.

DR. RAPPAPORT: Excuse me. Before you go on, I'd like to go back to the first question just

briefly.

ACTING CHAIRMAN KATZ: You want to start all over again?

(Laughter.)

DR. RAPPAPORT: That was the question on formulation, and I know at one point Dr. Tobin said in passing that there may be a place for combination drug products in pediatric patients, and we didn't really follow up on that, and it's a big question not only for us, but for the other division at the agency that deals with analgesic drug products, and there are obviously a lot of them out there, and there are a lot of regulatory issues that come to us because of that.

So if we could spend just a couple of minutes on that.

ACTING CHAIRMAN KATZ: yes.

DR. SCHREINER: I think for the postop surgical patients there are an awful lot of day surgical patients for whom Tylenol is not enough, and right now at least in the Philadelphia area, I would say the most common drug that's prescribed is Tylenol with codeine not because it's the best drug, but simply because it's carried by the most pharmacies.

Our surgeons would like to use oxycodone because they prefer it, but there's only one

manufacturer of liquid oxycodone, and it is not uniformly available at most pharmacies.

So I think there is a need for combination products for those short-term treatments where kids need something more than just acetaminophen, and the surgeons would want to prescribe those. IT's easier for patients to give one drug than two.

And I realize, you know, for my use they don't have much place as an anesthesiologist, but they certainly, I think would be a benefit to children.

ACTING CHAIRMAN KATZ: Dr. Roberts.

DR. ROBERTS: I would echo that. The other thing I'd ad, and it's more of a delivery system issue, but it relates, and I've long wondered why -- and it probably has to do with very low absorption, but why people haven't looked more at inhalers.

I mean, for instance, with kids with asthma it's pretty easy as young as even four years old to get them to use an inhaler dependably, and if you're concerned that you don't want it to look like candy and things like that, it gets around that.

You know, the intranasal stadol is about as close as we've had, but I think that's an area of pursuit that might be worth investigating.

ACTING CHAIRMAN KATZ: Dr. Schechter.

DR. SCHECHTER: Yeah, as regards to the previous point about combination drugs, I do think that for the most part pediatricians are comfortable with them. Families are reasonably comfortable with them, Tylenol with codeine, percocet, whatever, following surgery or for otitis or pharyngitis for a short period of time.

I think in the situations where somebody is going to be on, you know, two percocet every four hours for a long period of time, they're more likely going to be in the hands of a pain specialist or someone else who would more than likely recognize the potential hepatotoxicity and whatever is associated with that.

So I think for the short run where they're typically used, they're a comfortable drug for most people and reasonably efficacious. So I think they do have value in the pediatric population.

ACTING CHAIRMAN KATZ: So it sounds like there is a sense that for short term use, particularly in the postoperative setting, there is a role for combination products.

Dr. Ashburn.

DR. ASHBURN: One voice in opposition. At Primary Children's Medical Center where I run both

the chronic and the acute pain services, one of our leading indicators of adverse drug event monitoring that we've identifies as a potential cause for harm is analgesics that contain acetaminophen in combination products in that the routine dose that's commonly written by surgeons for postoperative pain management write a dose and then if it's given every three hours as ordered, within 24 hours they frequently are subject to receiving potentially harmful doses of acetaminophen.

I'm not sure of any studies that show that the combination products are better than individual opioid products by themselves titrated to effect. Now, you all may know otherwise, and I suspect that it's a matter of convenience that these products are translated from the adult population down to the pediatric population, and it's a matter of convenience, availability of the product in those issues that the product still remain available and have a role for the care of patients, but given the ideal world, it seems to me like safety would be improved with oral solutions containing codeine and hydrocodone and oxycodone being available as an alternative to combination products with regard to the overall safety of using these medications in an acute

pain setting, as well as especially in the chronic pain setting.

ACTING CHAIRMAN KATZ: Dr. Portenoy.

DR. PORTENOY: I just wanted to make the point that at least in New York I think it's also an issue of concern about regulatory scrutiny. You know, we have to use a special prescription to prescribe codeine without acetaminophen and no special prescription to prescribe acetaminophen with codeine.

And you know, there are some data to suggest that as soon as a special prescription is needed, the prescribing drops like a stone and other drugs are prescribed instead.

And I would agree with you. I don't know of any data that would suggest that the combination products would work better than the appropriately titrated single entity, and I think that it's other than convenience and those sort of regulatory issues that there's really no value to it that I can see.

DR. ASHBURN: So the irony is that the regulatory situation is such that we're more likely to prescribe a drug that can cause harm than one that might be safer.

ACTING CHAIRMAN KATZ: Let's go to Dr. Foley and then Dr. Tobin.

DR. FOLEY: I mean, the emphasis on this conversation here has been on codeine, but ten percent of the population can't metabolize codeine. So it raises the question of how many pediatric patients that might represent, and we don't have any data related to that.

What was not brought up is the whole role of hydrocodones and that whole class of drugs and the use of combinations, and I think that's sort of untested. It would seem to me a reasonable consideration to have that looked at to see.

The value of using them, I think, is more than convenience. It's thought to be opioid sparing, and that can have advantages. There is data to show that when you have an opioid and you add a non-opioid, you have additive analgesic effects, and the rationale of using combinations is this construct of opioid sparing because of the side effects of opioids, specifically, let's say, constipation or it might be nausea or some other ground.

So I don't think -- I think that we shouldn't focus on codeine, but focus on the spectrum of agents out there for which combinations might be appropriate, and what those combinations might be.

But broadly I would argue that there's so

much difficulty even moving this forward that it would be helpful if we had some good studies on the single agents and then deal with the formulation piece as a second aspect.

ACTING CHAIRMAN KATZ: So I'm hearing that there is clearly a role for -- a potential role -- for combination products in pediatrics. However, there is a lack of data to determine whether those combination products are advantageous over appropriately titrated pure opioids, and that those data are needed, as well as the fact that there's a quirk as far as scheduling goes where, in fact, these safer drugs may be more tightly regulated than the U.S. safe drugs.

Any other comments about the combination issues? Dr. Rappaport, did you have any particular methodological or other issues? We certainly have a potential safety concern that was mentioned.

I'm sorry. Your turn this time. Dr. Foley went first last time.

DR. TOBIN: I just want to ask if the panel here would have an opinion or I expect many, about the ethics of a sponsor or an investigator initiated trial about pediatric pain evaluation using normal volunteers, and that it's currently a standard that when new analgesic agents are being used in our

research, that we have standard heat probe placement to the foot of the human volunteer, and we look for efficacy. Then we have the same with other mechanisms of looking at hyperalgesia and aledenium (phonetic).

The reason I bring up the question of public forum is because there are certain IRBs which have turned down applications by moderate or intermediate and very senior investigators calling this unethical to in any circumstance cause temporary, but we would consider it absolutely reversible energy applies to the skin with no long-term injury solely for the effect of looking at a new analgesic measurement, and it's either pharmacokinetics, dynamics, or efficacy in a healthy patient population of, say, ages six to ten.

ACTING CHAIRMAN KATZ: Thoughts about the efficacy of human pain studies in pediatrics? Dr. Rodriguez?

DR. RODRIGUEZ: There is in the pediatric page a publication in the Web of the Advisory Committee, the subcommittee on pediatrics on ethics, and they address the issue of who to enroll in these studies, and essentially, first of all, the premier on the people I call patients. They're not called subjects. So, therefore, they must have the

condition.

Now, I suppose that you could say, well, if they can have pain one time in his life or something like that, but essentially it spells out situations in which the studies can be done, and you must have a condition in order for you to be enrolled in the study.

So in other words, healthy individuals usually are not involved. It's interesting because in the back of my mind I think of patients with vaccines, and I think of patients and -- well, they're likely to get the disease, and I think of patients with otitis media, and in prophylaxis where you don't have the disease, but they're likely to have the disease, or have the disease.

But overall, generally speaking, the participants must have a condition to be treated according to this recommendations of the Ethics Panel on Placebo Control -- not placebo -- on Trials in Pediatrics. You may want to take a look at it and derive your -- but I just wanted to bring it up.

DR. SCHREINER: I attended that meeting, and actually they presented a variety of scenarios, and the issue of using normal children in trials for otitis media, the majority of the committee felt that

that was acceptable because all children get otitis media, although you could find a better population, namely, children with frequent otitis media.

So the question is: is a condition so prevalent in childhood that the condition itself is childhood? Do all children have pain?

I mean most people would say if you have a new drug for fever, all children get fever and, therefore, it would be okay to do a PK study in normal children, but those are about the limits.

Then the other issue is once you get beyond having a condition, there are other ways that you can improve a trial in children, and you can improve it if it's of minimal risk. So you have to decide whether applying pain to a child for a brief period of time is minimal risk, and when you consider psychological and other issues, you may or may not -- your committee may or may not accept that.

And if they don't have a condition and it's more than minimal risk and it's more than a minor increase above minimal risk, you know, if it's not of direct benefit to them, you're not going to be able to do the study, unless you follow the route of, you know, appealing to the Secretary of Health and Human Services.

ACTING CHAIRMAN KATZ: Dr. Portenoy and then Dr. Smiley.

DR. PORTENOY: I just had two comments in response to that. The first is given the concerns about whether or not kids at the age of six and seven can assent, I think that would raise a concern in me, and then secondly, why would parents agree if there is no incentive? And if there is an incentive, then it raises the ethics of incentivized parents putting their kids under that situation.

So I think there are concerns about it.

DR. SCHREINER: Could I just say something about assent as well? Assent is not exactly the analogy to consent for adults. Consent for adults springs from the principle of, you know, respect for principle for autonomous people.

But the national commission, when they construed the need for assent for children, construed it as a benefit that we should appeal to the altruism of children. It was not a parallel exactly to consent. We should keep that in mind.

DR. SMILEY: Obviously you need a higher standard to do these kinds of studies on any vulnerable population, and obviously kids are, but I think it's difficult to justify because almost all of

us around the table have pretty much said that we believe that these drugs that we're talking about, opioids work pretty much the same in kids and adults.

So I think it would be hard in most studies I can think of to reach the standard necessary to justify studying normal, quote, unquote, volunteer children because we don't actually believe there's a crying need for it if the pharmacology is sufficiently similar.

ACTING CHAIRMAN KATZ: Last question. As new products become available for home use in younger patients, there may be a risk to family members of accidental ingestion, overdose, or deliberate abuse and diversion of these medications. Discuss the strategies for risk communication and risk management that should be considered at the time of pediatric opioid drug approval.

Of course, we discussed this to some extent earlier. Does anybody have any specific suggestions or comments about how one can communicate risk or manage it more appropriately when the opioids are developed?

Dr. Bitetti.

DR. BITETTI: I'm not sure that it's really any different from parents having digoxin or

amioterone (phonetic) in the home, but I think what we're sort of getting back to here is the diversion issue, which seems to be the reason that this question is there.

And we've spent most of the afternoon talking about the difficulties of developing pain medicines for children's new formulations, the incredible need for that, and I think personally that worrying about diversion, that that should not be an emphasis in developing new formulations and worrying about whether or not they have enormous diversion potential when it seems like there's such an incredible need for patients to have pain medicines.

And in general, I don't know what the problems of the FDA is versus the DEA in terms of whether or not our major concern is safety of the patients who are taking the medications and the abuse potential perhaps for those patients or whether or not our major concern should be abuse potential by other members of society.

DR. RAPPAPORT: Do you want me to just briefly?

ACTING CHAIRMAN KATZ: Yes, please.

DR. RAPPAPORT: Our regulations allow us to look at the safety for the patient who's taking the

medication, but we're a public health organization, and when we see that there's a potential problem to the population at large, we're responsible for at least bringing that to light and doing whatever we can to protect the public.

ACTING CHAIRMAN KATZ: Dr. Bitetti, does that answer your question about whether the FDA has jurisdiction in the central diversion issue?

Dr. Roberts.

DR. ROBERTS: I don't quarrel with the FDA having jurisdiction. I guess it's just a problem that I don't see as a large problem. I think the problem of pain control is a far greater one.

When you look at diversion for other pharmacologic products, whether it's acetaminophen or aspirin or alcohol, for that matter, and kids getting into that other, you know, family members developing health problems, that's a far larger issue than with prescription drugs of this sort.

So I just don't, frankly, experience it or see it much. I think it makes for great news print, but not necessarily great public policy.

ACTING CHAIRMAN KATZ: I'm going to take the liberty of tabling the diversion question until tomorrow. And just to make sure that we didn't

neglect to answer a piece of the question that's still there, did anybody have any comments about risk communication or risk management in terms of accidental overdose or other potential issues when these medications go home with kids?

Dr. Holmboe?

DR. HOLMBOE: Yeah, I can think of a couple of things worth considering. The first is we know from at least literature in adults, and I'd be interested to hear from the pediatricians, that the quality of counseling that occurs between patients and physicians is actually quite poor.

In a study published by Clarence Braddock in JAMA in December of 1999, he found that using fairly minimal criteria, only nine percent of visits met those criteria for effective, informed decision making.

So I think given the risk-benefit ratio of this drug, this is probably something that needs to be looked at in which to see if there's data in the pediatric literature, but how good the counseling actually is.

So one of those will be what sort of adjunct should drug companies or doctors who use opiates need in the office in order to discuss this

with their patients.

The second is what sort of information do parents need at home to use these particular drugs, and I think some discussion of, you know, the concerns about overdose, what to do in those situations probably needs to be part of that.

One approach might be to use something like a MediGuide that's more pediatric specific that's been used for some of the other drugs FDA has recently approved with more difficult risk-benefit ratios. So those are some of the potential things that I think need to be considered.

ACTING CHAIRMAN KATZ: Is there data in pediatrics about the adequacy of counseling when kids take home medications? Does anybody know?

DR. SCHECHTER: Well, there is data about in general the amount of counseling that goes on in a typical pediatric encounter which in a typical 12 or 15 well child supervision visit about 90 seconds. So, in general, you know, anticipatory guidance in those sorts of things obviously the short shrift just in general.

I think though when we're dealing with these sorts of medications very often there is a fair amount more care given, even more instruction than,

for whatever reason, than traditionally even with antibiotics or whatever. So I do think at least in my experience people are so anxious about these medications in the primary care setting that they do spend some time discussing them.

That's totally anecdotal, and you know what we've all said about anecdotes.

ACTING CHAIRMAN KATZ: Anyone from the primary care world want to comment about that compliment that you just received?

DR. HOLMBOE: I still have concerns that, you know, you're carrying a certain bias based on your own experience because of your experience in having to use these drugs, and I think any time somebody steps out of their comfort zone a little bit I'm not so sure that the amount of the discussion going on in the office, particularly somebody who studies this from a research point of view, is actually occurring.

And so I have real concerns about it, and again, I can't speak to the pediatric population because I don't work in that particular arena, but I know that anywhere from adolescence to older age adults it's still a problem.

ACTING CHAIRMAN KATZ: Dr. Roberts.

DR. ROBERTS: Well, a couple of things. I

mean, we know that in an average encounter the patient, if you're lucky can take away three things, and so one of the problems is you may have 22 things about a particular drug alone, much less all the other advice you gave, that you may be asking people to remember.

And so I think MediGuides or almost any mechanism that you could make available to people would be good because various people learn and remember and retain things differently, and you know, whether it's a telephone call-in line that they can call with questions, you know, about a particular medicine they're on or a piece of paper they go home with or a conversation with the doctor, the nurse or whomever, that's all good.

My experience has been that parents tend to be actually much more discerning and questioning about the medicines you're about to give their children than they would be on their own behalf. In fact, sometimes they're a little embarrassed to ask tough questions on their own behalf. They have no problems really pushing to the wall when it comes to their children.

So, in general, I would view it as perhaps less of a problem in the pediatric setting than in the

adult setting, but I say that just with my own anecdotal experience.

ACTING CHAIRMAN KATZ: Dr. Foley.

DR. FOLEY: I think in this whole area, both for adults as well as children we probably haven't done enough of creating safe environments related to these drugs and the information that people need.

And remember that these kids are not always with their parents, but they're with their friends, and they're going to school and they're sleeping over and they're doing a variety of other things.

And I think that if we look at how juvenile diabetes has sort of addressed this issue with a lot of information, I think that we could benefit with much more information and also with what would -- if someone took your drug and took an overdose of it, what should be done with that someone because increasingly you're seeing, at least in the Oxycontin, seeing these teenagers take these drugs in which all of their friends have identified them as sleepy and no one ever thought to get them to an emergency room and give them naloxone, and they were all clearly salvageable.

So I think that depending upon the age group, particularly if we talk about a teenage population that might be taking these, I think that we should escalate up the safety issues.

And we've had experience with elderly cancer patients taking their medications at home and having young children in the home who inadvertently because it's sitting on a table take the drug. And so I think instructions of where it has to be placed, the idea of safe havens for it, the kind of information and what happens if someone takes this.

And I think that kind of is positive, not negative information.

ACTING CHAIRMAN KATZ: Do you think it's appropriate for the FDA to require those sorts of instructional programs on approval of opioid analgesics that will be used in children?

DR. FOLEY: yes, I do.

ACTING CHAIRMAN KATZ: Anybody else have any thoughts about that? Yes, Dr. Reidenburg.

DR. REIDENBURG: Yeah. I think the problem is the same for opioids used in adults and taken home. I don't see that the issue is the pediatric formulation, but the opioid in a home.

ACTING CHAIRMAN KATZ: Dr. Carlisle.

DR. CARLISLE: A parallel situation that we deal with all the time as anesthesiologists, we give patients medications that alter their ability to remember. Then we tell them something. Then we give them a written instruction, and then we send them home, and then we call them, and they still don't remember.

So I think that we don't do a very good job in many circumstances, and we need a better way to do this.

ACTING CHAIRMAN KATZ: Dr. Holmboe, did you have comments?

DR. HOLMBOE: I just wanted to add my yes to Dr. Foley's with regard to the requirement.

ACTING CHAIRMAN KATZ: Anybody else? Dr. Schechter.

DR. SCHECHTER: We have started requiring -- Russell alluded to this before -- a contract when we're using these chronically in children and starting in the teenage years, and basically it says a couple of things. I won't loan this to anybody else. I'll only use one particular pharmacy. I know what some of the side effects are, and there's a little bit of education.

And we've just gotten to the point where

we feel we're more comfortable. That will at least definitively state that these things have been discussed anyway, and we read it together and the child has to sign it. Again, we started that.

Whether there should be differences in the way we use that as opposed to other medications, I don't know, but we have felt more comfortable doing that.

ACTING CHAIRMAN KATZ: Dr. Schuster.

DR. SCHUSTER: Well, I can't speak to the issue in a clinical setting, but when we do informed consent, you know, our laboratory in experimental settings, we have taken to having a very short three or four item quiz that at least we know that the person that we have just supposedly explained what they're getting into has understood sufficiently that they can answer these very simple questions.

I don't use them to prevent people from entering studies, but rather to insure that I can go over those particular items which they obviously have not misunderstood. So I'm saying at the bottom of the informed consent, you could have three questions.

ACTING CHAIRMAN KATZ: Dr. Roberts?

DR. ROBERTS: Well, that reminds me of one other thing. In genetics counseling, one of the

things that's being increasingly used are interactive programs where to be able to progress all the way through to signing the consent form, you have to be able to get a series of questions answered correctly.

And it seems to me those more innovative strategies around testing knowledge and communicating information might also be helpful directions as people think about new ways of assuring proper use and safety.

ACTING CHAIRMAN KATZ: Dr. Rappaport, did you have any other questions for our pediatric agenda for this afternoon?

DR. RAPPAPORT: I have a couple other little things, but I think rather than keep everybody here much later today, I'll try to slip them in tomorrow.

ACTING CHAIRMAN KATZ: Well, then we have actually completed our job a half an hour early today. Congratulations, people around the table, for helping with that and for a helpful discussion, and I'll see you all tomorrow morning.

Kimberly, did you have any housekeeping announcements to make?

MS. TOPPER: Yes.

ACTING CHAIRMAN KATZ: Will everyone just

hold still for a minute?

MS. TOPPER: Will the committee members who are attending the dinner this evening, since we have finished early, we're going to meet in the lobby at six o'clock. That will give you an hour to relax and chill out. It is very casual. Please be prepared to be casual. No ties allowed.

Thank you.

(Whereupon, at 4:58 p.m., the Advisory Committee meeting was adjourned, to reconvene at 8:00 a.m., Thursday, January 31, 2002.)