FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

JOINT MEETING OF THE

ANESTHETIC & LIFE SUPPORT DRUGS ADVISORY COMMITTEE

AND THE

DRUG SAFETY & RISK MANAGEMENT ADVISORY COMMITTEE

O P E N P U B L I C H E A R I N G

Friday, November 14, 2008

Gaithersburg, Maryland

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P R O C E E D I N G S

(1:10 p.m.)

DR. KIRSCH: I'm going to start the meeting. This product is for the open public hearing. Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decisionmaking.

To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you the open public hearings be heard at the beginning of your written or oral statement -- to advise the committee of any financial relationship that you may have with a sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at this

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

The FDA and this Committee place great importance in the public hearing process. The insights and comments provided can help the Agency and this Committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy and respect.

Therefore, speak only when

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recognized by the Chair, and thank you for your cooperation.

Again, I would ask that if haven't done this, silence your pagers and your cell phones.

Our first speaker is Albert Ray. Before you begin, there is a lighting system at the podium. The green light will go on; it will last for four minutes. At the end of four minutes, a yellow light will go on. When the red light goes on in five minutes, the microphone will be turned off and we will ask you to sit down.

DR. RAY: My name is Bert Ray. I am a pain physician in Miami, Florida. I have a private practice there, and am a voluntary faculty member at the University of Miami Medical School. I have been the past president of the American Academy of Pain Medicine, and past president of the Southern Pain Society, and I am currently Chairman of the Board of the National Pain Foundation.

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I am here today to represent the National Pain Foundation. I have absolutely nothing to disclose about my relationship with Alpharma.

Pain is the most undertreated disease that exists in the United States today. It's estimated that 75-80 million people live in chronic pain on a daily basis. Having proper access and proper treatment for that pain is critically essential. It is costing the United States over $100 billion a year in lost wages and in medical care.

The problem we have also relates to drug diversion and abuse, and we certainly know there's a certain number of people who have an addictive disorder, and we work to try and get them proper treatment for that. There's also a certain number of people who want to divert and use medication without an addictive disorder.

Those problems create pressures to then create solutions to that problem. One

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of the solutions tends to want to be political pressure to create laws and regulate medical care. That doesn't work. You cannot regulate medical care through legislation.

The unintended consequences, unfortunately, of those laws begin to preclude proper access for legitimate patients to get medical care.

Examples are: in Utah, there are about seven deaths a day from unintended deaths as a result of medication usage. In Florida, there's about nine deaths per day unintended, not overdoses -- unintended from the use of medications.

So we are looking for solutions to try and solve this. The National Pain Foundation is dedicating the 2009 and 2010 years to working on projects to work for patient access to care, as well as patient safety.

In terms of patient safety, we are

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working on a program called Zero Unintentional Deaths. We are starting this program in Utah, working with the Utah Medical Board, the Utah Medical Association and many other organizations to do this program, which would be an educational program for both practitioners and the public on the proper and safe use of medications.

In terms of access to care, we feel it is critically important for medications such as EMBEDA to be formulated in an abuse-deterrent way. The more medications that we can get like that and the more efficient they are at abuse deterrence, the better it becomes to use for the public to create good, efficacious treatment as well as safety.

It cuts down the abuse potential because people don't want to divert it. If they can't crush it or drink it or shoot it and get a high out of it, there is very little street value to it and people don't

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want to use it. So to have more drugs like that available to the public will help change the situation that we are dealing with at the present time.

It is estimated between 30,000 to 40,000 people die each year from medication usage that are not intentional overdoses. Abuse-deterrent medications will allow practitioners a better access to appropriate medication, using it at appropriate doses. A drug seller in Florida, for example, is pushing to have a threshold law rather than a patient prescription validation program in place. Threshold laws cannot work.

The unintended consequences: they medically limit the amount of medication a patient can get before they require a special consultation. There are not enough pain doctors in the United States to provide those consultations, so that system does not work. What works better is a drug that the drugees don't want to have.

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I thank you for your time, and the ability to testify with you.

DR. KIRSCH: Thank you.

Next is Cameron Muir.

DR. MUIR: Good afternoon. My name is Dr. Cameron Muir. I am a full-time Board-certified hospice and palliative medicine physician. I'm here on behalf of the National Hospice and Palliative Care Organization, and as the immediate past president of the American Academy of Hospice and Palliative Medicine.

I have nothing to disclose. I drove here from our care service area in the D.C. metropolitan area.

I welcome the opportunity to speak on behalf of the 4,000 hospice programs in the United States, the nearly 2,000 hospital-based palliative care programs in the United States, and more importantly, on behalf of our patients and the families that we serve.

Access to appropriate pain therapy

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is an important part of hospice and palliative care. We understand that many of the important therapies that are so useful for controlling pain are also drugs of misuse, diversion and abuse. We agree that education and appropriate patient selection are important, and that prescribers, dispensers and patients should all understand the benefits as well as the risks of using these medicines.

The labeling for opioids, which are key to appropriate pain care in many situations, already warn of the appropriate indications, the risks of addiction and dependence, and the dangers of misuse. In addition, the Controlled Substances Act places restrictions on who can prescribe and dispense these medications, and they place quotas on the quantities manufacturers can produce.

The public record was shared at the FDA's meeting towards requiring risk

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evaluation and mitigation strategies, or REMS, for new opioids and some existing opioids. We would urge that if the FDA deems this necessary, that they proceed with care.

If REMS are required of some but not all opioids, the danger exists that prescribers will move away from medicines with burdens attached to them, and prescribe those that do not have the burdens associated with REMS. This would be harmful to patients and their families, and could create unnecessary suffering.

Also, history would show that when it is difficult for those who would abuse these medications to obtain them, that abuse shifts to other legal or illicit drugs. Therefore, if REMS are necessary for opioids, it would seem advisable to approach the implementation of REMS as a class issue, since all opioids carry the same or similar risks and benefits.

A few additional questions to

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consider; if REMS are required on multiple drugs, would each company be required to educate and certify the prescribers, dispensers, and track the patient community? And if so, it would seem to place an undue burden on the entire system.

Since these medicines are not drugs prescribed for very small populations, as is the case in existing REMS, a system of multiple REMS would seem unworkable. Would multiple companies be required to educate hundreds of thousands of prescribers and tens of thousands of dispensers, while keeping millions of records of patients who use their specific medication?

If these tools have been measured for their effectiveness in preventing patients from being exposed to the risks of medications, if these tools have been effective in preventing non-patients from diverting and abusing these medications, and if these tools have been evaluated and found

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not to interfere with appropriate patient care, then such a system cries out for a global solution.

Governments should find a way for state medical boards or FDA or DEA to educate and certify prescribers and dispensers as a condition to their obtaining DEA registration. Or at a minimum, FDA should find a way for all companies to fulfill such requirements through one private entity.

One system, not many duplicative systems, would seem more logical. Furthermore, patient registration kept by individual companies about companies' medication would not seem to address the problems where patients are taking multiple medicines. If the individual registries are keeping track of individual drugs, we run a very high risk of not knowing when patients or non-patients pretending to be patients are seeing different prescribers and going to different dispensers.

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And we do not capture the situations where legitimate patients are taking more than one track drug, as is often the case.

Simply put, our concern is that these important medicines are used appropriately and that our patients and their families are not denied access to needed medicines. At the same time, we do not want to see REMS become so burdensome that the reverse occurs.

We urge FDA to approach this issue with caution. The solution requires a cooperative effort with all concerned. The FDA should collaborate closely with manufacturers, prescribers, dispensers, caregivers, patient groups and others before moving forward with many individual REMS that we believe are a real danger of becoming unworkable and overly burdensome on the health care system.

As organizations that provide care

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to patients and families living with the pain of chronic progressive illnesses, and the patients who specialize in hospice and palliative medicine, both the National Hospice and Palliative Care Organization and the American Academy of Hospices and Palliative Medicine stand by ready to help.

Thank you for the opportunity.

DR. KIRSCH: Next, please.

MS. BROWN: My name is Nicky Brown, and I represent the American Pain Foundation as their Director of Advocacy. I'm also a past president of the American Society for Pain Management Nursing. And I have no financial disclosures.

As a team committee member, I am a nurse who has worked with pain my entire career for of over 30 years, and there is not one day that has passed that I am not amazed at what individuals who live with pain must encounter at every attempt to find some respite, some moment or some glimmer of hope

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that their pain will be relieved.

Imagine pain that is so piercing that you can no longer hold your children. Imagine sustaining a back injury, leaving someone now to go to the grocery store just to carry a gallon of milk. Imagine having so much pain that someone innocently shakes your hand, and fiery sensations shoot up your arm, so much that you wish that it would be cut off.

Imagine going to sleep each night with great difficulty, only with the hope that when you awake, your pain will be gone and it is not. These are the faces of people with pain. There are people like you and I, but their stories are often untold.

Regretfully, people with pain continue to be stigmatized and ostracized in our nation, just like those who live with mental health disorders, substance abuse and/or addictive disease. They are judged as if intolerable pain was a character flaw

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rather than a medical problem that must be managed as we do with other chronic conditions like diabetes, heart disease or hypertension. Many on this committee and in this audience are all too familiar with the barriers that impede access to appropriate care, and it is our duty as health care professionals, regulators and as human beings to dismantle these barriers rather than erect new ones.

The pain management community recognizes that prescription drug abuse is a serious public problem in our nation. But efforts to address this issue cannot and should not come at the expense of patients with pain who are already struggling to get the care they need. We must recognize that both prescription drug abuse and the undertreatment of pain are both serious issues that must be dealt with wisely without pitting one problem against another.

Our job is not either or, it is

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both.

Opioids, like most medications, have risks as well as benefits. Not all pain is reduced by opioids. That does not mean that opioids do not offer significant value as a safe, effective strategy to relieve pain and to improve functioning in appropriate selective patients with careful monitoring.

The value of opioids have been demonstrated over decades with a utility. A balanced perspective of risk and benefits of opioid analgesics must adopt methods to reduce the likelihood that these drugs fall into unsafe hands without deterring access to those in need.

The development and approval of new formulations of medications that reduce pain that include these extended release formulations that are less easy to adulterate are a welcome advance. However, we are recognizing that knowledge of prescribers, dispensers and recipients is also just as

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critical.

The American Pain Foundation and American Society for Pain Management Nursing and others in the pain field do not hold opposition to programs and processes that increase safety or surveillance of outcomes, as long as these systems do not become so complex that it's a set-up for failure and frustration for all stakeholders.

The unintended consequences, unfortunately, will fall on those who live with pain, and that outcome is not acceptable. REMS appears to hold promise. However, there are potential problems that could be forecasted, as the previous speaker did mention, but the other issue that was not included was what about these multiple registries for patients?

You know, who is going to ensure their privacy, and who is going to deny access to those who choose not to participate in these registries? And will the pharmacy

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requirements place undue burdens administratively so that they cannot be efficient in their work and they can deter them in stocking appropriate drugs? And what impact will this have on drug abuse?

Will it help or hurt this problem? One could argue that if access to appropriate care continues to be hampered, some will continue to go to the street out of desperation. APS and ASPMN along with other pain organizations wish to contribute to solutions alongside the FDA.

One recommendation we would like to see considered is to exercise the legislative provision of the FD&C Act in U.S. Code item 5 that covers the evaluation of elements to ensure safety. We would hope that the FDA will decide to recruit a special workgroup of stakeholders for expert opinions and work on creating collaborative solutions.

These stakeholders should include health care professionals, licensing boards,

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professional organizations, industry and patient advocacy groups.

DR. KIRSCH: Thank you. Next is Fredrick Burgess.

DR. BURGESS: I'm Frederick Burgess. I'm currently the Chief of Anesthesia at the Providence VA Medical Center, and I'm a past president of the American Academy of Pain Management and Clinical Associate Professor at Brown University. And I have no relationships with any of the companies involved.

What I would like to do is present to you sort of an evolutionary story of my personal experiences in pain treatment. I started off as an anesthesiologist with training in pain, and became subspecialty-certified and board-certified in pain medicine.

So my practice over the years has been divided between treating patients in chronic pain in varying settings, from 100 percent full-time pain to percentages of

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it.

Over the years, there has been quite a change in how we've approached pain. When I first went into pain as a resident, I was actually trained at the pain clinic to get patients off of narcotics, and that's how we approached it. However, I frequently found, in view of many of these patients, that there are some difficulties. For example, I had a young patient who had sustained some serious injuries, was being treated with a modest dose of opiate, actually Tylenol with codeine, and was doing fairly well with it, but because of my training, the idea was we have to get him off the opiate and get him onto something else, so I switched him to a non-steroidal.

His pain was not necessarily any better controlled, and in fact, about two months later, he perforated an ulcer and ended up with surgery. So I began to look at the use of other agents as being potentially

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more harmful than the opiates. Around that time, we had literature appearing that demonstrated that the opiates in fact were useful; they could be used for long-term durations with good success, and began to switch more patients to this.

With the advent of the sustained-released products, we were really excited, because many of our cancer pain patients had great difficulty tolerating the brief episodes between dosing of short-acting medications. However, we then encountered difficulties with the crushing of the tablets, the rapid absorption and the substance abuse issues.

So this became a concern for us, and many people backed away from using the medications as freely. We wanted to look for an alternative, and methadone reappeared. It had been used for years for treating opiate addiction. This became another alternative that we could use, because most of us looked

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at it as being an agent that is probably not likely to be abused.

And we saw a lot more use of this product, and I personally used it a great deal, and it is a very effective pain medication, particularly with patients' resistance to many other opiates. However, with recent information coming from radars and monitoring systems, when you look at the opiates prescribed, by far, Hydrocodone and OxyCodone are the predominant ones.

Methadone is probably prescribed tenfold less, but yet it accounts for one-third of the deaths associated with opiates. So when we look at this, we realize it's not an alternative or great solution to the problem. And really, what we need are some additional choices, and I think that when you look at the products that are under consideration, the tamper resistant products, I think these are going to be very useful in managing some of our very difficult patients.

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One of the things we are seeing in the literature now is that more people are looking at patients who, for example, who do have a history of substance abuse, and surveys that have been done looking at patients in substance abuse management programs, many of these patients will describe severe ongoing pain problems.

So it leaves us a dilemma as to how we approach treating these patients, and we are kind of stuck because we don't want to go prescribing sustained release OxyCodone to a patient who has an abuse history; methadone is not necessary a good choice -- and I can give you an example where I had a patient referred to me from the local prison facility with a chronic pain problem, was being treated in the prison with methadone and was directed to me -- I initially was very reluctant to actually take the patient, but the director badgered me into it.

And so I brought this patient into

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my clinic and managed her with methadone for a sustained period. I monitored her very closely and was very suspicious about some of the behavior, but I could not pan it down.

Urine drug testing showed she was taking her methadone. Low and behold, I found out through secondary information from relatives that in fact she was taking methadone. She was going to a methadone clinic, and was selling my methadone to buy other medications, including cocaine. It was not something that I could have predicted or accounted for, so it makes us very concerned in treating this population.

So we need drugs that are not prone to being abused as easily. The products that are under consideration at present appear to fit that bill, so I would ask you to consider them.

Thank you.

DR. KIRSCH: Thank you. Next is Phyllis Zimmer.

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MS. ZIMMER: Good morning. My name is Phyllis Zimmer. I'm a nurse practitioner and have been for the last 30 years, and a faculty member at the School of Nursing at the University of Washington in Seattle. I'm past president of the American College of Nurse Practitioners, and of the National Organization of Nurse Practitioners Faculties, and currently serve as president of the Nurse Practitioner Healthcare Foundation.

Part of our role as nurse practitioners is to be an advocate on behalf of our patients. That is why I'm here today, to share my thoughts on some of the challenges we are facing in monitoring care for those who experience constant pain in their daily lives, and to discuss the issue of medication diversion. With 75 million adults suffering from chronic pain, nurse practitioners with prescriptive authority are among the providers who manage these patients.

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Managing pain is one of the biggest challenges we face in primary care. Because patients respond to pain in highly individual ways, an array of options is needed. Often, we have to titrate medications to achieve pain control. Unfortunately, we also sometimes find ourselves working with health care professionals who underprescribe painkillers because they fear the potential for addiction.

This opiate phobia leads to undue suffering for millions of people who don't receive adequate pain relief. In fact, opiates are often the most effective treatment for many patients, particularly, those with terminal cancer.

Opiate analgesics have a unique power to enhance the quality of life for people with pain. With proper pain management, patients can eat, sleep, socialize, go to work. Patients with chronic pain deserve care equal to that given to

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people with other chronic illnesses. They should be treated with dignity, respect and enough pain medication to lead a productive life.

I work with patients whose pain is not being well-managed. Patients respond to pain and pain treatment in different way. The responses may have to do with different cultural norms, family values, upbringing and individual physiologic parameters. We not only need to change attitudes about treating pain, we need a wider number of options available for pain treatment. So if one medication doesn't work, we have others to try.

About 30 percent of the nurse practitioner workforce practices in rural underserved areas, helping to care for those who lack access to pain clinics, medical centers or even good primary care services. Many of our patients have low health literacy levels. They don't know who to call when

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they are having pain; they don't understand how their pain medicine works, and they don't know how to navigate the health care system when they are experiencing escalating symptoms. We need to educate these patients and their families on how to manage pain at just the right moment, and understand how their medicine works so that they take it correctly.

Take the example of a chronic cancer pain. In many cases, the patient is written off as terminal, and I have had the experience of being called in to manage that patient's pain. The primary care provider has often under-prescribed medicine, given the rationale that I don't want to have my patient addicted -- which we need to alleviate the pain and improve quality of life not matter how months, weeks or days that person has to live.

So what do we need to do to help our patients cope with chronic pain? Don't

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ask us to prescribe fewer pain medications. That's not a viable option for patients experiencing moderate to severe pain on a daily basis. Instead, we need more education in pain management, streamlined protocols to make it easier for families, and a variety in way of medication so that care can be individualized. Importantly, we need pain medications with built-in mechanisms to guard against abuse.

Finally, I would like to address this issue of pain abuse medication. We need more treatments that will better control patients' pain without exacerbating our national substance abuse problem. If a new pharmacologic option is available that can meet both these goals, we would like to use it.

One of the biggest challenges is the incredible availability of drugs that are misused. I took care of a dying patient whose teenaged grandson had stolen her

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time-released opioid product and crushed it before ingestion in order to enhance its effects. If a new product were available that was formulated to ease my patient's pain but could not be misused by someone else, I would welcome the opportunity to prescribe it.

I'm certainly not suggesting that we are going to win the War on Drugs with a new medication that makes it more difficult to misuse certain types of opioid medications. However, if a mechanism exists that would render these opioids useless if they are crushed or otherwise tampered with, doesn't it make sense to implement this technology and maybe lessen the problem of drug diversion?

Nurse practitioners believe in a prevention model for health care services. We would rather prevent the problem then combat the problem after it has occurred. New pain medications are needed that are

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effective when used appropriately, but are rendered useless when misused. This is a critical health problem worthy of our attention. I urge you to do what you can to make this happen.

DR. KIRSCH: Thank you. Next is Charles Cichon.

MR. CICHON: Good afternoon. I'm Charles Cichon. I'm the Executive Director of the National Association of Drug Diversion Investigators. I have nothing to disclose.

NADDI is a non-profit organization dedicated to providing education to its members and the public on the issues surrounding prescription drug abuse. The majority of our members are law enforcement, but also included is a considerable population of regulatory agents, health care professionals and health care fraud investigators.

Due to the ongoing problems with drug diversion in the United States, NADDI is

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a strong proponent of the new controlled substances that would possess abuse-resistant qualities and yet still provide quality relief to the patient.

NADDI has a strong believe that the diversion of prescription medications can many times ultimately negatively affect the legitimate patient, and the vast majority of those who use controlled substances. NADDI has provided grants to law enforcement across the country, most notably to the Tennessee Bureau of Investigation to begin a statewide drug task force -- that not only includes law enforcement, but a broad utilization of education and awareness for the citizens of Tennessee on the issues of pharmaceutical diversion.

Our national conference is ending today in Nashville, Tennessee, and one of the highlights of the week was the scheduled program entitled "Teens in Crisis." This session involved a group of teenagers that

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had a severe addiction to prescription drugs and are traveling around the country to tell their story.

This program was sponsored by Alpharma, and was offered not only to our 400 attendees at the conference, but an evening program was also provided to health care professionals in the Nashville, Tennessee area.

Alpharma continues to support NADDI in its preventative educational efforts in many ways, which makes this program and others possible. NADDI applauds Alpharma in their efforts to produce a divergent resistant pharmaceutical drug that also provides pain relief for the patients.

Thank you.

DR. KIRSCH: Thank you.

Next is Lance Merrill.

MR.MERRILL: Yes, my name is Lance Merrill. I'm founder of Dads Against Drug Dealers. My flight and my wife's was paid here

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by Alpharma. I fund Dads Against Drug Dealers out of my pocket. I do appreciate the opportunity to come speak about this subject. I'm passionate about it.

Right now, there are 15.1 million Americans abusing drugs. Right now. That's six percent of our population. This is a huge problem. It's an epidemic that is sweeping our country. Unfortunately, I have seen that journey of death that opioids and heroin can bring firsthand. When you think of a heroin addict, I don't think most people picture someone that looks like this beautiful girl.

Jenny -- we buried Jenny when she was 19 years old. She, two years earlier, had gotten pain medication out of my medicine cabinet. A few months later, she turned to OxyContin, and nine months after that, she started using heroin. Within two years from the time she first took pain pills, she was in the ground. And this is not an unusual

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story.

Dads Against Drug Dealers has been functioning for two years since Jenny passed away. First of all, we started off doing a $500 bounty for people who would give us drug dealers, information that leads to their arrest. We soon found there were many other problems facing the country with drug issues.

We had problems getting police to arrest the drug dealers, and so we found that we had to help make some changes in Utah. We got a new system in Utah where the Attorney General takes tips in -- they chart it and track until they come back and get reported on. It has led to a big increase in arrests due to citizen tips. We also found a lot of citizens did not know where to turn when it came to drug addiction problems.

Our website has helped try to facilitate this. We also got a law passed that allows a citizen to take a dealer to civil court. So we have an option besides a

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baseball bat when you find out who's selling drugs to your child. I think this is a battle we've got to face on many, many fronts.

We are in an epidemic state. Right now, the statistics that graph opioid use in the United States say that heroin is at a static point. However, if you look at the CIA numbers of opioid production, the major country that supplies most of the opium and heroin to the United States between '06 and '07, their production numbers were up 61 percent, and that's being consumed in the United States. Heroin use is not static.

Another statistic: in '06, there were 91,000 people who used heroin for the first time. That same year, there were 533,000 people to use OxyContin illicitly. We are facing an epidemic that we've got to face. There's a need for these opioids, but there's a huge problem. In the Middle Ages, we saw the Black Plaque kill millions of

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people.

And in the 21st Century, we are facing a wide epidemic. And we will see literally millions, if not hundreds of millions of people, die because of opioid abuse. We as a community here in this room have the power to change this.

We can close the bridge between opioids and heroin. The baby boomers -- we all knew heroin kills and -- everyone seemed to start with marijuana. We all know people that had addiction problems, and now they're upstanding citizens.

The drugs of today are different. The entry level drug of today is not marijuana. It's opioids. People are starting on the road to heroin. They are starting with the drive of opioids behind them. And after they can no longer afford the pharmaceutical opioids available, they do turn to heroin. For the last five years, more than twice as many people in the United

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States have died from drug overdoses than from automobile deaths. That's a staggering statistic. Everybody is talking about wearing seatbelts and all this automobile safety. Opioids alone killed more people in the United States than automobiles for the last five years. Why isn't everyone concerned about this?

We need to close the fatal bridge of opioid addiction, and the opportunity we have here to have a tamper resistant opioid that makes it available to people what is needed in pain but at the same time prevent the problems -- it's a road we've got to keep open, but a bridge we've got to close.

I thank you for the opportunity to address this.

DR. KIRSCH: Thank you.

Next is Gwen Herman.

MS. HERMAN: Hi. My name is Gwen Herman. I'm the Executive Director of Pain Connection, and the Maryland Palliative Pain

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Action Leader with American Pain Foundation. I have no financial disclosure.

Esteemed committee members, I'm a Maryland state leader of the American Pain Foundation's Power Over Pain Action Network, which is a grassroots network of volunteers to help people with pain, caregivers, and health care providers. As a state leader, I help to raise public awareness, help people advocate for themselves and provide information and resources.

I have my undergraduate and graduate degrees in social work. I have worked in the field for over 30 years with many different cultures, all age groups, in the field of alcoholism and addiction, physical and sexual abuse. I'm also someone who lives with chronic pain.

Thirteen years ago, I was rear ended in a car accident, and in a split second, my life changed. The accident left me handicapped for chronic pain in the neck,

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shoulders and legs.

I was thrown into a world of medical decisions of which I knew nothing about and began searching for information about cervical disks, myofacial pain, [inaudible] conservative alternative treatments and various medical procedures. I was frustrated by the lack of awareness and understanding the chronic pain by medical professionals. The pain changed my personality.

I became short tempered, isolated myself, became depressed, couldn't focus, dropped things all the time, and cried everyday after my children left for school because I didn't know how I was going to make it through another day with the pain. My friends faded away. They couldn't understand why I couldn't move on. My husband took over my chores, which made me feel even more helpless. I was put on many medications. I had horrible reactions from most of them.

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Doctors wouldn't return my calls when I had a reaction from the medications. I had disc surgery and a hip graft which helped some, but still I had pain. I had a (inaudible) operation which helped, but resulted in nerve damage. I was still in pain. I was prescribed medications that were denied by my health insurance. I was told the pain was in my head when the doctors couldn't resolve it and I wasn't getting better, or was told I just had to live with it, which made me feel suicidal.

I (inaudible) through this nightmare. I didn't know there was some (inaudible) until I went on mine. It took at least 20 medical professionals before I was finally diagnosed with fibromyalgia. I'm now on disability. I now have a doctor who understands and works with me. My treatment plans consist of medications for my pain and to help me sleep at night. Herbal remedies, supplements, massage therapy, acupuncture,

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trigger point injections, guided imagery, meditation, and completely changing my lifestyle.

After intervention, my migraines became more manageable and I started a chronic pain support group. After three meetings of the support group, I saw the (inaudible) people and founded Pain Connection Chronic Pain Outreach Center, Inc. in 1999. We teach members how to normalize their pain, deal with losses due to pain, explain how pain has changed their personality and their relationship, how not to live in the past and accept how the body has changed, and then to recreate who they are with their body as it is now.

We teach guided imagery, meditation, breathing techniques to help lower the pain level. There are stories of medical professionals being condescending, there are few who listen to patients, and patients suffering through long waits.

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Many patients are mistreated and mistrusted and ignored because of the pain. The invisibility of pain is what makes it so baffling to others. I mean, I look fine today. You have no idea what my pain level is. I can go home today and maybe tomorrow I'm not going to be able to do anything.

They tell me to exercise and exercise makes me worse. They do not realize that living is my exercise. I have pain during the day and I do not sleep well at night. Getting up in the morning is exercise. Taking a shower is exercise. Getting dressed is exercise. Now it is to receive the proper medications for pain patients. I have heard many stories from members over the ten years. One went to the pharmacy to pick up his OxyContin and the pharmacist asked to see his medical records before he would give him his medication.

A woman was only given ten pills of her medication because insurance would not

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fill the prescription. A woman's doctor prescribed a specific medication, the pharmacist gave her something else, and she broke out in hives. Another woman who has Rex syndrome was only given six pills of Klonopin. A doctor told one man that he was going through male menopause and he had several broken ribs.

On the other side, there are families of loved ones who have died from OxyContin and other pain medications. There losses are great and my heart goes out to them. I was (inaudible) to know the important of appropriate treatment planning. I'm appalled at how some physicians freely distribute medications without doing a psychosocial evaluation. Doctors need to be educated about chronic pain and how to treat it. Doctors need to be educated about the differences between tolerance and addictions.

Patients that have pain and have addiction problems need to be treated

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properly by having a contract (inaudible) receiving counseling and be monitored with dignity. In my ten years of running a support group, the majority of chronic pain suffers do not have problems with addiction. The majority should not be denied appropriate treatment.

DR. KIRSCH: Thank you.

Next is James Broach.

MR. BROACH: Thank you. My name is James Broach. I'm the Executive Director of the Reflex Sympathetic Dystrophy Symptom Association. We are a national organization dedicated to promoting awareness of Complex Regional Pain Syndrome, or CRPS. We are also funding research for more effective treatments and a cure. I have no financial disclosures. On behalf of RSDSA's 7,000 members, I'm speaking in favor of the drug application for EMBEDA.

First, I want to provide you with a snapshot of our constituency. In 2005, RSDSA conducted a web-based survey of people with

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CRPS in conjunction with Johns Hopkins School of Medicine. Abstracts from surveys are on our website www.rsds.org. 1359 individuals completed our survey. The average durational disease was greater than three years.

Average pain score of respondents was 7.9 out of a scale of 10 as the worst pain possible. Sixty percent rated themselves as disabled; most significantly, 47 percent had thoughts of ending their life, 15 percent had acted on impulse -- some of them twice.

The rate of suicidal ideation in CRPS is 250 percent that of other chronic pain syndromes. Pain psychologists at Case Western stated it well: "There are no pain conditions so associated with desperation that amputation is an attempt to relieve pain are not unheard of."

To strengthen my testimony today, RSDSA just completed an on-line survey regarding use of opioids and in people at

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CRPS, and specifically, what this population and their caregivers think about abuse-deterrent components in opioids. The survey consisted of seven questions on the topics of opioid use, physician prescription of opioids and abuse-deterrent components.

The survey was sent via email to 5,000 contacts on our listserv, and 513 responded -- over 10 percent. Out of the 513 responses of people with CRPS, 422 use opioid medication for the pain; 49.3 percent of this group take a sustained release opioid to manage their pain; 87.1 percent would not be deterred from taking the opioid if it contained an abuse-deterrent component.

We received many comments similar to this reply, "Patients with true pain don't want to get high. They just want their pain gone."

Respondents were about split, 44 percent yes and 55 percent no, on the issue of whether or not their caregivers

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would feel more comfortable if they were taking an opioid that included an abuse-deterrent component.

Our organization RSDSA strongly endorses this new drug application of EMBEDA.

Thank you.

DR. KIRSCH: Thank you.

Next is Catherine Walker.

DR. WALKER: Hi. Thank you for having me. My name is Catherine Walker. I'm a pharmacist, and I completed specialty residency in Palliative medicine and I'm a clinical specialist at a hospital in downtown Baltimore. I'm also an associate professor at University of Maryland School of Pharmacy.

I don't envy your position today. I think this is a really tough decision, and you really need to carefully balance the news of clinicians, patients, and really the implications of society as a whole.

However, as a clinician and seeing pain patients every day and most of them at

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the end of life, I can really relate to this. In some ways, I feel like a lot of the decisions I make every day, I'm forced to consider all of those things as well.

I guess I'm supporting this application because I feel like I need the tools to do my job well. We find ourselves in an untenable position with chronic pain management. We have 76 million Americans with daily chronic pain. This untreated pain crisis is more than problems with people that have diabetes, coronary heart disease and stroke, and it is more than the cancer population. It's a huge issue.

Access to pain relief has been promoted as an essential human right by many international agencies, and I wish that I could tell you that in America, this was true. However, it's not true for everyone. Of the patients I see in pain every day, most of the prescribers feel that treating their pain is related to diversion, in my

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experience.

I work in the inner city of Baltimore, but I don't think that I'm alone in this dilemma. I see three challenging issues in most of the population at hand.

First is that this diversion is not only for prescribers, but also patients fear diversion as well. I can't tell you how many times I've been consulted to educate an elderly patient, often at the end of life, with severe pain that's debilitating, and they're afraid of taking their medication because they don't want to become addicted, or they are afraid of having the medication in their household because they are afraid they will be harmed from the medication being stolen from them.

Keeping pain patients from accessing appropriate therapy. I feel that we should be doing all we can to protect both the patient and the prescriber. If there was something we could offer these patients to

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reassure them that this medication was at least considered and some safeguards were in place for tamper resistance, that would be valuable just in and of itself.

The second issue I think we have to recognize about drug abuse and diversion as many people have mentioned today is a problem. Sadly, the diversion of opioids has worsened the fate for chronic pain patients in America. From the survey done, 90 percent of people using pain medications non-medically originated from a legitimate prescription, and 70 percent of those were from diversion, and only 18 percent of those patients actually got it from a physician.

So diversion is a key issue, and while some of these patients that use the diverted medication are using them orally which this medication may not have as much of a role in protecting those people, but there is a significant population that diverted medications intravenously. And I see an

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important role for this drug to prevent the high that they are looking for and to combat that aspect of diversion. I think this agent can help negate a key portion of the diversion picture, and I think we need to protect some people from themselves.

Thirdly, the patients with a history of abuse, I see them all the time. This is a huge population of the pain patients I see are the patients with a history of abuse and legitimate pain. I think they have very limited options, and they are often left untreated or poorly managed.

One of the main reasons it is mismanaged I think is that there are no other options to reduce the risk for this class of pain medication. Countless times, patients with remote substance abuse will report turning back to heroin to get some relief for their pain. That's how dire this situation is.

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EMBEDA would offer some protection against diversion by providing a barrier to tampering and getting this high that they are looking for, and give some reassurance to prescribers so at least they would attempt to treat these patients' pain. Every other opioid formulation is able to be tampered with fairly easily to produce this high, and therefore, they are all valuable to abusers. EMBEDA offers us some hope in this situation, and hopefully, we will be able to help balance the high stakes problem of treating pain appropriately without contributing unnecessarily to the problem of abuse and diversion.

As a final comment, as a specialist in pain management, it's hard to believe that we have not had medications like this in the past. It's difficult to imagine that the technology we have today, that we have actually allowed pain medications that are so necessary to be so easily tampered with in

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the first place. I think it's a moral, ethical and imperative that you give practitioners the tools that we need to appropriately treat chronic pain patients.

Thank you.

DR. KIRSCH: Thank you. The last speaker is Mary Benson.

MS. BENSON: Hello again. I'm Mary Benson, and I have nothing to disclose. First, I want to express my gratitude to this committee for allowing me to present again today, and for the opportunity to remind this audience about the epidemic of pain in America, and the nightmare struggle that pain patients must endure to get effective pain management.

As the Director of the American Academy of Pain Management, the largest professional pain management organization in the country, I'm here again today to speak on behalf of the board of directors, the 5,000 clinicians who are members of our organization, the 76 million Americans who

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suffer with chronic pain, and the approximately 10 million patients who are currently taking prescribed opioid analgesics to alleviate it.

Although they can make an integrated approach to pain management, (inaudible) both are (inaudible) alternative approaches; we recognize that opioid analgesics remain the most effective medications for relieving pain, restoring function, and improving the quality of life for millions of people.

Yet misunderstandings and fears about abuse, diversion, addiction and regulatory scrutiny run rampant among prescribers. We know this not just in studies. We hear it directly and regularly from our members, and it's the most requested topic in our annual educational needs assessment. Unfortunately, we also hear -- for many of these clinicians that they are no longer prescribing opioids, even

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then they know that these medications would provide the most effective treatment. So who is bearing the burden of this?

Yesterday, we heard the powerful and heart-wrenching testimony of (inaudible), a young wife, mother of three. She said, "Even with health insurance, even with the top paying specialist as my physician, even having a doctor who was willing to prescribe opioids, even with (inaudible) and my ability to pay for my prescriptions, I have found myself again and again powerless to obtain the medications that I need."

The reality for many pain patients, myself included, is that the burdens of risk management are both directly and indirectly on our shoulders. I quoted her because I was so moved by this and realize that it really is the patient that is our concern.

For this reason, I'm here to briefly discuss two issues that affect our members. The first is to make the widest

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variety of pain medication treatment options available to clinicians, which includes (inaudible) abuse-deterrent opioids. Abuse-deterrent opioids may increase the likelihood that clinicians would prescribe these medications to legitimate patients. These medications also represent the technology that in fact has been long awaited by prescribing clinicians, pain patients, law enforcement, and by the FDA.

The second reason for my appearance for today is our concern about risk evaluation mitigation strategies, or REMS. We acknowledge and applaud the FDA's efforts to ensure that opioid analgesics are available for chronic patients, and we acknowledge its concurrent efforts to confront the problem of non-medical use of these medications. But while we recognize the need for risk management, we are concerned that the multitude of requirements for prescribers, pharmacies and patients may

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prove to be so complex, so costly, and so time consuming that they in and of themselves will prove to be a significant barrier to optimal pain management.

We have seen (inaudible) states where there has been prescription management for pain, but prescribers were more likely to give less (inaudible) to medications and (inaudible) medications had lower risk but are not as effective. Such a strategy may reduce diversion and abuse of these medications, but an unintended and far worse serious consequence may be that (inaudible) immoral, unnecessary and unacceptable health crisis.

And, of course, that's the only treatment of pain. In addition, rather than the product-by-product approach the FDA is currently employing, we suggest the (inaudible) REMS claim. They are the same standard tools would be used for all products with (inaudible).

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Finally, we recommend that the FDA bring together a panel of interested stakeholders, such as practitioners, pharmacists, professional organizations and patient advocacy organizations, to form desirable outcomes and how they would be measured, and to thoughtfully consider and address the most effective way to meet the dual objectives of ensuring access to the full range of necessary pain medications while reducing abuses.

DR. KIRSCH: Thank you. The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience.

The Committee will now turn its attention to address the task at hand, which is the careful consideration of the data before the Committee, as well as the public comments.

It's also time for a break. We will now take a short 10-minute break. My

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clock says five minutes after the hour. So we will reconvene in ten minutes, at 15 after the hour.

I would like to remind the Committee members, please remember that there should be no discussion of our meeting topic during the break amongst yourselves or any other member of he audience.

(Recess)

DR. KIRSCH: The next portion of this meeting, we wish to discuss and try to find some answers to the FDA. We have a total of three questions, each with two parts, that we would like to address.

The first question, like yesterday, is for the members of the Committee to discuss the adequacy of the tools we have to assess the impact of the novel opioid formation on abuse, misuse and diversion of the products in the community.

As in the other earlier session, if you have a comment, please raise your hand,

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but please don't speak until you get recognized.

Dr. Lorenz.

DR. LORENZ: I think one issue that comes through certainly with time limits, but also it's important because I'm not sure that it's fully addressed in the examples of the REMS that we have seen -- the necessity of monitoring REMS outcomes for patients with serious chronic pain, as well as understanding their effects on diversion.

And I think another aspect of that is ensuring that it's empiric and methodologically robust. And I know we talked about this a bit yesterday, problems with certain ways of monitoring it that don't allow causal attribution, and where there may be hot methods for dealing with that in terms of evaluation, I think -- again to stress something what maybe was mentioned in the passing yesterday -- is the importance of developing REMS tools that allow for that.

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And particularly because of the concern about the potential complexity of strategies that involve the patient-provider interface, allowing for a robust population approach are certainly important. So I think the other issue that may be worth reiterating is thinking about aspects of the REMS strategies that focus on post-distribution supply, and monitoring and limiting supply in appropriate but non-invasive ways potentially such as (inaudible) even though that doesn't fall under the regulatory authority, because of these concerns about potential impacts on access.

DR. KIRSCH: Can I just ask you to, if you can, expand a little on what types of tools you might think we could add to this process?

DR. LORENZ: Well, I don't want to suggest particular systems or places, but perhaps capture populations where the denominators and numerators can be linked. And I realize that there may be substantial issues

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that need to be addressed in the context of sorting that out, but certainly systems of national scope exist where the data is available and might facilitate the kind of monitoring you're looking at --

DR. KIRSCH: Are you sure you don't want to say what systems you're referring?

DR. LORENZ: I'm sure.

DR. KIRSCH: Maybe we can talk later.

DR. LORENZ: We can talk later.

DR. KIRSCH: Dr. Nessmeier?

DR. NESSMEIER: This is just a general comment. It's not really my area of expertise, but I found it rather disconcerting that there really are no studies regarding the feasibility or the efficacy of any REMS program, which is unfortunately, but the absence of evidence is not necessarily evidence of absence of efficacy, and I think we need to start somewhere. So although it's not my area of expertise, I would agree with some of the calls for consistency in REMS programs for the opioid class, and I think

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it's something that we will need to address.

DR. KIRSCH: Dr. Kerns?

DR. KERNS: Keeping in the theme about the REMS, I think I would agree with the comments about developing an evidence base, and in that context, I would encourage the developers of some strategies to consider oversampling two populations that I think deserve special attention. One is those that are known to be vulnerable in terms of undertreatment for pain; minorities, people with mental health, comorbidities, people with HIV-AIDS, to name four groups.

The other population is those that are known to be specifically at risk for addiction, abuse and misuse, which is people with a history of substance abuse.

DR. KIRSCH: Dr. Denisco.

DR. DENISCO: Just a comment. Many of the tools that have been discussed today, epidemiologic tools, surveillance for diversion, are funded by Sampson -- National Institute on

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Drug Abuse, and I don't know with the current economic situation that exists if we can count on or necessarily be assured that these will continue to exist, and if there are modifications or changes made in these surveillance systems, that back-ups will have to be developed to adequately assess the impact of these new medications.

SPEAKER: The methamphetamine crowd is pretty resourceful. I would like to address the issue of abuse. The methamphetamine crowd has developed laboratories that seem to be appearing in peoples' basements and warehouses. When we talk about abuse, we talk about how easily you can extract the opioid from the medication. The comparison should not be in terms of either you can crush the pill or you can dissolve in boiling water or other commonly available substances, you should always compare how easily can the opioid be extracted in terms of how difficult it is in comparison with the methamphetamine laboratory.

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And that should be the comparison in terms of the abuse.

DR. KIRSCH: Dr. Rosenberg?

DR. ROSENBERG: There is one aspect of this conversation that is very hard for me to imagine, but I would like to try and get my hands around it somehow, and that would be how to determine how much medication that's leftover from patients that have either died or have stopped needing their pain medication or they keep extra in reserve -- if we could get a sense of how that's being regulated, and if there's a way that we can encourage that behavior not to occur, given the public health concerns and the evidence that we have that a lot of the diversion is occurring from the families at no fault of their own, but at the fault of the people who take it from them.

So a tool to try to work with that particular parameter would be very helpful, and I'm trying to imagine how it we might be a management, get about that information, but

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that information would be very helpful in perhaps seeing a way to reduce diversion.

Yesterday, I can't remember who it was, but one of the speakers did mention that a lot of the federal agencies are thinking about doing this, and the problem has been the current regulations under the Controlled Substance Act don't allow return of drugs back into the cycle that was set up by that Act, so we have to figure out legislative ways to change that.

So there's a lot of discussion going on about how to fix that problem and create a system where drugs can be returned at death or when there is excess product available.

DR. KIRSCH: Dr. Wolfe?

DR. WOLFE: Take out novel opioid formation and substitute the impact of opioids on abuse, misuse, diversion -- I'm doing this simply because I think that there's a huge amount yet to learn from the opioids that are

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out there.

Dr. Rosenberg's question about obviously applies to opioids that are out there -- doesn't need a new novel opioid to try and answer the question. I think that short of some hard to imagine miraculous tamper and abuse-resistant product, if anything gets approved, it is going to be closer to the spectrum of what is out there right now, and I think there are certainly people who have at a local level at a national level done some evaluations that are helpful in trying to curb what is going on right now.

And I think those evaluations carry forward and will have a much greater impact on the total amount of (inaudible) drugs, abusing drugs in other ways, and very incremental at best addition of a novel formulation, because I think we have much more to learn about this, including the risk management strategies for existing opioids.

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I mean, it's not as though there's going to be a hugely different risk management strategy for a new opioid if there is one than what there is. I think that there is a lot of work to do, and I hope it gets done. I mean, a lot of it being done right now, and I think people are overestimating the magic of the novel formulation as opposed to the much harder work and much more important work which can affect the other 99 percent of opioids that are already out there.

SPEAKER: I just want to make one additional comment related to what I said earlier, which is what the companies can institute a buyback program for their drugs. That's one way to get unused drugs back in the system. Only one group that I know of who has done that so far from opioid and they have not actually activated the program. They just have it as something that's in waiting.

DR. KIRSCH: Dr. Pelosi?

DR. PELOSI: If the issue is general

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tools that are potentially available to monitor (inaudible) I think we had a better discussion yesterday when someone put forward more options, more alternative ways of monitoring it than (inaudible).

I thought that they were described today as more show in substance, and I think it's kind of annoying to be showing pictures of students in a high school computer class suggesting that there is some sort of high tech real time emergency response to the problem and correct it. It's somewhat how to interpret the data from the substance abuse treatment programs, (inaudible) just a suggestion maybe put some sort of mark or chemical in (inaudible) can be detected on toxicology so we can see when it's present in the data.

DR. KIRSCH: Dr. DeWit?

DR. DeWIT: I just have a couple of minor comments about this question of people having their drugs around for a long period of

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time. Certainly, there could be more education to advise patients and family members to get rid of unused medications as soon as possible. I've never seen any sort of public information of that kind. Similarly, there could be a shorter expiration time or a time limit in some way on the viability of the medication -- those would be solutions to the questions of this issue of drugs being around and available for periods of time.

DR. KIRSCH: Mr. Yesenko.

MR. YESENKO: I go back to the National Opioid Safety Course. How many opiates does Alpharma currently produce?

DR. STAUFFER: We just make one opiate. It's morphine and the formulation KADIAN. So it's long acting morphine for chronic pain.

MR. YESENKO: I just find it amazing that there's never been a national opiate safety course in place, and so I would like Sid maybe change the first question to discuss the

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inadequacy of the tools we have to assess the impact of the novel opioid formulation of abuse. That's my only comment.

DR. KIRSCH: Dr. Lasar.

DR. LASAR: I'm really struck between the differences between the data presented yesterday and the data presented today, given that it seems like some things were accounted -- it's I'm particularly stressed by -- that is early releasing drug, and another sort of disclaiming in today's presentation, and I think this was being talked about a little more yesterday, was why there wasn't a battery of tools to help us assess the ability to tamper with the product?

But one could be struck by the sort of positive things of yesterday's testimony and some of the positive things about today's testimony, but that they didn't seem to overlap very much, and so I was left with trying to assess that as a whole.

And so I think when trying to

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assess a product and trying to develop one of those different tools and assessments that need to be done for all drugs given the differences between specific drugs involved versus the formulation. I think we're going off wave and would sort of like to figure that out today, but I certainly was struck by the differences between the two days' presentations.

DR. STAUFFER: I would note that in these applications there's complete information that the pharmacokinetic profiles of the drugs which pieces of that the companies choose to present is made perhaps different.

SPEAKER: I've been struck by the comments that Dr. Lorenz and earlier Dr. Kramer made and several public speakers about the need to have commonality in one's processes. I have to look for commonality in assessing what are the important tests to do this to see whether something is (inaudible) tamperproof that we can challenge or look at from completely different

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companies and different products. I wonder if Dr. Kramer would want to add to what you said before or (inaudible) and have a standard in the community.

DR. KRAMER: I'm not sure how much more I can say. But I think if you think about it from a perspective of the individual practitioner, obviously, the educational component as we just heard is (inaudible) products and there's no reason to have individual educational programs. I think practitioners are looking for an integrated source, an independent integrated source, of information on alternative choices. And I know that the FDA is in a very difficult position to write some sort of integrated guideline for the practice inclusion.

Maybe it would, maybe it wouldn't, but I could even imagine a collaboration -- free associating now -- but maybe a professional society with response to or come up with a description of the

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alternative treatment options and the pros and cons that wouldn't be presented with the worry that it came from the marketing department of the sponsor company that is putting together this packet, and I'm just really worried with the way it is right now that we're going to see all these packets of information, and there's skepticism about the objectivity of it.

SPEAKER: And let me respond to that. I think we are all on the same page here. There is no question we agree in both areas that there should be a standard set of tools to look at how to assess the abusability of a product, and there should be a standard set of tools to look at how whatever those features are that would be approved for products actually impact the community. Far better than multiple ones in terms of the clinical setting. So the question posed to you today was what should the components of those tools, and what should those various pieces be that go into creating this

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best practices for assessing feasibility and for surveillance of usability. And I would like to say that I think we've heard a fair amount of useful information in that regard today.

DR. KRAMER: If you're saying that you're looking for information about the components, maybe we should just go through that, because if we've already identified that there is the general educational component that was already launched in terms of all of the information we got presented to us today as well as yesterday in terms of the risk of abuse.

So people have said that physicians are not adequately trained in this area, so that's one component that could be provided. But then a guideline for physicians treating pain patients in terms of the alternatives I think would be another type of component where you're really providing the information about integrating information across multiple products for physicians, and I think that should be another component.

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DR. KIRSCH: Dr. Lorenz.

DR. LORENZ: This is a little bit of an out and about kind of comment about how education materials can be perceived as very important one, especially have them accepted by the professional community. One issue that's important too in thinking about this is talking about productive change, in that I think strategies to improve care ultimately and reduce diversion and risk to patients are ultimately about quality improvement, practice improvement or practice change, and so part of the challenge getting beyond a program it doesn't make a difference (inaudible) making sure that it's empiric and grounded is actually, honestly, increasing knowledge in this area.

Part of what is needed is a bit of an agenda, frankly, for what's lacking what we understand about REMS programs and about translation research in terms of improving clinical practice. So a workable framework for what one's intended to do and where the

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gaps lie would be helpful.

DR. KIRSCH: Dr. Rosenberg.

DR. ROSENBERG: There are a wild variety of pain guidelines to talk about how to administer chronic opioid therapy. And they are remarkably similar. They talk about not using chronic opiate therapy in the substance abuse population. They talk about various medical conditions that you should not use opiate therapy for. But in fact most of the problem patients that we're talking about here today are those who fall in the gray areas of the guidelines or in areas the doctors decide that in the interest of wanting to help the patient, trying to do everything possible to try to relieve their pain, they will choose to bend the rules a little bit because for the vast majority of patients, chronic opioid therapy is not controversial.

It's just for some of the small number of them with a very diverse (inaudible) that it becomes more difficult.

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So if guidelines for chronic opiate therapy exists by numerous sources, but the question is, for the very difficult patients, how we can better serve them and society, and that is going to require a lot of expertise and that is very difficult for many primary care physicians who have 17 minutes to see their patient and try to work with them.

So a lot of these ideas about coming together with a common package; I think that's an educational package. That's easy. It's been done. We could pick three societies, put their guidelines together, they might vary about whether or not they recommend a drug screen. Absolutely not.

And some of them would vary with do you require a opioid contract if you're going to be prescribing medication for more than three months or six months, but these are small points, but they are very similar. The guidelines are very similar and I don't think it will be hard to pick a standard one if you

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really wanted to.

DR. KRAMER: So I guess the question then that I would like to ask is would you perhaps suggest ways we could get physicians to read these guidelines to accept the guidelines, endorse them or to perhaps commit to following them and how do we do that? So there are guidelines that exist, there are programs that are proposed by the company; what do you do to actually get the operationalized?

DR. KIRSCH: Dr. Pollack.

DR. POLLACK: I have two brief comments. I wanted to address Sharon's question, but the first was to agree with Dr. Rosenberg that there is a good set of guidelines with the exception of that very difficult patient -- well-recognized; despite what we've heard today, physicians out there who believe that extremely difficult group of patients really shouldn't have chronic opioids.

The chronic abuse or recovery patients. It is definitely a little bit of

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controversial in that small group of patients. But I might suggest that you want to consider something that the ASA has done as far as task force. The way those guidelines are established in the small group of people and work on a guideline with an epidemiologist for a couple days and then those guidelines are taken out to a variety of different meetings with stakeholders, people that are generally physician groups that might be involved and there's opportunity for public input in those different groups. And that does seem to at least within our small society get more input in that kind of guideline.

DR. KATZ: My question isn't how do we establish guidelines. My question is once the guidelines are established then how do you get the buy in?

DR. POLLACK: Right. And that's part of the buy in is taking these very public forums and you present the guidelines and people have

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opportunity for input and I'm sure it's not a perfect system but then they are voted on and in this case it's the House of Delegates of the American Society of Anesthesiology.

SPEAKER: The problem here is we are talking about every general practitioner, internist family practice in the country.

DR. KIRSCH: Dr. Brull.

DR. BRULL: Thank you. I wanted to echo and perhaps follow-up on some of the things that have been said. I think that we all feel that that education is commercially-driven. As I look around the room, I think that one of the strengths of these advisory committees is that we have so many people with various expertise and so many different areas. If we leverage that to our specialty societies and I will take that -- your question was how do we implement this? I think that as long as we have the specialty society buy-in and as long as they get recognized as guidelines for practice, I think they will become really universal, and it's the

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same guidelines that pertain to management of chronic pain by the American Society of Anesthesiologists and the American Academy of Pain Medicine and all the others, then the document can be one document to which society subscribes, and they form into guidelines.

SPEAKER: As long as the members are on the Committee who have developed the guidelines are from multi-specialties in a variety of groups. An example is the American College of Cardiology. Particular guidelines pertained to preoperative care and certainly anesthesiologists, family medicine, internal medicine, surgeons all follow those guidelines because they have gone through the process that you suggested.

SPEAKER: We do appreciate what you all are saying, and you all are specialists and have experience with this, but just keep in mind that what you're talking about is every physician on the front and primary practice is prescribing these medications and it's not a

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matter of implementing some type of guidelines in that it's a matter of forcing that they attend to them and that they follow them and how do you enforce it? How do you ensure that its been enforced? That's the problem when dealing with that large a group of professionals and that varied group of professionals.

DR. DENISCO: From the discussion I've heard, the problem with all of those guidelines is they are not evidence-based. They are consensus expert opinion guidelines. They do not carry the full weight of the evidence base. And they're the best we have right now. There are studies that are underway that we should see some significant major publications in the next couple of year that are from what I've been privileged to see so far are going to go against the common knowledge that we all hold in those guidelines based on large population studies of three percent of the U.S. population.

So I think we are going to see a radical change in our thinking on this topic

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based on the evidence and not on an expert opinion. And without that evidence base, you're not going to have the authority that it will be accepted and go into wide stream medical practice, because whenever one person does something one way, the other -- there's no evidence to balance it out to make a convincing argument.

So when the evidence base exists then it becomes a variety of ways, including medical regulations and so forth. At that point in time, it has the weight and the authority to become implemented as a "standard of care" and is much superior in weight to expert opinions.

DR. KIRSCH: Dr. DeWit?

DR. DeWIT: We've been focusing here with the discussion mostly on education REMS and I'd like to grab your attention to the post-marketing part of it. We are all anxious to try new products and test them out, but one of the things that holds us up in our enthusiasm

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is that there may not be a system in place to detect a problem quickly once the job is marketed. I think if we could agree on timely surveillance method, then it would be much easier for the FDA to agree on taking a little bit of a risk with a new formulation if there's some assurance that the problem would be detected quickly.

DR. KIRSCH: Dr. Kramer.

DR. KRAMER: I would like to address Dr. Rappaport's question about how we would actually get doctors to read guidelines. First of all in timely response to some of the other comments as well. We've done some research Therapeutics, American College of Cardiology, American Lung Association, guidelines that do address the statement about evidence base. It really addresses the fact that even if you had the fear that everything (inaudible) not based on expert opinion will surely fall away from a situation, you get there just because there are huge gaps in evidence. The fund mechanism to

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answer a lot of the difficult clinical questions that practitioners do are really not there. Things for developing new products. But when you start talking about (inaudible) it's really obvious we're needing evidence and all the other questions that we have so I just wanted to make that comment.

But we've also done some study about how practitioners respond to guidelines. One of the things that's happening as the level of uncertainty increases with any particular question in the guideline, the guidelines get longer and longer because it's hard to explain the recommendations when there's not definitive evidence. So we had a situation in cardiology -- full guidelines were pages long. And even the extracted (inaudible) are 21 pages long. Take a family practitioner in their natural day at work and they are not going to be reading these guidelines. So the first thing I would say from that long

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introduction is if you want family practitioners and all the people on the front line to use these guidelines, they have to be condensed to the core message that is most important, number one. I'm also just thinking off the top of my head but every doctor who prescribes a narcotic has to have their DEA number on a regular basis and when I have to get my IRB certification renewed, I have certain modules I have to do and if I don't do them, I don't have IRB certification anymore. So I would hate to even think about another requirement, but there are ways to get people to do things if it's that critically important.

And then, secondly, I omitted something really important when I spoke earlier. It's fortunate Dr. Lorenz got at it. Any component of any risk management program you put in place has got to have the evaluation piece in terms of what the impact of it is, a broad -- and there shouldn't be

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any REMS program in place that doesn't have the evaluation. And to the question of surveillance after these things get on the market, I think you could look at some of the ideas being put forward in the initiative in terms of active surveillance because the problem is we don't have numerators and denominators and we can't assess these things if we don't have both but with some of the proposed ideas with Sentinel, I think you could get the--

SPEAKER: Let me just make two clarifications. One is with Sentinel that, yeah, we are definitely thinking about that in our Office of Surveillance and Epidemiology is keeping a close eye on how we can employ that initiative in this area.

For just again to clarify the issue of timed registration to education and how to use opiates and treat pain has been discussed for many years and it falls under the authority, the registration, under the

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authority of DEA and the Department of Justice and I can't really speak to why it hasn't happened.

DR. KIRSCH: Dr. Lorenz?

DR. LORENZ: On the issue of guidelines. I think the question about how to make guidelines effective, in fact, for me guidelines should be prioritized -- consideration of tools that are potentially at your disposal. I guess when I made a comment, that is actually what I meant.

Guidelines are the effective tool. Part of the thinking needs to be about what REMS is intending to achieve, about the range of tools that at our disposal and effecting practice change, thinking about how drugs like this strategically deployed to either (inaudible) that may be more effective than anything we're using now in areas that we have gaps in knowledge or applied to already effective strategies infrastructure that we need to attribute and think more globally

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about this problem. So the question about guidelines is very legitimate but I guess I want understanding, and that's where I'm maybe lacking some understanding myself.

SPEAKER: Let me just reiterate that as I said earlier. This is the infancy of REMS. This law was only passed the end of the previous year and it's still being sorted through, so yeah we are here today to get more information from you all, from the companies, from the open public hearing speakers, to help us sort through all those things and figure out what needs to be in REMS if we're even going to have them for these products.

DR. KIRSCH: Dr. Rosenberg.

Dr. Wolfe.

DR. WOLFE: I think it's advertising. I mean, if OxyContin was that dangerous and is dangerous, maybe it would be off the market. But the number one culprit, number 2, 3,, 5, 6 and 7 and the reason for the $650 million criminal penalty was misleading advertising

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promotion. And I think once they realized what the company was doing and withholding, FDA says chronically and they are absolutely legally but we regulate drugs, not doctors (inaudible) authority that is to force or be able to get companies to put in these programs, but it's the company that is being regulated, not the doctor. The doctor in too many ways is being regulated by advertising. If you ask what is the name kind of information that most doctors -- Dr. Rappaport when we're talking in terms of numbers, practitioners, general practitioners, internists and so forth, they are heavily around by advertising and promotion by the companies. So I think this whole REMS idea, which is an excellent idea and it's long overdue to have the authority, it still does not put FDA in the position of regulating a doctor's behavior. That is up to state medical boards, it's up to the DEA, and to send organizations, so I think that REMS we still have to focus heavily on advertising promotion.

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Any company that wants to develop, as I hope they will, a product that is novel and has significant benefits over the existing products which I haven't seen in the last couple of days, is going to spend a huge amount of money advertising and promoting. They will hopefully steer clear of some of the criminal activity but they are going to go out as far as they can, understandably they have a fiduciary responsibility, they are stockholders, to sell as much of this drug. I think this is a huge dilemma and I'm not answering the question -- everyone should pitch in on REMS, we shouldn't have ten different REMS programs but yet it's FDA's regulatory data is at the level of the company not the general public.

DR. KIRSCH: We have other important questions to answer. I have six more people on the list for this question. We're going to go through the six but not take any additional names for this list. So next is Dr. Brull.

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DR. BRULL: Yeah, it's already been discussed.

DR. KIRSCH: Dr. Burlington.

DR. BURLINGTON: My comments were going to be remarkably similar to what we've just heard from Dr. Wolfe. I think it's important that we not focus on trying to enforce physician adherence to guidelines because it is really FDA's job to regulate the industry, not practice medicine.

DR. KIRSCH: Dr. Pelosi?

DR. PELOSI: That had limited impact. I think in part it's because there are a lot of data-duped physicians out there for guidelines or interactions with the drug company or disciplinary actions or courses are ineffective, if not a joke. I think that an expanded and strengthened the prescription drug monitoring programs in states to look at individual prescribing practices to identify prescribers with particular patterns, to make the data with law enforcement and special state-issued forms

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for controlled substances. Those are the kinds of things that I have some chance of having an impact.

The other thing is that 40 percent of opioids in recent years were prescribed through the emergency room department so a lot of that is that's acute pain, so we need some development of acute pain guidelines; 30 days of Percocet to everybody who comes in behind on in terms of chronic pain guidelines.

DR. KIRSCH: Dr. Tortella.

SPEAKER: We've been talking about educating the physicians here and I think that one thing we haven't touched on is really educating the patient or the abusers or potential abusers or actually the young people that are out there being effected in large numbers here and I think one of the things I've seen a lot of kind of passive tools, but they are good tools. I do think we need some more active tools, such as public health

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announcements or public awareness campaigns, not so much just don't take drugs, but prescription drugs. I'm not sure that our young people today are really very aware of the dire consequences of these drugs and perhaps putting something on (inaudible) or MySpace or, you know, some of these areas where young people really are on these sites quite a bit will make a real difference. Thank you.

SPEAKER: That's an excellent point. I would just like to note that currently we have a working relationship with SAMSA where this group is putting up public health announcements and young people to address the issue of prescription opioid abuse. So they're actually doing that now. It needs to be grown, clearly.

DR. KIRSCH: Okay, we're going to go on to 1-B. We had a healthy discussion on 1-A. 1-B, discuss whether or not the available data suggest that this formulation will be less susceptible to abuse and misuse.

Dr. Nussbaugh.

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DR. NUSSBAUGH: My conclusion from the day is that it's an advance. It's a small advance, but it's an advance. I have a lot of concerns about issues like the high variability among individuals and drug liking. We didn't really hear anything about the potential for snorting or chewing this formulation. We didn't really get an answer regarding heating or cooking it on a spoon and what would happen. We know that there are probably issues with the safety of IV injection although there are animal studies in progress. As with yesterday, it would be really laudable if the company had trials and people who have acknowledged addiction. But in the absence of that, I still think it's probably at least a small advance.

DR. KIRSCH: Dr. Horowitz.

DR. HOROWITZ: In a way I would like to reiterate that and I think in another broader way to put it is that we would like to see a standardized battery that reflects common forms of abuse across all products that are being

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considered because one of the things that I think has come up in our discussion is how innovative people are who want to abuse drugs and today's approach to abuse for a product may be different tomorrow if, in fact, the tampering is accessible one way and not another. So I think we would like to see some standard battery with maybe an emphasis on forms that are common and for those existing products.

The other issue is the issue of clinically relevant outcomes and I just -- an expert in pharmacology of abuse or in the use in some of these tools, I think there are two levels at which that's coming up. One is standardized instruments, particularly, those that reflect subjectivity -- that deal with efficacy in terms -- and also in terms of the effects of these drugs and euphoria and the potential for abuse. Clinically relevant population question, I think, the other issue being again it's really just to reiterate is that before we can make claims about the

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ability to reduce the risk of abuse, we would like to see data in populations that we're quite certain are going to be generalizable.

DR. KIRSCH: Dr. Burlington.

DR. BURLINGTON: I have no doubt that any formulation that can be absorbed by the human body can be defeated by pharmaceutical (inaudible) and the active ingredient can be extracted and separated. And I also have no doubt that sooner or later we will see recipes for how to do this on the internet and they will become available to the people who are dedicated to try and defeat the mechanisms. However, I do think that this is an advance in the sense that it does make it more difficult and so while it can't be tamper proof, I think there is a real potential for decreased abuse potential built into the mechanism that we've heard about here today.

SPEAKER: I think (inaudible) issues is in the context of other available products on the market, it's really hard to assess how much

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advances we provide. If it's more expensive the insurance companies are not going to cover tamper resistant products. And so we forward yesterday, can the marketing of a opioid product, whether it's immediate release or extended release, be simply defined by the best of breed tamper resistant characteristic that we can define and given a period of time that other products meet those requirements (inaudible) to the markets similar to some other precedence have been set by the FDA.

DR. KIRSCH: Dr. Wolfe.

DR. WOLFE: It's a little bit like the discussion yesterday since it's the same question, but my concerns are that both in the two solvents, I believe two or three whatever they were, where the company itself admitted that it would not really defeat the extraction of morphine (inaudible) very questionable results showing very little if any significant advantage over crushing their product over the product without the naltrexone. I think that on

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that side, I don't think it is clear that this formulation would be less susceptible to abusing, and however small that is almost by definition if this were to be approved, there would have to be similar acknowledgement in some way or another about the "advantage," and I would argue strongly that history would teach us that the disadvantage of this which is the wide spread use of something that was perceived to be more tamper resistance or less subject to abuse would greatly outweigh any benefit however small it is right now.

DR. KIRSCH: If it's okay with the FDA, I'd like to give the sponsor an opportunity to respond to that comment?

SPEAKER: It's important for us as a company to make sure that we use the right ways to sell this medication. And when I say the right ways, I mean the appropriate ways and, specifically, I'm talking about not creating the unintended consequence of a false sense of security. That's very important to us. I think

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it's important to, for all pharmaceutical companies, and particularly in our situation because we are talking about subjective end points. We are also talking about a lot of subjectivity in the way that physicians and patients and pharmacists will approach this medicine. And so we take our role in that regard very seriously and we have tools in place to do that. One of the other questions I heard come up before was are there other tools in place that we can do to -- once the job is on the market to really understand how it will work, what type of impact will it have and if I could just have slide C69 up, please. That isn't the slide.

My apologies. That was the wrong slide. It's the slides we have under consideration for epidemiologic studies, R69. My apologies. This is the one. These issues are complex and I think we've talked about them here. There's not going to be a simple solution, not now and not even going forward,

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but these are some of the ideas that we have under consideration and under development right now.

There are complex questions on both sides of these trials as well as epidemiologic trials. We are trying to get at some of those patients that we talked about, the patients at risk. This is one way I believe that we can do this as part of the REMS to understand and do this the right way. These are not problems that we are going to solve here in here room, I understand, but this what we think we can do as a company different than what's been done before. And so that along with appropriate education which is only one piece we agree is going to be the way forward.

At the end of the day, we are trying to make positive steps and not over promise anything and that's critical for us and so I wanted that to kind of sink with you today.

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The other piece, and I'll end on this one, is that there is no perfect solution and, clearly, this is not one either. On the other hand, we think we've struck the right balance by making small steps and that's what we're trying to do without creating an unintended consequence.

MR. YESENKO: My concern is regarding sponsor slide C29. I go back to the potential to minimize abuse in solvent two, potential to minimize abuse in IV, no, minimize abuse in solvent three oral, no. That's why we are here, to minimize abuse. Discuss whether or not the available data suggests that this formulation would be less acceptable to abuse and misuse. I think we have an answer. I do anyway.

DR. KIRSCH: Dr. Kramer.

DR. KRAMER: I would like to express my opinion. It seems to me that one of the sponsors mentioned that with oral administration and crushing, that there is -- it doesn't mean it's across the board (inaudible) of what was

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just pointed out that we have problems with potential intravenous administration. And the part that concerned me was the individual patient variability. Analgesic does look better and I do think -- I think the sponsor said that, obviously, it's not going to solve all the issues, but I don't think it's right for us to say it does not provide some advantages over Kadian for instance.

DR. KIRSCH: Dr. Pelosi.

DR. PELOSI: I think one of the issues in terms of abuse is exposure because most of the mechanisms we have considered here have to do with crushing pills for injection and oral routes and (inaudible) information about that. Some of the data presented, like on slides 13 and 14, show different lots of exposure, as opposed to incidence data so that actual percentage of emergency room visits, for example, aren't any different.

Morphine -- and choose for yourselves -- distribution and lots of

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exposure. I think it's better to have all forms of morphine information about why people choose a drug. If they are just swallowing the drugs, then that reduces the benefit of crush. I appreciate the data on chewing but I think in the future is to get better data somehow -- those people (inaudible) products such as this.

SPEAKER: From the standpoint of the global term of abuse resistance, I didn't see enough data to be abuse resistant with regard to crushing and some of those manipulations. It does appear to have advantages. Again, I said this yesterday -- laboratory data to extrapolate and make clinical decisions and that's difficult. This question doesn't ask whether there's a cost benefit advantage to the gains or anything like that, but I do think that from the commonly abused way of crushing medication that this does offer an advantage.

DR. KIRSCH: Dr. Rosenberg.

DR. ROSENBERG: As an incremental

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improvement of potential patient and other safety, I would say this formulation is an improvement and I would like us to consider that the value of morphine deaths in abuse is much, much smaller. So as a place to test where this incremental improvement is a good one, potentially expose the smaller amount of the population to risk. So as we collect post marketing information, we can see if the addition of the naltrexone to the formulation is an incremental improvement. Thank you.

DR. KIRSCH: Dr. Zuppa.

DR. ZUPPA: I just want to state that I agree with the data presented today in case what is shown is not susceptible. But I would like a few other studies.

DR. KIRSCH: This is a very important question, so what I would like to do is for those of you who have not responded, I would like just to get your thoughts or comment on this question.

Dr. DeWit, you're first.

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DR. DeWIT: I guess I think the drug abusing population with a little bit of time and ingenuity is likely to find a way to get the active drug out without the naltrexone and the question is how much risk can we tolerate and detect it so I think on the face of it has a less likelihood of abuse, but that a small group of users will still be able to extract the active drug and misuse it and it's a question of how much of that misuse can we tolerate.

DR. KIRSCH: Dr. Kerns.

DR. KERNS: The one thing that I would say has been said. I feel that there's an incremental benefit so I think that there is some benefit to this drug in terms of less susceptible to abuse in misuse but I think it's marginal and I grin with the idea that it's marginal because it's methadone and not a codone product so that lowers my concern. And more supportive. I do want to mention that we can't predict reliably people that are likely to abuse or misuse or whatever the case is of the

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medication. For those that -- there are a variety of people that fall into that category, including the people that misuse the medication unintentionally. I do have some concerns about the people that potentially are at risk for abuse and misuse that they may be vulnerable to unexpected adverse events related to the medication naltrexone and the risk for unexpected withdrawal or even overdose as they try to overcome those mechanisms.

DR. KIRSCH: The next person hasn't said anything. I think there is some incremental benefit. However, my biggest concern about abuse in the IV preparation and I'm greatly concerned. I don't think this formulation addresses that issue. It's not your compound, but it'd be awful nice to see Naloxone in this product as part of the product which I think would deter as we've seen before intravenous use.

Next is Dr. Brull.

DR. BRULL: Thank you. This is a very

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difficult question and whenever I'm faced with a very difficult question, I try to boil it down to the core. To me it's risk to benefit ratio. I do think it provides an incremental benefit and I would have drawn an analogy with which I think a lot of people would be familiar and the analogy would be computer viruses. Having Norton Antivirus or whatever antivirus program, will not ensure that there are no viruses. We have to start somewhere. And to me the question that I have will the use of the computer virus application, antivirus application, be providing me enough benefit of allowing me to have a virus-free computer versus the slow down that it produces. And it's the same thing with this medication. It does provide me significant incremental improvement in decreasing the potential for abuse. In at least today's session, I'm less concerned about the potential complications form its use. I mean we don't have any data about the snorting and the intravenous administration. I have slightly

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more concerns about yesterday's product in terms of safety and so I think individually we have to look at what our risk tolerance is and I think overall for at least with this product it does provide an incremental benefit. It's not perfect and none the antiviruses are perfect either.

SPEAKER: Much of my comments have already been said. I think my first impression on seeing the Naloxone core, this is a very clever idea. But as the day progresses I see the idea had not been developed as carefully and studied as carefully as many of my colleagues had pointed out that we need to see more of the development and the safety and the other IV use. I'd also like to hear the company that developed a lock that seems to be only one way to deliver the pill, you swallow the pill, that's the only way to avoid the Naloxone. After you build the lock, you have to find the key. So what is the method that the really motivated abuser will use to get the opioid out and we have to figure out

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what is that shortcut and see how really difficult that is. Maybe it's easy. Maybe it's easier than we think. You have to think about that side of it also. Thank you.

DR. KIRSCH: Dr. Krusack?

DR. KRUSACK: Thank you. I agree that it is an incremental improvement in finding the lock and that key. I would hope that we could provide together some of those motivational abusers -- criminal lawyers and find out exactly how they can fix and idea but not this one.

SPEAKER: Just another point of clarification that's not such an far reaching idea, we are requiring that of all the companies now.

DR. KIRSCH: Dr. Pollack. Dr. Pollack is gone. Dr. Tortella.

DR. TORTELLA: I think it represents an incremental benefit, yes.

DR. KIRSCH: Okay, the last comment on this question will come from Dr. Kramer.

DR. KRAMER: I just forgot to mention.

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I had some concern about whether the dose of naltrexone is high enough. I realize this sponsor is very careful to make sure if taken whole as intended for pain patient there was no issue of having the effect of the naltrexone. But with the variability that was shown, it looked like there was a fair percentage of patients that wouldn't have adequate naltrexone to reduce the abuse problem.

DR. KIRSCH: Next question. Many of the cases of addiction, overdose and death are associated with abuse with intact, controlled, released opioid products. The data is related to released naltrexone oral physical manipulation and the questions are; discuss whether conclusion of data on the released characteristics of the naltrexone in this new formulation into the product label could potentially mislead prescribers or patients that this new formulation when taken as directed is likely to be addictive or unlikely to be (inaudible) addictive or unlikely be abused or

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result in addiction or overdose.

Comments from the Committee.

Dr. Nausmeier.

DR. NAUSMEIER: I think it certainly would be fair and probably of some benefit to have a caution regarding withdrawal symptoms or lack of efficacy after crushing due to release of naltrexone. That should definitely be included somewhere on the labeling. Also, the usual cautions regarding dosing. I mean 100 milligrams is 100 milligrams to an opiate naïve patient.

SPEAKER: I think the REMS studies as proposed on the face of it and from what we can tell from the way they are described, seemed like the sorts of studies that will facilitate labeling consistent with the claims that it has potential to deter abuse. Until then, I think it's important to be cautious about its implementation and its labeling and I think it should reflect the specific -- not to the degree that allows to be tampered with but labeling

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should reflect that it's a novel formulation of the product, I think, rather than one that can lay claims to be clinically effective in reducing abuse potential.

SPEAKER: Clarification here. That's the baseline. Nobody's getting claim of reduced abuse liability until they prove that. At this point, the question is only information about the change in formulation have any kind of negative impact.

DR. KIRSCH: Dr. Kerns.

DR. KERNS: I replied to this earlier. I think that one unfortunate side effect of this medication being put on the market with kind of labeling would be further -- certain variable vulnerable populations. We can't predict who shouldn't get this drug because of potential for abuse or misuse but we do have people that use their biases to make predictions about that, including race for example and so I have concerns about that.

DR. KIRSCH: Dr. Kramer.

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DR. KRAMER: I do think that there's a concern that no matter how you write the label that there could be a false sense of security and I think given that that the label should probably say something to the effect that prescribers should not consider that this will overt misuse of these or misuse of the preparation. Something to actually indicate that this won't solve your problems.

DR. KIRSCH: Dr. Pelosi.

DR. PELOSI: I think of the possibility with any opioids for us to evaluate this. I guess I think that for this particular molecule it's relatively safe pool to dip your toe into; less likeable among abusers. Representatives in the emergency departments and visits for overdoses and deaths, I think it would be a relatively safe product to start with to sort of see what happens with respect to that.

DR. KIRSCH: We are going to 2B. If you believe that patients or prescribers could

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be mislead, discuss whether the risk is acceptable concerning the potential benefit of the changes to the formulation.

SPEAKER: I already addressed that. If anybody else has comments, we'd be interested in hearing them.

DR. KIRSCH: Dr. Burlington.

DR. BURLINGTON: I would like to comment on question two sort of as a whole. First off we have to understand that FDA understands labeling would be more than just the packaging insert or the immediate container label. They also look at advertising programs and count them as labeling. So we don't know what that label -- but I would imagine that a (inaudible) of FDA given then control over the packaging insert and the advertising promotion of the product, as well as the other communication tools that are provided under the REMS provisions of the legislation. It would be extremely clumsy of them if there were many prescribers left uninformed. So will somebody

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not get the message? Undoubtedly. But I think it will reach a vast majority of folks, yeah.

Dr. Zuppa. Never mind. I thought your hand was up. We will go to question three. (inaudible) believe that the data suggests that the formulation of controlled-release morphine is likely to reduce its abuse and misuse, discuss whether or not any of the data should be included in the product labeling.

I'm looking at you, Dr. Nussmieir --

DR. NUSSMIEIR: Well, again, I will just reiterate I would definitely include the data regarding the inclusion of a naltrexone center that's released with crushing or chewing. It's just an obvious mild deterrent at least to a common form of abuse and it's good for the clinicians to know that and it's good for the abusers to know that.

SPEAKER: It's also good for the patients to know about that because they might

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(inaudible).

DR. KIRSCH: Dr. Zuppa.

DR. ZUPPA: I just want to have the opportunity to completely agree with that statement.

DR. KIRSCH: Dr. Wolfe.

DR. WOLFE: This really gets down to the issue of the other people -- certainly a problem with OxyContin a false sense of security. At the level of the prescriber, would you be anymore willing to prescribe this drug if you knew that this core of naltrexone was there and that there was reason to believe that there was data to believe that actually reduced abuse? I think that the problem with that is measuring two unknowns. Marginal at best is all I can say in terms of the benefits because the data just are not that clear at all. In terms of the risk, any kind of lowering of the threshold for a given physician to prescribe to someone who they wouldn't have prescribed if it didn't have this property is an immeasurable risk on the

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other side. So you're really talking about a benefit both of which are immeasurable and, again, the history of OxyContin teaches us that the immeasurable safety false sense of security turned out to be very dispositive and very dangerous.

DR. KIRSCH: Dr. Brull.

DR. BRULL: Yes, thank you. I also wanted to take the opportunity to completely agree, but beyond that I think that in order for us to assess the risks, one of the questions that was asked before is what would happen -- my concern would be if I were to give those to my patients, what would happen if they overdosed on this drug? And we do not have any data on large doses and that would certainly make me not want to prescribe it because I would not know what effect it would have on my patient if they overdosed knowingly or not.

SPEAKER: We heard yesterday how health care people versus assistance, I don't know who, were crushing pills. I would be very

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careful to emphasize that crushing with medication could precipitate withdrawal which would be a very unfortunate and could have serious consequences if it were to occur in an elderly patient with compromised cardiac function. So the safety measure of this medication in terms of abuse potential, I would be very careful to make sure that this stuff is not crushed and whatever can be done to help assure that it is not crushed and precipitate such a problem in our elderly population or nursing home, whatever.

DR. KIRSCH: I wanted to go on to 3B, but I think we've answered it already. So what specific data do you think should be incorporated into the labeling? I think we've addressed that.

Are there any other comments about these questions? The FDA has some comments.

SPEAKER: I just want to say a few things. When I left yesterday I was a little concerned because I didn't feel like I was

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getting a lot of useful information to answer these difficult questions, but in thinking about it and discussing it with my colleagues and then I was reading more today, I think the conversation got a little bit deeper today. And in thinking back about what I heard from yesterday and today from the companies and from the open public hearing speakers, I think there's actually been quite a bit of useful information that we've gotten from you all from these two days. It's going to help us move forward on this, so I want just thank you. I want to thank the FDA speakers and other folks on my staff who put in a lot of time behind the scenes to do this and the people who spoke at the open public hearing gave us their perspective on this and to all over you, I really appreciate your comments and spending two days to do this. And, in particular, Dr. Kirsch who stepped up at the last minute to fill in for Dr. Flores so thank you very much for doing a great job.

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DR. KIRSCH: Thank you. I think this concludes our meeting. Thanks for your attention, everybody, and your helpful comments.

(Whereupon, at approximately 4:00 p.m. the MEETING was adjourned.)

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