FOOD AND DRUG ADMINISTRATION (FDA)

CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

IMPACT OF APPROVED DRUG LABELING ON CHRONIC OPIOID THERAPY

PART 15 PUBLIC HEARING

Thursday, February 7, 2013

Bethesda Marriott

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P R O C E E D I N G S

Presiding Officer Opening Remarks

DR. THROCKMORTON: If people will take their seats, we'll begin the meeting.

Good morning. My name is Doug Throckmorton. I apologize for the state of my voice. I'll be using Altoidstoday. I am the Deputy Center Director for the Center for Drug Evaluation and Research at the FDA. I would like to welcome you to this Part 15 Hearing of the Impact of Approved Drug Labeling on Chronic Opioid Therapy.

I am going to be the presiding officer today, and we have a distinguished panel of experts from the Center for Drugs to listen to your presentations and comments.

As we're all aware, opioid issues have been a particular focus of public health concern and discussions continue about the proper use of opioids in general. The purpose of the hearing today is for us to obtain information for members of the public of the diagnosis and understanding of patient pain, the understanding and adherence to labeling for pain-

treating products, and on their potential impacts on opioid prescription and use.

A few housekeeping items before we start. First, please turn off all cell phones, as they can interfere with the audio in the room. And we ask all attendees to sign in, and I know that many of you stopped at the desk. This is scheduled to end at 4:00 this afternoon and tomorrow.

The rest rooms are located outside the main conference room. We are planning for a one 15-minute break during the morning session and one 15-minute break during the afternoon. Today's lunch break is scheduled between 5 after 12:00 and 5 after 1:00. The hotel has a quick lunch option, and they said that if you were interested, there is a form at the registration desk that they ask you to fill out sometime before 10:00 so they can have it all ready.

I would like to now introduce the members of the panel from the FDA. I'll start to my right with Dr. Sharon Hertz.

DR. HERTZ: Hi. I am Dr. Sharon Hertz. I am the Deputy Director for the Division of Anesthesia,

Analgesia, and Addiction Products.

DR. RAPPAPORT: Bob Rappaport. I'm Director for FDA.

DR. THROCKMORTON: Again, I'm Douglas Throckmorton. I'm the Deputy Director for Regulatory Programs in the Center for Drug Evaluation and Research.

DR. STAFFA: I'm Judy Staffa. I'm the Director of the Division of Epidemiology II in the Office of Surveillance and Epidemiology.

DR. KLEIN: I'm Michael Klein. I'm the Director of the Controlled Substance Staff in CDER, of FDA.

DR. THROCKMORTON: And there is going to be one other member who will be joining us at some point during the day, Dr. Jenkins, from the Office of New Drugs.

A couple of other items. We have a total of 55 speakers that are scheduled to present. I have asked to go over a few ground rules just so that those presentations are able to go as smoothly as possible.

First, the meeting is informal, and Rules of Evidence do not apply. No participant may interrupt the presentation of another participant. Only FDA panelists will be allowed to ask questions of a presenter. FDA may recall a presenter for additional questions as necessary, assuming that time allows and the presenter is still available.

Public hearings under Part 15 are subject to FDA policy and procedures for electronic media coverage. Representatives of electronic media may be permitted obviously subject to certain limitations to videotape, film, or otherwise record, that's for your awareness.

This meeting will be transcribed, and copies of the transcripts can be ordered through the docket or accessed on our website approximately 30 days after this public hearing. Each registered speaker has been given a 7-minute slot on the agenda. After each group of four speakers -- so the four chairs here in the front -- speak we intend to move to the next panel and if a speaker ends early, we intend to move to the next speaker and increase the time of questioning for the

panels.

Please pay attention to the slide presentations, as we would like to be in groups to make this as efficient as possible. For those of you who did not register to make an oral presentation but would like to present your comments, you may speak at the open public comment period at the conclusion of the hearing tomorrow. There is a sign-up sheet at the registration desk, and we would like you to notify us of your intent to speak in that session by the end of today.

The meeting is being webcast live. It is not an interactive webcast, and the participants who are participating will be unable to speak.

This hearing is not your last opportunity to comment on the questions that we posed in the docket. The docket will remain open until April 8th, and we strongly encourage all interested parties to comment and submit additional materials that they think would be useful in elaborating on the points that they make today. Please see the Federal Register for details on that.

Given the full agenda, we request that each speaker keep to the allotted time so that we will be able to keep to a tight schedule.

We thank you for your interest and participation today in this seemingly important public health matter. We look forward to a very productive public hearing.

With that, let's begin with the presentations. I'm looking around for my presentation facilitator person.

Elizabeth? Mary? All set? Okay.

The first person I have on my list is Theresa Kroll followed by Ada.

UNIDENTIFIED FEMALE SPEAKER: All speakers should go up to the tables first and register.

DR. THROCKMORTON: The first eight speakers could come and sit at the table, ideally one through four and then five through eight.

UNIDENTIFIED FEMALE SPEAKER: Exactly.

DR. THROCKMORTON: Pull that off, and then we'll get started. So five through eight would be Wendy Foster, Zxy Atiywariii, Patricia McDonald, and

I'm not sure, maybe Robert Twillman, Mary?

Anyway, Theresa, do you want to get started, please? Thank you.

MS. KROLL: Good morning. My name is Teri Kroll, and I'm the proud mother of two, Jamie and Tim. I have been married for 34 years to Frank. We're a regular working family. We have always paid our bills. We save where we can, and we couldn't wait to have children, and we reveled in every part of their lives.

We have the typical extended family, dinners on Sunday with Grandma, and holidays with aunts, uncles, cousins, and friends. At home, among the four of us, we had fun. We enjoyed the simple things, always ate dinner as a family, Frank and I helped with homework, we went to teacher conferences, and we were a presence at school. As our children got older, we asked questions, "Where are you going? Who are you going to be with? And when are you going to be home?"

Tim was always a happy kid. He was the source of lots of pride and laughter. He was always my good boy. Tim liked to be outside and active, he liked to cook with me, he loved to surf with his dad, and he

was a snowboarder. He took apart any computer and put it back together again. His teachers got a kick out of him, he fell in love a couple of times, he had a few very good friends, and he loved his family. He was my big, beautiful boy.

If you're a parent, here comes the part where you and I probably differ, at least I hope that's the case, because I've been to hell and back, and I wouldn't want that part of my life on anybody.

Tim had a few very good friends in high school, and together they decided to be straight edge. You probably know that that means no drugs and no drinking:

every parent's dream. Then the headaches began, and for reasons we still don't understand, Tim started suffering from severe headaches and anxiety attacks. We were told there was a doctor who could help us. When we made the appointment with Saji Francis, we did not know he was not a doctor, he was a drug dealer hiding behind a certificate that indicated he had completed medical school.

We live in a society where doctors are

trusted and respected because their goal is to help sick people get better. My husband and I were active members of that trusting society, and we raised our children to be members of that trusting society as well.

I had limited interaction with Saji Francis because during our first appointment when he discovered that Timmy was 18, he made it clear my presence was not necessary for future appointments. He explained that since Tim was an adult he could come to the appointments on his own and in fact could get prescriptions filled without my supervision. I trusted his opinion and Timmy's desire to take care of himself.

Francis prescribed pain medication for Tim at the very first visit. He told him to come back one week later for a follow-up. It wasn't until a few months before Timothy's death that we learned exactly what happened next. Tim went back and told Francis the pills weren't working, so he was giving a prescription for oxycodone. Before long, Tim became addicted and fell into a life of psychological despair and torment. The lifestyle that we once enjoyed as a family was now

a thing of the past.

Without going into too much detail, I can tell you that our family life was gone. Our life became a constant frenzy surrounding Tim's addictions. There were suicide attempts and many visits to the hospital. Gone were the days when we would sit and watch a movie together. Tim couldn't sit still long enough. He was wracked with anxiety. Sunday dinner with the extended family wasn't even in our radar. We knew that Tim was in there somewhere.

We did whatever we thought would work for this young man. We bought a king-sized bed because the anxiety would keep him up at night, and the only thing that could get him to sleep was to crawl in bed between me and my husband. Our 6'3" beautiful boy would lie between us in bed, and it took the three of us to calm him down to sleep.

In June of 2009, Tim decided it was time we knew the full story. He told us about Saji Francis. He mapped his path of drug use, now street drugs, directly back to the second visit at Francis's office. He knew there were others who were in the throes of

addiction because of that man, and he wanted to do something to stop it. So he asked me to go to the police with him.

Tim came home from work on August 29th, he had worked late and was tired, but he was in a great mood. He had just finished an overtime shift running at work wiring in an office building nearby. Tim was happy and we were seeing the light at the end of the tunnel, and my son's face was shining in that light. He told us he loved us and he headed up to bed. He wasn't going to need to sleep with us that night.

I woke to a ringing phone on August 29th. It was Tim's supervisor wondering why he hadn't gotten to the job site for the wiring project he was working on. I was surprised, too. I went to his room and found Tim with his eyes wide open barely breathing and unconscious. It had been a while, but it was a familiar sight. I yelled for Frank to call 911 and I dragged him out of bed to begin CPR. He had a heartbeat, but it was slight. I knew the ambulance would get there and the EMTs would get him through this just like they had many times before.

My last moments with my son were in the ER treatment room. The doctors and nurses very compassionately and graciously gave me a few moments alone with my big beautiful boy. I asked for a tub of water and a cloth, and as I washed the blood from Timothy's face and neck, I told him I was proud of him and that he could rest now.

When I got the call from Detective Collins (ph) on the afternoon of December 8th telling me that Saji Francis had been arrested, I realized that Tim had left a legacy and I was very proud.

Look at me. I'm just a normal mom. I'm not an absentee mom. I was involved, I asked questions, and ultimately my son, when he could make his own choices, he made the right choice to be a straight edge kid. In our case, it was a doctor who led my son down the path that would ultimately kill him.

I implore you folks to listen carefully to my story and the stories you will hear over the next 2 days -- some medical, some personal, but all important -- and as a parent who will forever grieve the loss of my child, I'm begging you to carefully consider the

1972 Controlled Substance Act and how it could be strengthened to enforce the laws of prescribing these highly addictive drugs to patients who can easily fall into the black holes of addiction and succumb to the effects of these addictive drugs. I am not the first parent to lose a child, but I certainly want to be among the last.

Thank you.

DR. THROCKMORTON: Thank you.

Ada? I don't want to guess on how to say your name. Thanks.

MS. GUIDICE-TOMPSON: My name is Ada Guidice-Tompson. I live in Ontario, Canada. Thank you for the opportunity to speak to you today. I am a bereaved mother of a wonderful young man, Michael, who died in 2004. Could we get his slide up? Oh, there he is.

The current labeling suggests that opioids are safe and effective for long-term CNCP, but there is no evidence supporting this assumption. In order to improve long-term outcomes for pain patients and end the epidemic of death and addiction, we need to understand the broader context and focus on evidence-

based prescribing.

The focus on business and financial rewards has created unsafe medical practices. In 1992, almost 90 percent of physicians recognized the very real risk of opioid addiction. Then came a shift in practice and opioids began to be prescribed widely for CNCP. This change was based purely on assumption. In a recent article review, pain expert Jane Ballantyne, M.D., states, "The accuracy of that assumption has not been tested against accumulated evidence and the safety of opioids used long term has not been tested in clinical trials." Dr. Ballantyne highlights important epidemiological studies which document adverse safety events, especially death, and a reduction in the quality of life of CNCP patients on COT.

We can't resolve the epidemic with the same attitudes and perspectives that created the problem in the first place. Since marketing created misinformation to mislead the medical community, we need to analyze this carefully and stop basing our decisions on wrong assumptions and misrepresentations. The epidemic clearly tells us we don't know enough

about pain, opioids, and addiction, and yet doctors are asked to balance the risks and benefits of prescribing opioids based on marketing rhetoric.

A label change will provide more clarity for cautious and judicious prescribing and will prevent drug companies from marketing a drug for indications that are not supported by clinical evidence of safety and efficacy. Patients want safe pain relief and healthier outcomes.

Can we have the next slide, please? Sorry. Thank you.

This is a diagram showing the molecular structures of oxycodone and heroin. How did we ever make this leap of faith? We are legally providing heroin-like drugs and should expect nothing less than an epidemic of addiction and death along with poor pain management. The effects of opioids on the brain and body mimic those of heroin. They cause a marked neurochemical response, wreak havoc with dopamine on the reward-pleasure systems, may lead to opioid-induced pain sensitivity and increased pain and can depress breathing during sleep. This occurs regardless of how

the drug enters the body and whether they are obtained illegally or legally.

Opioids, such as Percocet, which contain 5 milligrams of oxycodone, may be perceived to be less problematic, however, a little bit of heroin is still heroin. For some patients, their very first exposure to an opioid starts them on a slippery slope. Many patients are started on a short-acting opioid for acute pain and end up on higher doses and on long-term therapy.

My son, Michael, was prescribed Percocet for acute pain caused by kidney stones. He took his medication as prescribed. Although his pain was classified as acute, the prescriptions continued for 2 years, until he died in his sleep from prescribed hydromorphone.

Balancing opioid benefits and risks sounds good but is very misleading. Our understanding of balance comes from drug companies that have downplayed the risks and exaggerated the benefits. Should we be attempting to balance the use of drugs that mimic heroin?

We have moved to marketing-based rather than evidence-based medicine. Under the current labeling, industry continues to misrepresent data and deflect attention away from the inherent addictive qualities of opioids. The promotion of the abuse-deterrent pill is the latest marketing attempt to legitimize the drug as safer and less addictive. We were also told that about the extended-release formulations. The common misconception is that opioids must be abused for a patient to become addicted, which ignores the common situation of abuse which occurs after the onset of addiction to a prescribed opioid.

To focus on abuse and nonmedical use as the driving force behind the epidemic is inconsistent with science and reality and overlooks three important points. It is the increase in prescribing that has fueled the epidemic. The majority of patients swallow their pills whole, as prescribed. Abuse deterrent or not, the inherent addictive qualities remain.

Simply using opioids as directed is not sufficient to prevent addiction from occurring. Dr. Ballantyne has stated that patients taking opioids as

prescribed are not protected from harm. Once a patient becomes addicted, misuse and abuse are common behaviors. The current label indications are vague and suggest a free-for-all to treat all pain. The lack of clear warnings of the potential dangers is also of concern. Just one opioid pill can be deadly in an opioid-naive patient, and in an opioid-tolerant patient, a small increase in dose can often tip the scales and cause a patient to stop breathing.

I support PROP's petition but feel it does not go far enough. We should be looking at using opioids in very selective medical situations. Opioids should be reserved for severe CNCP and for the shortest period and lowest dosage possible. Such a label change on all opioid products would assist prescribers in recognizing such therapy as extremely risky and to be avoided if at all possible. Patients already on opioids will require appropriate continued support and effective treatment services. A label change will not prevent doctors from prescribing opioids where medically appropriate.

Medical boards, and not the FDA, govern this.

The FDA must ensure that opioid data and information are accurate and that pharmaceutical companies do not mislead doctors and the public. This requires an entirely new framework beginning with a transparent drug approval process and disclosure of all data. Patent laws and industry profits should not trump patient safety.

Industry's primary role is to their shareholders. FDA's mandate is to the public.

Thank you.

DR. THROCKMORTON: Thank you.

Mr. Israel.

MR. ISRAEL: Can we get the slide up?

Good morning. My name is Avi Israel, and I'm here on behalf of my son, Michael David Israel, and countless other kids who have lost their life following doctors' instructions.

On the contrary to what pharmaceutical companies all tell you, and Pain Management Association, they all got addicted by following doctors' directions and taking the pill as prescribed. I can stand here and use my 7 minutes to tell you the

details of how my son's addiction was so out of control that he killed himself. Instead, what I would like to talk about is how my 20-year-old son, Michael, reached a point where his only alternative was to take his own life.

Michael's three doctors prescribed him simultaneously addictive medication. Michael was getting hydrocodone, Xanax, Simbalta, all for Crohn's disease. So here we are on June 4th of 2011, after 2 years of being prescribed hydrocodone for Crohn's disease, Michael got to a point where he saw no way out of his addiction and hated what he was becoming. Michael put a shotgun under his chin and blew half his head off. I held my boy as he took his last breath in my arm.

In the next couple of days you're going to hear and see all kind of information and statistics about opioids, what it does to you, what it doesn't do to you, some will be favorable, some will not be favorable. What we're not going to hear is what it does to a family, what opioids and addiction do to the American family, the unspeakable devastation it leaves

behind.

Now, imagine your loved one having to use an opioid as a treatment. Would you want to know the medication is addictive? Yes, you would. Would you have the right to know? Yes, you should. With the information that we have today, would you want to stay on that medication? No, you wouldn't.

The problem with all opioids, we have been misled by pharmaceutical companies, by their mouthpiece, the Pain Management Society, that the drugs are safe.

I'm here to tell you, and you guys know it as well as I do: All opioids are highly addictive; all opioids are not effective for long-term use; all opioids cause depression and thoughts of suicide; all opioids are nothing but synthetic heroin. heroin is illegal in the U.S., so why are we putting it in the form of a pill?

So those of you on the panel, if you don't agree, raise your hand, Mr. Rappaport, and let me know if you want to give your child opioids, want to give your husband, your wife, and I'll guarantee you that

you'll end up in the same place I am today, with a dead loved one.

Our society have been lied to, have been misled, have been lied to by big pharma and the rest of their cronies, the Pain Management Society. These two groups are focused on nothing but profits. Follow the money, you can ask anyone over here who is pro-opioid who paid for their travel, and you'll find big pharma is behind it. You can ask any one of the pain patients over here, who paid for their travel and how did they get here? You can find big pharma right there. One way or another, big pharma is involved in this.

Purdue was fined $600 million for lying to the American public. How can we trust that any pill that they put out is safe? How can we believe anything they say? We rely on you, the FDA, to do a job of protecting us, but for the life of me, I can't understand why that pill is still on the market after knowing what they lied.

Opioids are prescribed today just like Halloween candy, every doctor gives them out, everybody hands them out. My son was taking hydrocodone. This

is my son's grave. That's where my son ended. I cannot, I cannot, get used to the idea that to have to go see my son, I have to go to a cemetery. That tears me apart. That should tear you apart. You were there, you are there, you are here to try to make sure that this kind of stuff does not happen.

An American family is the average of four people. Do you know what it does when one person in a family is addicted? You get over the last 10 years or so we have over 100,000 people who have died, we have over 20 million people who are addicted. That brings us to about 500,000 people in this country who have been destroyed because of addiction. That's a half a million people.

Ask any one of us who went through it or are going through it right now what it's like to have a loved one addicted. Life as you know it cease to exist. It's watching someone you love dying slowly and you can't help. And all that can be avoidable if we inform the medical community and the public in a very strong unmistakable way, you are taking a medication that can destroy your life.

You've been entrusted with this job to serve as the people's protector. Stop passing the ball around and do your job. If you go back 60 years, that's what Hitler did. He brainwashed the people that the Jews are subhuman. You know. Big pharma is back as Hitler and the Pain Management Society is their Gestapo, and you, at the FDA, are keeping quiet. All addicts are not subhumans. Michael was not subhuman. Adrian (ph) McDonald was not subhuman. Daniel Placek was not subhuman. Adam Stroka (ph) was not subhuman. You can change all that today. Please, please, have strong warning on the bottle, "This medication can be addictive." Let the doctor inform us of the danger. Let's stop overprescribing. Let's stop the long-term use of non-cancer use of this medication.

I would just like you to look at some of the pictures of some of the kids that lost their life. None of them were subhumans, none of them wanted to be addicted, none of them were street dwellers. These were all very productive people.

Thank you.

DR. THROCKMORTON: Thank you.

Mr. Jackson?

MR. JACKSON: Thank you. I'm Pete Jackson, and I am President of Advocates for the Reform of Prescription Opioids, a nonprofit organization in the U.S. and Canada working to end the epidemic of death and addiction that according to CDC has resulted directly from the overprescribing of prescription opioid analgesics. ARPO represents families from across North America that have been devastated by prescription opioids. Our mission is to ensure that opioids are marketed, prescribed, and used in an evidence-based manner. The majority of people for whom we grieve were pain patients.

I'm here because in 2006 my 18-year-old daughter, Emily, lost her life after she consumed one OxyContin pill swallowed whole that had been offered to her by a relative. My daughter was a wonderful young lady, the babysitter next-door, the pitcher on her softball team, the friendliest girl you could ever possibly meet. This was not supposed to happen to her. The OxyContin that killed my daughter was not her prescription, however, her case underscores how easily

and how innocently an unspeakable accidental tragedy can happen with these dangerous opioid medications. We are fooling ourselves if we continue to believe that these medications can be widely prescribed across the board for virtually all types of levels of pain and not result in many more tragedies like hers to patients and nonpatients alike. The loss of life will continue to rise each year and it will be on your watch, FDA.

Any review of the labeling of prescription opioids must begin with an understanding of the harm that is being inflicted on the public under the current labeling. During the past decade or longer, policy changes at FDA have not been responsive to the escalation in deaths and addictions from opioids. Your deliberations in this proceeding must never lose focus of the many tragedies that we continue to suffer. You must recognize the failure of the current labeling to protect the American public health.

This graph provides conclusive evidence that we are living in a time of unprecedented access to opioid analgesics. Between 1999 and 2010 there was a fourfold increase in the sale of prescription opioids.

We consume 80 percent of the world's opioid analgesics. The result has been a fourfold increase in deaths, a sixfold increase in treatments for addiction to prescription opioids over the past decade. We are losing more than 16,000 people a year, and since 1999, over 100,000 people have lost their lives to prescription opioids. The correlation between sales on the one hand and deaths and treatment admissions on the other is irrefutable evidence that overprescribing is driving this epidemic. This is not an epidemic of abuse. It is an epidemic of overprescribing.

FDA plays a key role, as FDA is required under federal law to review and approve a drug only after it has been proven safe and effective for a particular indication. This came about as a result of the Food, Drug, and Cosmetics Act of 1938, which required premarket approval of all drugs based on a demonstration of safety. A manufacturer must prove a drug is safe as labeled before the drug can go to market.

Then in 1962, the Kefauver-Harris Amendment added the requirement that a drug's manufacturer must

also provide substantial evidence of a drug's effectiveness.

In stark contrast to these mandates, the overly broad indications on opioid labels are not supported by medical evidence. Placing a "moderate to severe" label on all opioids has amounted to an open invitation to the drug companies to market these lethal narcotics broadly with little restriction and they have responded by heavily marketing opioids to prescribers.

OxyContin provides a perfect example, with Purdue Pharma spending as much as $200 million a year on promoting a single opioid. Books, medical literature, and court documents all describe in detail the all- expense-paid symposia held at resorts, branded promotional items, targeting the highest prescribers of opioids, manipulating and mischaracterizing clinical data, and intentionally misleading doctors about the true risk of OxyContin. Media coverage and the ongoing Senate investigation highlight what levels a pharmaceutical industry will go to in order to increase sales. FDA has encouraged this heavy marketing push by industry through its lax labeling of opioids.

ARPO believes that this meeting offers FDA an important opportunity to change the current labeling of opioids to reflect the very real dangers of overdose and addiction and to more reasonably align with what the science tells us about the safety and efficacy of long- term opioid therapy. We strongly support the proposed labeling changes in the PROP Citizen's Petition because they will restrict industry marketing to that which is supported by clinical evidence while placing no restrictions on prescribing for patients.

If FDA wants to implement truly effective prescriber education, start by fixing the misleading labeling currently on all opioid labels. And how can FDA not seriously consider labeling changes for a class of drugs that has the same addictive qualities as heroin when its commissioner has stated publicly that heroin has, quote, an addictive potential that makes its medicinal use dangerous and inappropriate?

My daughter lost her life through a one-time accidental encounter with a dangerous opioid drug. Teenagers don't always make the best decisions. Who knows why she chose to accept that pill? She had

cancer and an associated anxiety disorder, and she got some bad advice from someone she trusted. She had no idea of the risk involved. But other people lose their lives when no accident is involved. They become addicted after being put on a doctor's prescription. Both of these scenarios are occurring much more frequently as a result of the overprescribing that has resulted from the unrestrained marketing of opioids. The challenge for FDA is to indicate through labeling the uses for which these potent drugs are proven safe and effective and to discourage their nonselective use for all types and degrees of pain across the board.

FDA, it's time to get the labeling right. This is my eighth FDA meeting I've been to, and over that timeframe since my daughter died in 2006, I have not seen anything change. So it's about time to start by fixing the labeling.

Thank you.

DR. THROCKMORTON: Thank you, Mr. Jackson.

Ms. Foster? FDA Questions

DR. THROCKMORTON: I'm sorry. Did anyone on the panel have questions for the four speakers that

we've heard to date? I apologize.

(No audible response.)

DR. THROCKMORTON: Okay. Thank you.

MS. FOSTER: Good morning. I'm Wendy Foster, Senior Advocacy Ambassador for U.S. Pain Foundation, a national organization founded by people with pain for people with pain. I would like, if I may, a moment to ask each of you to imagine yourself as a person with chronic pain, not intermittent, but intense, unrelenting chronic pain. Now imagine taking years to find the right medication to help with your pain. Oftentimes the pain does not leave but merely has the edge taken off, but any relief is a victory to a person in pain.

Now imagine that you've been able to take the medication without many adverse side effects and you're beginning to feel that you can start to live your life even a little more fully. Now imagine that just when you've begun to feel that you may one day feel whole again you're told that you've reached the maximum duration allowed for taking this med, the very med that has allowed you to have peace at times. You're forced

to end the treatment. You now find yourself back where you started, in excruciating pain, looking for another medication to help. This is what will happen to many chronic pain sufferers if the regulations and caps on opioid analgesics for chronic non-cancer pain are put in place.

In my case, it could prove to be most difficult to obtain the necessary help via pain medicine, as I do not have a definitive diagnosis. Over 20 years ago, I was suddenly stricken by my as yet undiagnosed illness. It's been referred to as bilateral restrictive lung disease secondary to a proximal myopathy. In simple terms, the muscles closest to my torso are weakening. My diaphragmatic muscle is impacted severely, as I am not strong enough to take a full breath. When healthy, I have a total lung capacity of 50 to 60 percent; when ill, much less.

I also suffer from severe atypical migraines, which on at least three occasions have proved to be mild strokes. I have poor balance both from my weakening muscles and from the mild strokes. I have spinal stenosis, which is forcing three vertebrae into

my spinal column compressing my nerves, resulting in severe pain. On a good day, my pain level is an 8; on a bad day, 10 or higher.

These are just three of several health issues I face on an ongoing basis, all contributing to my severe chronic pain. I am blessed that I have my service dog by my side to help with the skills I can no longer accomplish myself as well as be my confidant when I am at my lowest due to an astronomically high level of pain. If a patient is fortunate enough to find a medication that works for their pain, it is their own doctor who should make the decision of what medication is right for that patient. It often takes a patient years to find the right physician, whether primary care or specialist. Once the medical professional is found who complements the patient's needs, he or she is the one trusted to make the proper medical decisions for their patient. The doctor should not be forced to follow a predetermined course of treatment, as each patient and each case is different from the next.

Although the U.S. Pain Foundation acknowledges the medical literature suggesting that

long-term use of opioids may be neither safe nor effective for many patients, especially when prescribed in high doses, we feel the recommendations of a maximum daily dose equivalent to 100 milligrams of morphine for non-cancer pain and a maximum duration of 90 days for continuous daily use are extreme measures. It is our opinion that the patient, the person living with the unrelenting pain, will suffer severe consequences from such drastic actions. A doctor-patient relationship is very important when looking at overall outcomes of patient care, not only protected, but also nurtured.

Physicians should be aware of a patient's entire history before deciding on the most appropriate care. Should it not be the responsibility of the patient's own physician to make the decision as to the proper course of action for their patient? The physician should be aware and responsible for the proper dosing and, if necessary, the limiting of the number of pills dispensed at any given time. More closely monitoring of the chronic pain patient and their pain medication regimen is in the best interest of both the patient and the physician. U.S. Pain does

not feel a one-size-fits-all mentality will help the medical or pain community. We agree there is a problem and are committed to finding ways to remedy it; however, we do not think strict mandates are the answer. We look forward to collaborating with all sides in order to find a solution to this undeniable problem while also making sure the right to needed access is protected for our members. It should not be necessary to accommodate one group at the expense of another; neither should be sacrificed.

Thank you.

DR. THROCKMORTON: Thank you, Ms. Foster.

Mary, I think we have a video testimony next?

MS. GROSS: Audio.

DR. THROCKMORTON: Audio?

MS. ATIYWARIII: (By audio, hard to hear.)

DR. THROCKMORTON: That was Zxy Atiywariii. I think I'm saying the name more or less correctly.

Patricia McDonald is next, Mary?

MS. McDONALD: I live in Buffalo, New York. I'm active with Save the Micheals of the World, a group dedicated to saving families from the devastation of

the current prescription drug use epidemic. Two years ago yesterday I experienced a mother's worst nightmare. At 3:00 in the afternoon my beautiful daughter, Adrianne, told me, "Mom, I'm going up to take a nap. When I get up, I'll cut your hair. I love you."

Two hours later, at 5:00 p.m., that Super Bowl Sunday, I called her from downstairs to see if she was awake yet. She didn't respond, which was unusual, even if she was sleeping. I got a sick feeling in my stomach as I walked up the stairs to knock on her bedroom door. Before going in, I again called her. There was no answer. I tried opening the door, but it was blocked. It took all the strength I had to push the door open. Adrianne was lying on the floor in front of the door on her back with her legs still crossed Indian style. My beautiful girl, my only child, laid on the floor dead. I had such a sense of deja vu that day in the fact that I kept thinking, I've seen this before, I've seen this before. I tried desperately shaking her to wake her up, but all I felt was my already cold, unresponsive, beautiful girl. My beautiful girl, my baby, was colored yellow-blue. I was reminded of how

blue she was when she was born.

This is my daughter. This is Adrianne. I was blabbering when I called 911 to come home. I called my sister, Eileen, to please come over. I rushed downstairs to put the dog in the yard before the police came. I ran upstairs again to stay with my daughter. I didn't want to leave her alone. When the police came, they kept me out of the room and told me to go downstairs, that it was better for me not to be there. My sister and her husband arrived while the police were there. I asked the cops if I could go upstairs to be with Adrianne again, and they agreed but only for a few minutes.

I didn't know Adrianne was in trouble. I was in the house just a floor below. It will haunt me for the rest of the my life that I didn't get to her on time. I can't forgive myself, nor can I forgive myself for the fact that Adrianne died alone and I wasn't there to at least hold her or comfort her during those moments. I can't shake the memory from my mind. Adrianne had just turned 27 years old.

You see, for 3 years prior, Adrianne was

prescribed hydrocodone for lower back pain by her primary care physician. Not once did he refer her to physical therapy or a specialty consultation. Not once did he order a simple diagnostic radiology exam. Not once did he suggest she titrate off the hydrocodone to a nonaddictive pain medication. But most importantly, not once did he inform her of the addictive nature of hydrocodone. Instead, he kept refilling her scripts and sending her on her way until February 4th, 2011, when he abruptly cut her off and informed her she needed an MRI. And I know this because I have her medical records. Two days later, being sick from withdrawal from hydrocodone, she went out and found the heroin that killed her. A week after that, I found text messages on Adrianne's phone stating, After 3 years, my doctor cut me off the Lortab without evening weaning me; what am I going to do with zero, zero pills? Explanation, explanation, explanation, question mark, question mark.

I don't need scientific facts to prove the point that opioids need stringent warning labels. Across America, my daughter, myself, and the thousands

of other kids lost and their grieving families are the statistics. I am a statistic. Adrianne is a statistic. Why is it that the FDA, an organization designed to protect us, finds it acceptable that every 19 minutes in America someone dies from prescription pill-related deaths? Why is it that until now the FDA has found it acceptable that patients aren't sufficiently informed and warned of the dangers of prescription narcotics? Why has the FDA not previously acted on the fact that opiate prescriptions are just as dangerously addictive, even when taken as prescribed, as heroin? Why has the FDA put more faith in what the pharmaceutical companies have to say and the pain management societies, who are funded by the pharmaceutical companies, have to say than we, the American people, who have already been proven to be devastated by these drugs? Why has the FDA not acted sooner and more aggressively to save lives lost to unnecessary addiction to these drugs?

Had the FDA acted sooner, when it initially became evident that lives are being lost at increasingly alarming rates to the prescription drug epidemic, I might still have my daughter, these

families in here before you who lost their loved ones might still have their children. I will never see Adrianne's beautiful face again. I will never hear Adrianne's giggling laughter. I will never watch as she gets married and share in the joy of becoming a mother. I will never again hug her. I will never again have the joy of hearing her voice on the other side of the phone saying, "Hi, Mom." I will never ever see Adrianne again.

I have nothing personally to gain or lose standing here before you. My world is already shattered, but you, the members of the FDA, have a chance to save your own kids, your own family members, and the next generation from this devastation by doing the right thing. Just do the right thing. Insist on proper warning labels and restrictions on prescription narcotics.

Thank you.

DR. THROCKMORTON: Thank you.

Mary, is there another speaker in this panel?

MS. GROSS: No. FDA Questions

DR. THROCKMORTON: Okay. And do any of the

panelists have questions for any of the -- okay.

Let me first thank everyone that's shared their personal stories with us here in the last two sessions. I'm going to suggest that we take a 15-minute break and come back and gain a little bit of time. So back at 10:15 let's say. Thank you very much.

(Break.)

DR. THROCKMORTON: And I would ask the next eight speakers to come to the table.

So I have Mr. Twillman, Mr. Manougian, Ms. Abernethy, and Charles Argoff are the next four speakers. Why don't we go ahead and have Mr. Twillman, please.

DR. TWILLMAN: Thank you very much for the opportunity to be here today. What I want to do is to give you three considerations to think about over the next couple of days as we look at the use of opioids for chronic non-cancer pain. I'm the Director of Policy and Advocacy for the American Academy of Pain Management.

These are my three key points. First of all, non-cancer pain is too diverse in its response to

opioids to be appropriate for any singular indication related to opioid therapy. Cancer pain versus non-cancer pain is a distinction without a difference and should not be used as a consideration in determining indications. And the absence of evidence does not constitute evidence of absence.

So with respect to the first point, non-cancer pain, it's a category that subsumes pain conditions associated with literally hundreds of diagnoses some of which respond very well to opioid therapy and some of which don't. Because some of these are severe and last a long time, we may need to use high doses or long duration of opioid therapy for some patients, yet for other forms of non-cancer pain, even low doses and/or short duration trials are generally considered ineffective and potentially even harmful.

You can see on the left there is a sampling of some of the conditions that we believe to be more appropriate for opioid therapy under chronic non-cancer pain, things like sickle cell disease, various forms of arthritis, and so forth. And on the right is a list of other non-cancer pain conditions for which opioids

might be much less effective and are not supported by use of guidelines.

So in conclusion, with respect to this point, opioids are recommended and appropriate for some types of non-cancer pain but not for others, so a blanket indication would seem to me to be inappropriate, and certainly for all types of non-cancer pain, individualizing each patient's care plan is absolutely necessary.

Now, with respect to the contrast between cancer and non-cancer pain, cancer pain has often been defined as being due to the cancer itself or due to its treatment. That distinction between cancer and non-cancer pain I think is a vestige of the state of cancer care in the 1980s and 1990s. At that time, the treatment of pain in people with cancer was very poor. Cancer treatment was often ineffective at producing long-term survival, and so what you wound up with was a situation in which many people died with cancer and uncontrolledpain. The oncology and the pain communities advocated at that time for policies increasing access to opioids for cancer patients, and

rightly or wrongly, that policy then was extended to non-cancer pain. The distinction between cancer and non-cancer pain has persisted despite the fact we've had substantial increases in long-term cancer survival and in chronic pain due to cancer and its increasingly toxic treatments.

How do you distinguish between cancer pain and non-cancer pain? At what point does persistent pain from cancer therapy, such as peripheral neuropathy, come to be seen as chronic non-cancer pain as opposed to cancer pain? Let me give you a case example that illustrates how complicated this can be. A 17-year-old female, status post allogeneic bone marrow transplant for the treatment of acute lymphocytic leukemia develops graft- versus-host disease. She is treated with a long course of high-dose corticosteroids and, as a result, develops avascular necrosis in both shoulders and both hips. She requires high-dose opioid therapy to achieve pain control, stays on that high-dose opioid therapy functioning very productively for several years before she undergoes four joint replacement surgeries, and

then is able to stop using her opioids. Is this cancer pain or non-cancer pain? In reality, the pain is caused by a complication of a treatment for a complication of a treatment for her cancer. How would the appropriate treatment differ if the avascular necrosis was not even remotely related to cancer therapy but caused by something else? More to that point, how do you treat the following differently: spinal compression fractures resulting from multiple myeloma versus from osteoporosis; phantom limb pain from an amputation-related osteosarcoma versus a traumatic amputation; peripheral neuropathy from chemotherapy versus diabetes; post-thoracotomy pain syndrome from a pneumonectomy for lung cancer versus a post-traumatic chest tube placement? How does our nociceptive apparatus and how do our opioid receptors know if we have cancer or not, and how do they change as a result of that?

So in conclusion, I think creating indications based on whether the cause of pain originates with cancer or not is inappropriate, and there may be other ways to look at this that may be

more helpful.

Finally, the absence of evidence does not constitute evidence of absence. I think by the end of tomorrow we'll probably all agree that we don't have enough randomized controlled trials of opioids that last beyond 12 weeks duration, meaning we have a relative absence of evidence. It's been implied by some that this means opioids do not work for chronic non-cancer pain; i.e., we have evidence of absence, and therefore they should not be used in this setting. I think that's fallacious logic. The absence of evidence only allows us to say we have an absence of evidence.

We have clinical and observational data that indicate that some people do indeed benefit tremendously from long-term and/or high-dose opioid therapy. And to get the right answers, we have to ask the right questions. I think one wrong question is, should we use opioids to treat chronic non-cancer pain? I think an alternative which may be one of the right questions is, in which patients should be use opioids to treat chronic non-cancer pain? at what doses? for how long? with which precautions? and with what kind of

monitoring? Once we have the right questions, then, we need to undertake the research that we need to give us the right answers.

And with that, I'll stop and let the others speak. Thank you.

DR. THROCKMORTON: Thank you.

Ms. Abernethy?

Sorry. Ed, Mr. Manougian. Edward Manougian?

MR. MANOUGIAN: (By video.) A few words about the hydrocodone acetaminophen issue. I think the major problem stems from chronic pain syndrome, which is a very difficult stage of the pain to treat, and it requires high doses of opioids, and the mixture of the hydrocodone with the acetaminophen does not sit well with that program. The stage of chronic pain and acute pain the acetaminophen would be appropriate, but it's not appropriate with the hydrocodone in the chronic pain syndrome stage, which is the exhaustion stage in the general adaptation syndrome.

If we had the hydrocodone alone without the acetaminophen, we would have another medication that can be used, and with the shortage of opioids appearing

in the market, I think it would be beneficial to have the hydrocodone alone. The acetaminophen-hydrocodone combination would be just fine for individuals with chronic pain or acute pain since they can be controlled rather easily. I have made an illustration to show the differences in this. The illustration is the pathophysiology of pain, which was developed initially by Hans Selye back in the 1930s and pretty well developed by the 1950s. It has the stages of the acute, the adaptation, the exhaustion stages in either recovery or death. And it's this stage of recovery or death that is the problem.

I'll point out these stages in this illustration. This is the opioid level needed to suppress pain, and here we have the opiate level, which is the drug level, to relieve pain, and if a person is injured and goes into pain, the acute stage, the opioid level will rise, and even if the treatment is successful, the opioid level will drop to its homeostatic level. There is always some present. But if the treatment is unsuccessful and the person goes into chronic pain, then the opioid level needed is much

smaller than it happens to be when the person arrives at the stage of exhaustion.

At this stage, the body is no longer able to produce the opioids, which is what this line depicts, it is no longer able to maintain the opioids, so to shore up the opioid level, more is needed here, quite a bit of difference, which leads to a lot of problems. Individuals are afraid to provide the patients with this much medication, they wind up oftentimes repeating visits to emergency rooms, going to the street to buy drugs, not knowing how to take the drugs when they get them on the street because there is no prescription with them, and if they get the long-acting or the sustained-release medications mixed up with the quick-acting medications, if they were taking the long-acting ones in place of the short-acting ones as though they were short-acting, then the drug piles up and can pile up very quickly and be very lethal.

So these are precautions that are needed. These people that are out on a limb trying to get their pain managed, I'm sure that a good deal of the deaths we see with the opioid overdoses are related to that

inability to take the right dose and getting drugs off the street. Now, they shouldn't be having to get these drugs off the street. If the doctors would treat them properly, we would not have that problem.

In 1987, it was discovered that the doctors were a big problem by not treating the patients adequately and were leaving them out to wander off for themselves and getting into trouble and wind up going to the emergency rooms frequently trying to get medications and found that a new name was provided in 1987, a pseudoaddiction, and it's clear now that any statistics that has to deal with addiction has to consider whether or not pain was involved, in which case it most likely is pseudoaddiction and not addiction. Therefore, any statistics that only mentions addiction and comes up with numbers with a comment about pain is invalid.

The process that begins with pain involves genetic changes, and these pictures depict the genetic change that takes place in over about a 6-month period. Usually it takes about 6 months for pain, persistent pain, to convert the brain from one stage to the other.

c-Fos is one of the immediate early genes that appear. It may well be that the sequence of immediate early genes that do arise may reach a point where we can use that point as a biomarker for the diagnosis of chronic pain syndrome.

The other thing that develops, which I haven't mentioned here, is the hypothalamus swings into action with the onset of pain putting out ACTH, actually putting out pro-opiomelanocortin, which has ACTH, endorphin, MSH, LPHM, indicating that we're going to have involvement of the immune system and also involvement of the GI system, and then things become complicated and the whole body starts to collapse, and that's part of this exhaustion here. All of the organs are now involved, it's a degenerative process, and can very well lead to death either by the disease itself or by suicide because people in this stage are frowned upon, they're called addicts, they're socially outcasted (sic).

DR. THROCKMORTON: Did we lose him?

UNIDENTIFIED FEMALE SPEAKER: I think that was the end.

DR. THROCKMORTON: That was the end? Ah, I see. Okay.

Amy? Ms. Abernethy?

DR. ABERNETHY: I'm over here.

DR. THROCKMORTON: Oh, okay.

DR. ABERNETHY: Hi. How are you?

DR. THROCKMORTON: Thank you.

DR. ABERNETHY: Hi. My name is Amy Abernethy. I'm an oncologist and a palliative medicine physician at Duke University Medical Center. I also direct the Duke Center for Learning Health Care and the Duke Cancer Care Research Program and I take care of people who suffer from chronic serious illness like metastatic melanoma and end stage lung disease.

I want to introduce you to three patients first. I would like you to know Janet. She's 44. She's got red hair. She developed metastatic melanoma. When we treated her with her therapy for melanoma, actually her disease is now gone, but she's been left with a horrible peripheral neuropathy and leg pain. She's been on a number of drugs, we've tried everything, and even the surgical therapies that are

options for her are going to leave her unable to walk. We've even tried three different clinical trials, and right now high-dose opiates allow her to be able to function as a hair dresser, act as a wife, and mother of her two children.

The second is James. He's 82. He's a gentleman with chronic ischemic heart disease. He's got an EF of less than 10 percent. I don't know if he's going to die tomorrow; I don't know if he's going to die in 2 months; hey, I don't even know if he's going to die in 2 years; but what I do know is that the combination of his heart drugs and opiates have allowed him to stay off of the floor crying like a baby in response to his continuous chest pain and, instead, sit on his front porch waving at people as they go by in their cars, which is how he spends most of his days.

The third patient is Steve, and Steve is 57. He is on the ninth floor at Duke Hospital. He's got recurrent lymphoma. It's throughout his lungs, and he's very breathless. We've tried everything. We have tried steroids for his pulmonary toxicity. We've tried to treat his lymphoma. He has had chest tubes and he's

had tubes around his heart, but he's still breathless. Despite all of this, he and his wife really keep trying to partner and to go forward during the last days of his life, but he can't even at this time open his newspaper because of the breathlessness when he moves his arms. We use morphine now to reduce the refractory dyspnea and allow him to talk to his wife and really have some relief from the suffering of the refractory breathlessness in his last days of life.

I come to you today in my capacity as President- elect of the American Academy of Hospice and Palliative Medicine as well as I'm a member of the Institute of Medicine's National Cancer Policy Forum and Co-chair of the NIH/NINR-funded Palliative Care Research Cooperative Group.

The American Academy of Hospice and Palliative Medicine is a professional organization for physicians specializing in hospice and palliative care, and we have nearly 5,000 members also including nurses and other health and spiritual care providers all committed to improving quality of life for people with serious and advanced life-limiting illness. We also

focus on how to best take care of their families.

I don't think anyone would disagree that there is a public health imperative to address the scourge of prescription drug misuse and abuse. However, we, at the

Academy, are very concerned that efforts to stern this tide do not keep individuals with serious and life- limiting illness -- illnesses such as cancer, COPD, AIDS, end stage kidney disease, heart failure, hemophilia, and sickle cell -- from also getting the medicines that are required to treat their pain and suffering because this is indeed suffering. Our Academy members care for the sickest and most vulnerable patients, including people at the end of life, and 100 percent of us will be there someday: my children, me, and you.

A central element of providing high-quality palliative and hospice care is timely and effective management of pain and other distressing symptoms such as the symptoms of severe breathlessness. In order to do this, opioid analgesics are a critical tool in achieving that, and we tailor and individualize this

for each specific case and individual person.

As to the FDA's specific questions, first of all, I would like to personally applaud the FDA for trying to get some of these specifics. My medical students, residents, and fellows ask the same questions all the time: Is this chronic or acute?; Is this cancer pain or non-cancer pain?; How do we define severity in this particular setting?; and, Is it defined by the physician or by the patient, him or herself? And I tell them all the same thing: it depends on the individual and the individual circumstance. Especially when taking care of people with advanced life-limiting illness, we must be able to carefully titrate intervention to circumstance.

Therefore, with regard to understanding patient pain, the FDA's request for input raises some concerns from the hospice and palliative medicine community. Categorizing a very diverse patient population with chronic pain into a group of chronic non-cancer pain versus cancer pain lumps subgroups -- for example, low back patients who have not benefited from multiple surgeries, advanced multiple sclerosis

patients, and elderly people with severe cardiac ischemia, like James -- all of these individuals have chronic non-cancer pain, and they're all very different circumstances. They differ greatly and there are different mediators of individual risk, such as history of substance abuse, that vary within each individual as well as each individual population.

We also know that the term "cancer pain" is vague when referring to the millions of people who are long-term sufferers, like Janet at the beginning of my story. What is the demarcation point for cancer pain to go to non-cancer pain, especially when we consider the story of people like Janet, whose disease is now gone but they're left with the suffering from the treatments that we used to treat their disease in the first place?

Cancer patients who suffer from chronic cancer- related pain also suffer from acute and/or chronic pain that is unrelated to their cancer, and it's very hard to figure this out and can be difficult for both the patient and the physician confusing both. Not only is it impossible and impractical to

distinguish what proportion of these patients cancer pain is related to the cancer versus how much is not related to the cancer, it's also impossible to target systemic opioids just so that they relieve cancer only and not the non-cancer segment.

There is a seminal article in the Clinical Journal of Pain that reminds us that pain is pain, nociception is nociception, whether cancer related or not, and that the pathophysiology is often the same. The difference is meaning, processing, and perception. What does the illness mean? Am I supposed to suffer? And the corollary issues like sleep and ability to get around and move your joints. But the nociception is the same, and it's hard to distinguish between the two, especially as we come to terms with care at the end of life.

Finally, distinguishing between acute and chronic pain seemingly ignores a third category of pain management. There are often special circumstances within the practice of hospice and palliative medicine that require high-dose opioids to assure comfort for pain and other distressing symptoms like the shortness

of breath experienced by Steve at the beginning of this narrative. Steve couldn't read his newspaper because of the breathlessness, but morphine gave him a simple quality of life issue back.

To date, there is no scientific basis to support calls to restrict the dosage and duration of treatment for pain, and we object to such considerations that would unduly burden patients for whom we care. Arbitrary regulations put real people at risk and don't allow us to focus on generating the right data needed to understand how to best take care of this person with the right intervention at the right time, including opioid analgesics in the palliative care toolbox.

The sad, remarkable truth is that we will all die. Horrible things have happened to real people because of misuse of opioids, and I absolutely agree, but we have to beware of putting that fact first and making it impossible to take care of the suffering experienced in the setting of chronic life-limiting illness.

For example, many hospice patients have acute

symptoms from non-cancer terminal illnesses and require more than 100 milligrams of morphine equivalents every few hours for sufficient pain and symptom control. Likewise, many palliative and hospice patients with non- cancer-related pain and other symptoms from serious or terminal illness experience these symptoms for periods of time much longer than, say, an arbitrary 90-day maximum that some have suggested, if there is a 90-day limit for non-cancer opioid pain management but we have to stop opioids in the last 10 days of life for a person dying of MS who happens to live 100 days instead of 90. Palliative and hospice care appropriately emphasize individualization, as I've highlighted, and I think we need to continue to do that.

Finally, we're similarly concerned about discussions focused on opioid labeling. Let's go back to the case of Steve and consider the conversation around dyspnea, which is a subjective experience of difficult or distressed breathing and is common in people with cancer, AIDS, emphysema, and other terminal illnesses. In fact, we see it in over 50 percent of

patients at the very end of life. One study noted that family physicians find dyspnea to be the most distressing symptom in dying patients. It is often alleviated by a titration of opioids, and refractory dyspnea even through these medications may not still go away. You can see how a requirement that adheres only to labels and approved indications would be catastrophic for the care of people with advanced refractory dyspnea at the end of life.

Further, restricting how opioids are labeled with regard to indications for pain, as some have proposed, is also likely to result in patients being adversely affected. Non-experts are liable to look at the label as reflecting a standard of care and withhold therapy from patients who could benefit. In addition, some payers may choose not to cover treatment newly considered off-label, and the costs of treatment will be transferred to patients.

In the end, if regulatory or legislative changes would restrict opioid therapy, such actions should only be based on rigorous scientific studies that demonstrate a reduction in opioid misuse and abuse

without burdening legitimate patients in need. Until then, we suggest the drug control policies should include ongoing efforts for prescriber education and target sources of drug diversion such as pharmacy thefts, forgery, and nontherapeutic prescribing, and that proven strategies aimed at substance abuse, diagnosis, and treatment that do not limit access to medications for legitimate indications should be expanded.

In 2001, the DEA Administrator, Asa Hutchinson, joined 21 health organizations, including the American Academy of Hospice and Palliative Medicine, in releasing a joint statement titled, "Promoting Pain Relief and

Preventing Abuse of Pain Medications: A Critical Balancing Act." This statement called for a balance in public policy between ensuring legitimate patient care and preventing diversion and abuse. The statement warned, "Focusing only on the abuse potential of a drug could erroneously lead to the conclusion that these medications should be avoided when medically indicated, generating a sense of fear rather than the

respect for the legitimate properties."

The American Academy of Hospice and Palliative Medicine stands ready to partner with the FDA and other federal agencies to develop a policy that strikes the balance necessary to curb the misuse and abuse of pain medicines in the United States while also preserving access for patients with legitimate need. This will require additional research, extensive, honest dialogue, and recalibration as unintended consequences become clear. Above all, though, it will require recognition that overdose deaths and untreated suffering are both unacceptable.

Thank you.

DR. THROCKMORTON: Thank you.

Mr. Argoff?

DR. ARGOFF: So thank you for the opportunity to speak. I am a Professor of Neurology at Albany Medical College and I direct the Comprehensive Pain Center there in Albany, New York, and I represent the American Academy of Pain Medicine Foundation as its president.

The first thing I would like to point out is

that pain management is not about opioids only, that when we talk about pain management in the medical community we should be talking about a comprehensive, multimodal approach to the management of an individual's pain that should be individualized to that person's need, that may include or not the use of an opioid analgesic, and that, as has already been said, needs to be considered on an individualized basis, but we can see from this slide how many other therapies are available.

We also can see from this slide, this is an extrapolation of what happens in the pain management community in the sense that we don't have evidence that any single treatment provides 100 percent pain relief to 100 percent of the patients to whom they are offered, whether that be an opioid or a non-opioid.

So, for example, in this study published in JAMA in 1998, an accomplished researcher and group of individuals demonstrated that gabapentin was superior to placebo in the treatment of painful diabetic neuropathy. However, to enter into that study, you needed 4 out of 10 pain or greater. The majority of

patients who successfully treated in the gabapentin arm still had enough pain at the end of that trial to reenter the study. Yes, it was better than placebo, but the pain intensity was still higher than the entry level of 4. That's reality. The reality is that any of these interventional treatments for chronic pain, as listed on this slide, do not provide 100 percent of people with 100 percent benefit, and, in fact, having written the national standards for lumbar epidural steroid injections and published these in Neurology myself, we know that they're only expected to give people between 4 and 6 weeks of relief on average based upon the best available data. So we have even in interventional pain management situations where not all treatments will work for all people and especially will only partially treat their pain.

So this dichotomy of pro-opioid and anti-opioid is false. It does not serve the health care professionals, patients, or society well. Ethical health care providers are pro-health and make treatment decisions within that context. Clinicians must learn how to select patients for all pain management

therapies when indicated -- and that's important, when indicated -- and manage patients on pain management therapies as safely and effectively as possible.

So let's talk about evidence-based medicine for a second. This is a definition that was published over a decade ago. Evidence-based medicine has been defined as a conscientious, explicit, and judicious use of current best evidence" -- and this is the most important part -- "in making decisions about the care of individual patients." Another evidence-based definition includes very much the same language, and the last line there is, "Evidence-based medicine is intended to integrate clinical expertise," yes, clinical expertise, "within the research evidence and patient values."

So how good is the evidence? Let's talk about that for one second. The minimum duration of analgesic clinical trials to establish efficacy from an FDA point of view -- registration viewpoint is 12 weeks -- once efficacy is established an open label extension period of 52 weeks is required by the FDA to establish the safety of that analgesic's safety, of that

analgesic, and safety is also measured during the 12-week efficacy trial. Therefore, the current FDA approval process examines opioid analgesics in a systematic manner for a time period far in excess of 90 days in trials involving patients with chronic moderate to severe pain. Although efficacy is not the designated endpoint of long-term safety studies, it is likely that patients who complete those studies for 52 weeks would not be remaining in those studies unless they were continuing to experience benefit and some of those published trials have actually documented the degree to which analgesic benefit continues.

Many of these studies, not all, have been published. An example of such studies would include a multicenter study of oxymorphone extended-release and long-term relief of opioid naive patients with moderate to severe pain in which 64 percent of the patients in that study completed a 6-month study. In a different study of oxymorphone extended-release, 40 percent of people completed the open label extension study after 1 year. In a study of oral hydromorphone, over 30 percent of those individuals completed a 1-year study.

In a long-term safety and tolerability study of tapentadol extended-release, 46 percent of patients completed that 1-year study. And I know that we've already said, there has already been a previous presenter stated, that headache is not a typical indication for chronic opioid use, but in the longest study ever done of this type published in Neurology in 2004, of 160 patients who were started for intractable headache on daily scheduled opioids at the Michigan Headache and Pain Institute, after 3 years, 26 percent of those patients originally started continued on opioids with a greater than 50- percent reduction in their pain.

So evidence-based medicine must yield to evidence-based practice. This is real. This is a real story. This came to my office as a request for consultation last week, and it's been de-identified.

"DR has been under my care for many years and has been on many regimens for management of a chronic post-cervical fusion pain including opioids and adjuncts. Currently, my colleagues and I are in the process of discontinuing prescribing opioids in

patients under 65. The lack of consensus in the profession about the efficacy of opioids in chronic non-cancer pain makes it difficult to justify use of opioids in primary care practice." And this is the most telling part, then he says in his letter, "Having said that, I think DR has done better on opioids than without them." We really need to think about the morality, the ethics of changing anything. People will suffer if there is a label change that does not allow people proper access to these treatments when they're appropriate for these treatments.

Thank you.

DR. THROCKMORTON: Thank you. FDA Questions

DR. THROCKMORTON: Do members of the panel have questions? I guess maybe I'll just start. I would be interested in if you could provide the citation that you mentioned about the chronic headache study. One thing we ask in the FR Notice is evidence on the chronic efficacy or safety of opioids, and if you could just submit that to the docket or something.

DR. ARGOFF: Right. Yeah. Can I copy it down? I can give it to you right after the session.

DR. THROCKMORTON: That would be useful. And then the other question for you, just to clarify. So if I'm understanding you, you're looking at the long-term extensions of the randomized controlled trials and inferring from continuing in the trial to be the same as efficacy. So if --

DR. ARGOFF: Well, if I may interrupt, in the real world, the fact that a person with proper monitoring, I think you may agree that there is significant monitoring in a clinical trial, even in an open label extension study, they're still being monitored, and I completely understand where you're coming from, that some of the studies, the open label extension studies, they may not be required to measure an ongoing efficacy, but some of them do measure it, and the ones that I brought up actually many of them actually document the actual pain intensities, especially the oxymorphone extended-release, they were designed to do that. And so, yes, there is an inference being made, but those kinds of studies reflect more real world clinical practice.

And so by no means -- and I have not said

that 100 percent of people in these studies, that 100 percent of people do remain or should remain, you know, treating people with opioid analgesics or treating people with beta blockers for hypertension, or treating people with simvastatin for hyperlipidemia is on a trial basis and you evaluate the potential benefits and risks and you follow that person. And I'm just saying that those 52- week extension studies give us an insight into not only the FDA process but the fact that people are being monitored on a long-term basis.

DR. THROCKMORTON: Thank you.

Do others have other questions or comments for any of the speakers?

(No audible response.)

DR. THROCKMORTON: Thank you. Thank you very much.

Mr. Michna?

DR. MICHNA: Hi. I am an academic pain physician at Brigham and Women's Hospital in Boston, Harvard Medical School, and today I'm representing the American Pain Society. The American Pain Society is a multidisciplinary organization the majority of which

are non-physicians, and we're dedicated to pain research, education, treatment, and advocacy.

The American Pain Society strongly agrees with the intent to promote responsible opioid prescribing and to reduce opioid-related harm. However, the APS does not support the proposed labeling changes, as we perceive an insufficient scientific evidence base to support these recommendations. Further, we're concerned about the implementation of these labeling changes, which would dictate indications, dosing, and duration of opioid treatment and will not accomplish the intended goals but instead have unintended negative consequences for patients including those not limited to untreated pain and a loss of access of individualized care.

And I would like to just relate a little clinical scenario that happened after these proposals were published and made public. Surprisingly, within 3 weeks of the publication of this proposal, one of my colleagues received a letter from one of our local insurance companies denying payment of continuing chronic opioid therapy to a patient that suffered from

a post- traumatic workplace injury, and he was on a stable dose of opioids, and, surprisingly, the first thing they listed as a reason was merely the proposal that was set forth that, of course wasn't discussed in a larger forum, wasn't reviewed by any regulatory authorities, but you can see how insidious this whole process is. You have insurance companies that are pressed to save money and they will use any evidence they can to deny access of care.

It is clear that there are subpopulations of patients with chronic pain for whom the risk-benefit balance is better for opioids, sometimes beyond the limits proposed by these regulations than for other available treatments. For some patients, opioids are a clinically appropriate treatment of moderate pain at doses higher than 100 milligram morphine equivalent or for longer than 90 days.

We strongly support additional research to better inform safe and effective practice with respect to opioids. For patients with pain, implementation of labeling recommendations would likely shift the balance of suffering away from the sometimes negative

consequences of opioid to the negative consequences of pain unless there was a simultaneous massive increase in available alternative and effective treatments for chronic pain.

The American Pain Society would like to focus the discussion of the patient, attention to the following issues we believe will help us achieve critical balance between optimizing pain management and reducing harm to patients and society. Like other medications, opioids achieve good pain control with minimal adverse effects for some patients but clearly not for others. At present, we lack adequate evidence to predict which patients are which. Certainly, additional research funding is needed to support long-term studies to address these issues.

There is clear need for developing new pain treatments and more widely disseminating current available therapies that achieve desired levels of pain relief and increased quality of life while producing less harm to patients and society. Additional research funding is needed for fundamental discovery and treatment targeted development as well as

implementation research to enhance delivery of the presently available but poorly disseminated treatments. Efforts are needed to increase availability of multidisciplinary care in order to provide patients with comprehensive evaluation and treatment of their pain. This will both improve pain outcomes and reduce reliance on opioids as a cornerstone of treatment of chronic pain.

Taking a regulatory approach is something that we all agree is a very complex issue, maybe shortsighted, when there are currently many initiatives in evolution that are expected to improve on the issue of opioid prescribing. In addition, numerous interprofessional initiatives, both national and at the state levels, are bringing together law enforcement, health care providers, licensing boards, educators, state agencies, and other stakeholders to implement multidimensional solutions to the broader problem of prescription drug abuse.

In the face of these promising initiatives aimed to reduce opioid-related harm, in the absence of adequate evidence to support specific labeling

recommendations and with the uncertain risk of unintended health-related suffering, we believe the FDA should not change its labeling of opioid products at this time.

Thank you.

DR. THROCKMORTON: Thank you.

Ms. Carr?

Mary Gross, could I speak with you for a second?

DR. CARR: Hello. Good afternoon. My name is Debra Middleton Carr, and I am a practicing pharmacist. I titled my presentation, is "Waiting on the World to

Change: A Song Written by John Mayer," M-A-Y-E-R. I am a practicing pharmacist with 23 years of experience in my profession. I have dispensed Schedule IIs to IVs upon the doctors' prescription orders to treat many medical conditions. I have seen a major increase for the dispensing of controlled substances for pain also along with antianxiety and sleep aids.

How do we in the health field treat pain management with success? Pain management is a growing

indicator which has alerted the health team of the abuse of hydrocodone and oxycodone products. Rescheduling hydrocodone products to a Schedule II level will only add to a larger uncontrolled system, which is already seen with opioids. The effects of the medically needed, social, recreational, and economic gain has also increased. The mental-physical dependence of this addiction has become the greater factor for its continuous use. Drug utilization reviews on patients majorly begins at family and internal medicine practices for long-term care.

The implementation of the prescription monitoring program centralized system will aid to monitor the use of schedule drugs, Cs and IIIs, to control and decrease the abuse. We must not forget the purpose of the pain management and drug addiction program which was put in place through the methadone program. Is this program really working? The system will be in place as a safety device for chronic use.

Drug addiction must be controlled by the user and help facilitate it by the medical professions. I see a need to alternate monthly with all types and

different formulations of drugs. The day's supply is a crucial factor in hopes to eliminate the supply excess that the patient can obtain and abuse. To control drug quantities and limit the pharmacist the amount of Schedule IIs and IIIs do not decrease mental or physical dependencies. It is quite the contrary because the need to obtain becomes greater. I experience this in my workplace daily by the presence of patients and telephone inquiries for the drugs and the needs to have it.

This impact should not be controlled by insurance companies and drug suppliers. I think rescheduling hydrocodone products to Schedule IIs is not the answer to an already crippling system. We need better educational programs and more stringent policies to allow pharmacists and medical practitioners to work closer together to better treat patients with all types of medical needs. The menace to society will be felt by many more in the community.

The epidemic has become a pandemic. My frustration is felt and also with my other colleagues in the pharmacy profession. Leaving is not the answer

but to help to make the change is the solution. I am glad to see and hear that the American Medical -- Medicine (sic) of Pain Management is here today because this is one of the requests that I ask for physicians, to see, have they actually been doing or looking at how do they prescribe for pain medication? I know it's a recertification program. It's not actually telling doctors what to do and how to do these prescribing because the hours that is required for a doctor to do and to treat pain medicine is a lot less than my pharmacist experience. So that's why we need to work together closer to find out what we can do to control the abuse of drugs.

And getting back to even the long-term use of medications and the change of the OxyContins, that did not help, I still have those drugs in my counter. Patients don't want it, they will not -- they just don't want it. Doctors do not prescribe it. So as pharmacists and medical professionals, especially physicians, writing prescriptions need to work closer together. I take my time out of my daily use to call the American Medicine Pain -- I'm sorry, the American

Medicine (sic) of Pain Management to get more information about how we can inform doctors just to know exactly what are the requirements.

Two years is substantial to know exactly how we should think that doctors should prescribe medications, but I have to call consistently to speak to physicians to verify prescriptions. It's very trying.

And I have deep sympathy for the patients and parents that have lost children here. I go home daily wondering, did I do the right thing? Have I given the right patient the right medication? They're begging. They're crying. So what do we do? How do I handle this? I can't do this alone. We need help. But rescheduling hydrocodone, I don't think that's going to be the answer.

Thank you.

DR. THROCKMORTON: Thank you.

Ms. Herman?

MS. HERMAN: Hello. Good morning. My name is Gwenn Herman. I have a master's in social work, licensed clinical social worker, and I'm a diplomate-

certified social worker. I am Founder and Executive Director of Pain Connection, Chronic Outreach Center, Incorporated. Pain Connection is a nonprofit corporation that works to improve the lives of people with chronic pain and their families and educate health care providers. I have been a clinical social worker for over 30 years specializing in alcoholism, substance abuse and addictions, physical and sexual abuse, mental health disorders, and for the past 13 years, chronic pain.

I am a person who has been living with chronic pain for 17 years due to a car accident. Since my accident, I have lived with daily pain, and it has affected every aspect of my life. I had to relearn how to live over the 17 years.

In my 30 years of experience in treating substance abuse, I have seen many drugs and substances of choice come in and out of fashion: Valium, Xanax, Quaaludes, heroin, glue, spray paint, pot, LSD, speed, cocaine, methadone, crack, Adderall, OxyContin, Suboxone. These drugs are frequently taken in combination with each other and almost always in

combination with alcohol. Throughout the years, one thing has remained constant, the ability of recreational users and people addicted to these substances to find what they want in high schools, colleges, medicine cabinets, in neighborhoods, on the streets, and now online with or without a medical prescription.

The problem of substance abuse in America is vast but severely neglected, as are most mental health issues. According to SAMHSA, the Substance Abuse and Mental Health Services Administration, last year alone 20 million people who needed substance abuse treatment did not receive it and an estimated 10.6 million adults reported an unmet need for mental health care. SAMHSA has also reported that the number of emergency visits involving attention deficit-hyperactivity stimulant medications more than doubled from 13,379 visits in 2005 to 31,244 in 2010. Hospital emergency departments linked to Suboxone, a medication used to treat opioid addiction, increased substantially from 3,161 visits in 2005 to 30,135 visits in 2010 with 52 percent -- that's 15,778 in 2010 -- involving nonmedical use. According

to the latest NIDA, National Institute on Drug Abuse, survey of teen drug use in 2012, 41.5 percent of 12th graders consumed alcohol during the previous 30 days, and 36.4 used marijuana. The figures for prescription drugs were Adderall, 7.6; Vicodin, 7.5; cold medicines, 5.6; tranquilizers, 5.3; OxyContin, 4.3; Ritalin, 2.6. I am citing these statistics not as a means to advocate the relative merits of safety of one drug or another but to emphasize that substance abuse is a major health problem in this country and that it encompasses a wide variety of drugs.

My major concern, as a mental health practitioner, is that the issue has been pushed to the background by the war on drugs, the war on opioids, and the war against government spending on health care, and in particular mental health. If we persist in treating this problem as one of classification or labeling, all we are doing is tinkering with the statistics. We may move a drug up or down the pop chart of drugs of choice, but we will have done nothing to address the overriding issue of substance abuse.

Against this background, I would stress that

we are all interested in the safe and proper use of all medications. People with chronic pain rely on a variety of medications, including opioids, in order to carry out basic daily functions and achieve a minimal quality of life. There is not one drug which suits all pain patients and there is no one-size-fits-all dosage. Each patient is a unique individual and each person's pain changes many times during the day and over time. Just looking at myself personally, I may have come in here at the level of a 6 and now I'm probably an 8 or 9 from sitting all day, which just shows you the fluctuation of pain in somebody's body. That is why establishing a satisfactory relationship between patient and physician is essential.

The problem, as I see it from my work with people with chronic pain, is a need to train physicians and patients alike in the proper management of chronic pain. There is no one prescription to address chronic pain. If the FDA wishes to ensure the safe and appropriate use of all medications, including opioids, then it needs to ensure that physicians are educated before writing a prescription.

Physicians should be required to prepare a treatment plan prior to the initiation of a course of treatment with their patients. Providers must be educated in the art of working with people with chronic pain. Both physicians and patients must understand that proper treatment is not just medications and that the psychosocial aspects of chronic pain cannot be ignored. I believe that this principle applies to all types of chronic pain from whatever cause and that no artificial distinction should be drawn between one type of pain and another, be it cancer or non-cancer, traumatic, or genetic. Pain is pain.

The following issues need to be addressed. Medication is just one component of a proper pain treatment plan. Chronic pain is best managed with a combination of treatment modalities including complementary alternative medicine, CAM, including acupuncture, mindfulness meditation, guided imagery, biofeedback, breathing techniques, massage therapy, herbs, vitamins, supplements, nutrition, Eastern and Western medicine, because since pain is constantly changing in the body, we need to incorporate all these

different modes of treatment.

The whole person must be treated because chronic pain affects every aspect of a person's life: the physical, social, psychological, career, hobbies, and spirituality. All these aspects need to be integrated when developing a treatment plan. The emotional impact of the pain can often lead to depression, and some may self-medicate and even commit suicide when there is minimal monitoring of the treatment plan, including the above aspects.

Pain Connection is one of a number of organizations that provide resources and support for people with chronic pain. Health care providers need to be made aware of and recommend these resources to their patients.

In conclusion, my heart goes out to all the families and significant others who lost their loved ones to legal or illegal medications and substances and also for not having the resources to know that there are other available options out there. So I'm really very sorry for your loss, and that's what we, at Pain Connection, try to do, is to give people hope and a way

of living to get a quality of life. So I'm really sorry for all of you, but let us not sacrifice people living with chronic pain due to these losses. These are two separate issues.

Thank you.

DR. THROCKMORTON: Thank you.

Ms. Kunins, could we just have just a second?

Mary, could you come up for a second? We're ahead of schedule, and I'm trying to sort out how to manage lunch, so give me just a couple minutes. That probably is important to many of us.

(Laughter.)

DR. THROCKMORTON: Be with you in just a minute.

(Pause.)

DR. THROCKMORTON: Thank you. Sorry for the delay, folks. We're going to see if we can move the next group up before lunch, if that's possible.

But in the meantime, Ms. Kunins, why don't you go ahead, please. Thanks.

DR. KUNINS: Thank you. My name is Hillary Kunins. I am an assistant commissioner at the New York

City Department of Health and Mental Hygiene. I am also an internal medicine physician and practiced and taught primary care for more than 16 years. I cared for patients with chronic pain and patients with substance use disorders.

Our comments today are based on a review of the literature and our New York City population and prescription data.

First, I would like to address the literature on efficacy and safety of long-term and high-dose opioids. There are very few randomized controlled trials which have evaluated opioid analgesic efficacy beyond 90 days or adequately assessed safety of high doses.

This slide, with small print, shows the few trials we found with longer than 90 days of follow-up. Time constrains us from reviewing each study here, but we will send details with our written comments. One thing we would like the FDA to know is that each study has very large dropout rates, shown in the second right column. Subjects dropped out mainly because of adverse events and lack of efficacy.

Most of these papers do not report the absolute numbers of patients who are able to tolerate opioids and obtain relief. The one study that did, Mitra, found just 35 percent with pain relief at 3 months, which decreased to less than 13 percent by 6 months. They note that tolerance could explain this dramatic decrease in efficacy over time.

As this next slide shows, none of the several systematic reviews of available research find good evidence for long-term control of chronic non-cancer pain with opioids. The slide provides reviewers' conclusions, and I will highlight Trescot's. Many patients who are dissatisfied with adverse events or insufficient pain relief from opioids. For patients able to continue on opioids, evidence was weak that their pain scores were lower than before therapy and that this relief could be maintained long term.

Because randomized trials have been relatively small and short term, they cannot accurately assess long- term safety. The best available safety evidence is from observational studies, including at least four well- designed cohort studies with longer

follow-up periods.

This next slide shows overdose frequencies among different populations taking opioid analgesics. Dunn's findings here are for patients specifically with chronic non-cancer pain. They find a 1-in-1,657 rate for fatal overdoses. Although these may not seem high, when you consider that an estimated 9 million Americans take opioids for long-term chronic pain, it is easy to see how these drugs account for more than 5,000 deaths.

These studies also examine overdose risks by dose. This next slide shows that risk increases with increased opioid doses. The orange bars show that compared with less than 20 morphine milligram equivalents, or MMEs, the odds of overdose is between 2 and 11 for doses greater than 100 MMEs.

Population-based data have also shown substantial and increasing opioid-associated adverse outcomes, as you can see on this slide. More than 16,000 people died of opioid analgesic-associated overdoses in 2010.

This slide is two side-by-side maps of New

York City. As they show, New York City neighborhoods with high opioid analgesic-associated overdose deaths are where New Yorkers fill opioid prescriptions at the highest rates. Staten Island, in the darkest blue, is a borough that has not higher rates of illicit drug use compared to other boroughs but ranks highest in both prescriptions for opioids and an overdose from opioids.

We believe methods to establish a maximum daily dose of opioids should weigh benefits of therapy against risks. Doses associated with an unacceptably high risk for adverse events or that account for a large proportion of them should be used to set a maximum daily dose. The indication for opioids should also be considered. Among veterans, for example, prescribed opioids for pain, most opioid-associated overdose deaths were among patients with chronic pain diagnoses. In addition, while a given risk of addiction and of overdose might be acceptable for pain control at the end of life, the same risk may not be acceptable when it could result in years of suffering from addiction or in years of life lost.

As Mark Sullivan noted in the Archives of

Internal Medicine and quoted here, "Death due to therapy for a nonprogressive, nonfatal condition must be taken very seriously."

A maximum daily dose limit of 100 MME would likely affect a minority of patients. Using New York State prescription drug monitoring data, we found only 7 percent of New York City residents filling opioid prescriptions, which is less than 2 percent of New Yorkers received doses of 100 MME or more. Some of these were surely for cancer or end-of-life care, so even fewer patients would be affected if limits were not applied to these conditions.

A 90-day limit would also affect a minority of New York City patients taking opioids. Again, only 7 percent of those who filled opioid prescriptions did so for more than 90 days consecutively in New York City. Substantial overlap exists between those using long-term and high-dose opioids. Forty-six percent of patients who filled more than 90 days of consecutive opioid prescriptions took at least 100 MMEs per day. While these limits would affect a small percentage of patients prescribed opioids, they would achieve

substantial public health benefits. CDC has estimated that patients on at least 100 MME account for 80 percent of fatal overdoses.

Limits on dose and duration need not lead to reduced pain control. There is not convincing evidence that opioids are more effective than other therapies when used long term. In addition, if opioids are reserved primarily for acute pain and for end-of-life care, opioids are more likely to remain effective in these serious situations. Under revised labeling, prescribers could taper to labeled dosing. Based on information about tolerance and hyperalgesia, patients might derive analgesic benefit from dose reduction.

Finally, and importantly, providers may also continue some patients on opioids long term and/or on high doses albeit in an off-label fashion.

We are aware of concerns that FDA labeling may affect drug coverage. We believe it actually will be unlikely. However, if it does occur, coverage for unusual situations in which benefits of long-term therapy outweigh risks could be addressed outside the FDA. FDA's charge is to aggregate public health

benefit of the product compared to its evolving risk profile and not to set payment policy.

Label limits would convey that in general benefits of high-dose or long-term opioid treatment do not outweigh risks. A maximum daily dose and duration of continuous treatment is likely to limit misuse, abuse, overdose, and overdose deaths. We now know that opioid use disorder is common. Boscarino found it affected 35 percent of patients treated with opioids for chronic pain.

Setting an expectation that indefinite and high- dose opioid analgesics are not ideal treatment for chronic non-cancer pain will decrease the number of people started on long-term opioid therapy, and this should decrease the number of new patients suffering from opioid use disorder and the number of patients exposed to risk for overdose and overdose death.

Thank you. FDA Questions

DR. THROCKMORTON: Thank you. And do people at the table have questions for any of the presenters?

(No audible response.)

DR. THROCKMORTON: I just have a couple, if I

could. First I wanted to ask some clarifying questions of Ms. Carr.

You spoke about a couple of alternative approaches, if I understood, you were suggesting in lieu of labeling changes. And you mentioned central PMPs. I wonder if you would clarify what you meant by that.

DR. CARR: Okay. Well, for the medications, instead of using opioids all the time or Percocets together, they should be alternated basically monthly using that of prednisones, methadone, liquid formulations of these drugs, because once they do the formulation in a liquid form, most of that is done at the doctor's office, so there is more better control of the medications that will be dispensed. So it will be on both sides. So the pharmacist is able to watch along with the doctor. There should be like basically lidocaine. There should be some kind of anesthesia, anesthetic medications. I don't see any of that happening.

So the level of pain, 1 through 10, I mean, I'm still trying to understand where they get that

number from and how does that affect people, because I can tell you I have level 10 now. Do I? Are you going to give it to me? Okay. So those are the things that I have to deal with on a constant basis, and trying to get to speak to a lot of physicians who deal with pain management, it's not always easy to do. But I have actually again requested forms from the American Medical Pain Management to help me, guide me, through this so we can do those.

Now, the central system is something that a few of the other states -- and I think it's in Florida -- that actually helps monitor. It's not going to stop the abuse, but it helps to control, so therefore we are able to watch again on both sides and then patients can't go from store to store, state to state, or however to get excess of these drugs. So we really want to treat the patient, but we don't want abuse of the drugs as well.

So that's the central program. And adding, again, the hydrocodones, which is actually at a high abuse rate, it lets you have that system in place. It's not going to do anything. And by not having the

pharmacists and the doctors coincide together and alternate by either drugs or the formulation of the drugs, I think we're going to still have that same epidemic.

Thank you.

DR. THROCKMORTON: Thank you. And then the second question I had is you spoke of abuse deterrent formulations development, and you made a comment about no one accepting them or something like that. I wasn't able to follow exactly.

DR. CARR: The OxyContins, the new change that they put where there can't be any alterations of the drug, because that used to be the drug of choice, the OxyContin, as they was writing, because they can actually manipulate the drug. They can't manipulate it at this time. So the drug of choice now in its pure form basically, the oxycodones. So those are the drugs that are being written by physicians, and the patients are dictating that that's what they want, and if they don't get that, they're not going to have the OxyContin filled. So the long-term care -- I mean, the extended-release OxyContin does not help. So changing the

formulation in that sense did not work.

DR. THROCKMORTON: And just to clarify, that's because they found something else to use.

DR. CARR: That's correct.

DR. THROCKMORTON: Gotcha.

DR. CARR: Right.

DR. THROCKMORTON: Okay. And then my last question I had was for Ms. Kunins. I'm sorry, I'm not getting your name pronounced right. Thank you for your comments about the relationship between chronicity of exposure and dose and risk of abuse and misuse. Obviously that's something that we have a handful of studies that people have alleged. And the 100 milligram morphine equivalent is an arbitrary -- I mean, it's just a cutoff. Are you aware of any data that look at the shape of the curve as opposed to just choosing a cutoff and then looking is it higher or lower? Is the curve a linear exposure? Is it some other thing? I'm just interested if you're aware of those data.

DR. KUNINS: So, as you know, many of the studies use cutoffs; 100 MMEs is a common cutoff. We

will have another look and put that into our written comments if we can find something to that effect.

DR. THROCKMORTON: Thank you very much.

Mary, should we go ahead with the next session, or what's the --

Dr. Kolodny, are you able to make your presentation now?

DR. KOLODNY: To the entire panel?

DR. THROCKMORTON: Yes, the entire panel, of course. I think just the four, we do the four, and then we want to make sure, if we didn't have time for questions, we would have questions and follow-up.

(Pause.)

DR. THROCKMORTON: Whenever you're ready. Thanks.

DR. KOLODNY: My name is Andrew Kolodny. I'm Chair of Psychiatry at Maimonides Medical Center, and I'm President of PROP. I am especially grateful to FDA for holding this meeting because it gives us a chance to address some of the concerns that have been raised about the petition that we filed.

Our request for striking the term "moderate"

for adding a suggested maximum duration and dose have been widely misinterpreted as a request for FDA to impose strict limits on how opioids can be prescribed. This was absolutely not our intention, nor could this happen, because FDA does not regulate the practice of medicine, FDA regulates drug companies, and it is better regulation of drug companies that we are seeking.

Our petition was signed by several pain specialists who prescribe long-term opioids. They would not have signed the petition, and I would not have signed the petition, if this effort could lead to patients who are doing well on opioids being forced off after 90 days or if this change could interfere in any way with clinical decision making. We are asking for a more narrow indication and more specific instructions on labels such that use beyond the suggested parameters would become off-label. Off-label prescribing is perfectly appropriate and legal and at times off-label use of a particular medicine can be the standard of care.

The slide that's about to pop up was made by

the CDC with the intent of demonstrating that the increased consumption of opioids, demonstrated by the green line, is fueling an epidemic of opioid analgesic overdose deaths, the red line, and opioid analgesic addiction, the blue line. Over the past decade, the red line translates to the loss of more than 100,000 lives. The CDC tells us that increased opioid prescribing is fueling the worst drug epidemic in the United States's history.

Clearly, we are paying an enormous public health price for the overprescribing of opioids, yet we are lacking evidence of a public health benefit. We are lacking evidence that we are doing a better job now of treating chronic pain. Our per capita consumption of opioids is greater than the per capita consumption in France, Germany, England, Spain, and Italy combined, yet there is no evidence that the U.S. is doing a better job of treating chronic pain.

What caused the green line to shoot up? It was a response to a brilliant marketing campaign that convinced doctors that we were too afraid of addiction, convinced us to believe that legitimate pain patients

don't get addicted and that opioids are safe and effective for chronic pain.

So while the CDC tells that for this epidemic to be brought under control, we need to make the green line go down, we have drug companies that are trying to get that green line to continue to go up. We have drug companies that continue to promote opioids as if they have been proven safe and effective for chronic pain and they don't simply put out advertisements like this one or advertisements like this one, they are also sending their sales force into primary care offices where primary care doctors are encouraged to aggressively prescribe these medications.

Drug companies, their pain groups, and their consultants, have asked FDA to deny our requested label changes. In their defense of the existing label, they argue that we failed to prove that the label changes would reduce non-medical use. In other words, they say that the group on the right, that they call drug abusers, that we failed to prove that it would help that problem but that our effort would penalize the group on the left, pain patients. They argue that the

trick for policymakers, represented by the little man in the middle, is to find the right balance. They say that label changes are not balanced. They say let's not punish pain patients for the bad behavior of drug abusers.

But we didn't show the evidence they say is lacking because the primary intent of our label change isn't to reduce non-medical use. Our primary goal is to reduce harm caused to pain patients. The pain specialists who signed our petition did so because they believe that chronic opioid therapy is harming many patients. They know that the distinction that industry has painted between these two groups is false. They know there is tremendous overlap between these groups.

In Fleming's survey of 800 primary care chronic opioid therapy patients, 63 percent reported non-medical use. Boscarino found a third of primary care patients on chronic opioid therapy met criteria for an opioid use disorder. And just a few months ago, a study out of Utah by their medical examiner's office in which they looked at a few hundred cases of opioid analgesic overdose deaths, they found that 92 percent

of the overdose death victims had been prescribed opioids for chronic pain.

There is a balancing act, though, that needs to be performed, and that is the weighing of risks verse (sic) benefits, that a clinician must do when they consider opioids for a patient. The massive overprescribing we see is good evidence that they are not doing this well, they are underestimating risks and overestimating benefits, and they are not weighing risk verse (sic) benefits properly because the broad label gives drug companies a license to put their finger on the scale.

You have heard today, and I'm sure you will hear again tomorrow, that we can make this treatment safe by teaching doctors to closely monitor their patients, which is basically the approach taken in the ER/LA REMS blueprint. Now, all of these things listed here are good to do and should be done when patients are on this treatment, but none of these things allow a prescriber to identify addiction as it's developing and stop the treatment before it's too late. Counting pills or checking urine will not tell a prescriber if

the pills are going up the addicted patient's nose, and checking a PDMP and finding out a patient started doctor shopping, that doesn't prevent addiction; the doctor shopper is already addicted.

At best, close monitoring might allow a prescriber to identify addiction early, but it doesn't prevent addiction. The prescriber can decide to stop prescribing, but the addicted patient's addiction doesn't go away. The patient is left holding the bag with a devastating life-threatening illness that may kill them.

There have been concerns raised about our petition. It's been argued that if opioid prescribing is reduced, if that green line begins to come down a bit, which is what the CDC is saying needs to happen, that that means that pain patients will be harmed, but reducing overprescribing will not result in more harm to pain patients if it's pain patients that are being disproportionately harmed by overprescribing.

It's been argued that prescription plans won't pay for opioids if we make them off-label, but better regulation or changing the label will not result

in prescription plans refusing to automatically cover. Their prescription coverage decisions are not linked to a drug's label. There are examples like Lyrica, which is on-label for fibromyalgia but prescription plans prefer Neurontin, which is off-label. Their decisions are based on the cost of the medication, not the label.

It's been argued that our suggested label changes are bad for pain patients, but if doctors are able to make better decisions, if they're better able to weigh risks verse (sic) benefits appropriately, that's good for pain patients. Our proposed label changes are bad for drug companies, not for pain patients.

There are many concerns about access to opioids from patients who are on opioids who feel they are being helped by the medicines, and their concerns about access are warranted. We're seeing signs like this going up in pharmacies across the country where pharmacies, pharmacists, are opting out of prescribing opioids, not because of efforts to change the label but because they're worried about getting robbed. As the epidemic continues to spin out of control, we'll see

more signs like this going up, and if FDA doesn't take advantage of its authority, if it doesn't take advantage of its ability to use the Controlled Substances Act, or to enforce the Food, Drug, and Cosmetic Act, then states which do regulate the practice of medicine will have no choice but to start passing laws which do interfere with clinical decision making. That's when pain patients really do need to be worried, when politicians start telling their doctors how to prescribe opioids. Our effort to regulate what drug companies can claim about their products is a balanced approach that preserves clinical decision making and does not interfere with access to opioids for patients who are helped by them.

So I would like to finish with a question, and my question is whether or not FDA made a mistake 10 years ago when you held a very similar meeting to look at opioid labels, and at that meeting you asked a group of doctors, doctors who had been championing opioid therapy, during the height of the enthusiasm about opioids for chronic pain, Dr. Rappaport, you asked them whether the label was too broad, and you asked them

whether or not it was appropriate to give a drug company a broad indication based on a 60-day trial of efficacy for back pain patients. At that time, 10 years ago, the people you asked, who were working for industry, who were championing this effort, said, yes, they wanted the broad label, and you've listened to them. I think we have enough evidence today to suggest that a very serious mistake was made and it's time to fix that mistake.

Thank you.

DR. THROCKMORTON: Thank you.

Roland Gray, I believe, Mary, is next?

DR. GRAY: Good day. My name is Dr. Roland Gray, and I appreciate the opportunity to give this presentation before the FDA. I am a Fellow of the American Academy of Pediatrics and a Fellow of the American Society of Addiction Medicine. For the last 12 years, I have served as Director of Tennessee's Physician Health Program and as a consultant to Renewal House, a long-term residential program for addicted mothers and their children, and the Davidson County Drug Court.

I have no relationship with the pharmaceutical industries, and I will not be discussing any unapproved or off-label uses for any therapeutic agents today.

We currently are in the midst of the worst drug epidemic we have ever seen in the United States, and it's a prescription drug epidemic. Although every community is involved in some way, Tennessee has been particularly hit hard by the overuse of these prescription narcotics. Today I want to share with you some of our data on some of the most innocent victims of this prescription drug epidemic.

What this slide shows is the increase in infants that are born with neonatal abstinence syndromes. These are infants whose mothers took drugs during their pregnancy, which they become dependant on, and then the infants, when they're born, are also dependent on them and they experience withdrawal. As you can see from this graph, in 1999, 2000, 2001, we had fewer than 100 cases a year reported. Over the last 2 years, we've had over 1,000 babies born in Tennessee with the neonatal abstinence syndrome.

Between 2000 and 2010 there has been a tenfold increase in the numbers of babies born to mothers who are dependent on prescription narcotics.

I feel that this data is compelling for another reason, in that we're talking of a class of citizens who, as a group, as a whole, are young, are of child-bearing age, and should be experiencing few chronic health problems.

This is the data from one of our neonatal intensive care units in Tennessee. This is from East Tennessee Children's Hospital, has a neonatal intensive care unit, and I'll just very briefly show you that in 2011 there were 135 admissions for neonatal abstinence syndrome; in 2012, there were 280 babies born with neonatal abstinence syndrome. Currently, at East Tennessee Children's Hospital, about once a day a baby is admitted for neonatal abstinence syndrome.

Now, the impact of neonatal abstinence syndrome on infant care is problematic in many areas, and one of these I'll point out to you is financial, and these are from our TennCare data in the State of Tennessee. TennCare is Tennessee's version of Medicaid,

and the average cost to deliver a TennCare baby is $7,285. If you look at the babies -- and there were 512 during calendar year 2010 who were born with neonatal abstinence syndrome, the average cost was $40,931.

Another consequence of babies that are born with neonatal abstinence syndrome are the numbers of babies that get into the custody of Division of Children's Service of DCS within 1 year of birth. This was in calendar year 2010. Of the instance of the 56,498 babies born in calendar year 2010 in our TennCare population, 754 wound up in the custody of DCS within the first year of life. This was just a little bit over 1 percent. If you look at the numbers of infants with neonatal abstinence syndrome, 95 of 512 infants were in DCS custody within their first year of life. This was over 18 percent of those babies.

Now, what are some of the long-term consequences? Although these babies at birth are very problematic, they have a lot of complications due to their withdrawal, we know that long term we're going to have these infants with us for quite a while. These

babies are at risk for attention deficit disorder. Over the past 10 years, we've seen an absolute explosion in the diagnosis of attention deficit disorder, and this is at least one of the reasons for that in the State of Tennessee. These children have difficulty with hyperactivity. They have difficulty in transitioning between tasks, a lot of difficulty at impulse control. These children seem to lack a filter that gives them the ability to stop and think before they get involved in activities that is going to cause them problems within the criminal justice system. A lot of difficulties with sleep disorders. They don't sleep well. They rarely get a good night's sleep. Sensory disorders, hypersensitivity syndrome, sensitive to sounds, tastes, smells. And very problematic.

We know now -- and this is over many years of study in our experience at Renewal House -- is there is an extremely high risk of a future risk of addictive behavior in these children. When these mothers become dependant on prescription opiates, it doesn't affect just the mother, it affects the entire family, and particularly the children of these mothers. We know

that if not some form of intervention takes place, that these infants will go on to become addicted themselves and get involved in other high-risk behaviors which will wind them up in the criminal justice system.

We currently, in the United States, have over 2 million of our citizens incarcerated for drug-related crimes. Many of these children will wind up in the jails and institutions. And unfortunately now in the U.S., our jails and the criminal justice system have become holding cells for those with alcohol and drug problems and mental health issues.

Ladies and gentlemen, again I appreciate the ability to share with you briefly some of our results from Tennessee on infants with neonatal abstinence syndrome, and I come to you today on a personal level as a prayer for relief, that you will enact and do the right thing that will cut down on the overuse, misuse, of this category of drugs.

Thank you very much.

DR. THROCKMORTON: Michael Baron is next.

DR. BARON: Good morning. Thank you for allowing me to present my research, which is very

relative to these proceedings. I adamantly support the change in the wording of the drug labeling for chronic opioid therapy.

Hello. My name is Dr. Michael Baron. I'm a physician and have a master's degree in public health. I am board certified in psychiatry, anesthesiology, and addiction medicine. I am a Fellow of the American Society of Addiction Medicine.

In 2010, I was appointed to the Tennessee Board of Medical Examiners by Governor Bredesen for a 6-year term. However, I am speaking to you today as a physician that treats patients in my office that have chronic pain and addiction, so I see and hear both sides of this issue regarding opioid prescribing and chronic pain.

I have not received grant money for the research I'm about to present, and I have no financial relationships to disclose.

I want to present data that I published in the peer-reviewed journal, the Journal of Opioid Management. This data was gathered while admitting patients to the Vanderbilt Psychiatric Hospital at

Vanderbilt University Medical Center in Nashville, Tennessee over the course of about 6 months.

All of the patients that were included in the study were detoxed because they wanted to get off high-dose opioids for three main reasons. Reason one, the doctor would not increase the dose anymore. Reason two, their side effects were too severe, such as constipation and urticaria. And reason three, when they went to the pharmacy, the pharmacist made them feel like they were an addict.

Figure 1 is the amount of morphine equivalents that these patients were prescribed. These were 23 patients that were in a row. They were not randomly selected, they were all referred to me by a pain clinic or multiple pain clinics. They were all electively admitted to the Vanderbilt Psychiatric Hospital, and they were all followed up after the acute withdrawal period. As you can see, many were prescribed very high doses of morphine or morphine equivalent opioids. The medications included hydrocodone, oxycodone, fentanyl, methadone, meperidine, and hydromorphone.

Figure 2 shows us their pre- and their post-detoxification pain scores. The pre-detox scores were when they were seen by me in the preadmission process. None of these scores were while the patients were in withdrawal. The post-detox scores were when they were being seen for follow-up after the acute withdrawal period. Every pain score decreased from beginning to end. Let me say that again for clarity. Every patient's pain score decreased when they were on high-dose opiates to when they were detoxed to no opiates.

Figure 3 let's us look at that data another way. The patients had less pain on average a 3 on an analog pain scale of 0 to 10 off of opiates, whereas they had a mean pain score of about 8 while on high-dose opioids. This research has been repeated. It goes against common sense and our usual understanding of pain control and of opioids. In fact, this research goes against most of what I learned in pharmacology and in medical school. High-dose opioids makes pain worse. This is not the rare phenomenon of hyperalgesia syndrome; this is a phenomenon that happens when a patient is prescribed high-dose opiates over a long

period of time.

Unfortunately, we have no long-term efficacy studies that are any good, so we don't really know what happens at the receptor level when a patient takes high- dose opiates for a long time. What we know, from my and other people's research, is that the homeostasis of the opiate receptor gets completely annihilated by high-dose opiates. As well, moderate pain gets amplified to severe pain with the use of high-dose opioids. From my study, one can see that high-dose opioids does more harm than good. Using opiates for moderate pain will eventually cause more pain.

So I'm asking, please restrict labeling of opioids for severe pain and limit the dose. Otherwise, we are causing more pain and doing more harm than good for our patients.

Thank you for allowing me this time.

DR. THROCKMORTON: Thank you.

And, Mary, is there someone else, or is that -- okay.

DR. KOLODNY: I think there was, Irfan Dhalla's presentation.

MS. GROSS: Someone is going to present.

DR. KOLODNY: Oh, oh.

DR. THROCKMORTON: I think there is an afternoon session that was going to capture that. FDA Questions

DR. THROCKMORTON: So do members of the panel have questions? I guess for Dr. Kolodny. I'll start.

So, Dr. Kolodny, you made a passionate argument that the labeling changes that you've proposed would not affect appropriate patient access, and we've heard that in a variety of settings. A variety of opinions have been expressed this morning obviously. Measuring that would be important. I wonder if you're aware of any tools that are available to measure appropriate access to pain medicines.

DR. KOLODNY: Well, I think the concerns that have been raised are that if this treatment were to become off-label, that that would interfere with access and I think we've got overwhelming evidence of medications that are off-label that are very widely prescribed. As a psychiatrist, I prescribe medications off-label quite frequently. So, for example, I

prescribe trazodone, which is indicated for depression, rarely prescribed for depression, I prescribe it for insomnia.

In terms of dosing, I think you could tell me this, Doug, but I believe many, if not most, medicines have an upper suggested dose limit on their label. For example, Zoloft has an upper dose limit of 200 milligrams, but for severe OCD, myself and many psychiatrists very frequently exceed that dose level, and I don't know of any evidence that it interferes with access of patients who have severe OCD receiving effective treatment.

DR. THROCKMORTON: Right. I was asking a sort of slightly different question. I was asking if there are formal ways of assessing that as opposed to the experiences that you mentioned. I've asked this question in a variety of settings. I think that the answer that I've been told is no, but I was just curious if there were things that you were aware of.

DR. KOLODNY: Well, I mean, I think there is an interesting way of -- I don't think this is going to exactly answer your question, but there is an

interesting way of thinking about this, and that would be to try and answer the question about whether or not the Food, Drug, and Cosmetic Act has done a reasonable job of protecting the American public health, and I think we have many examples of how the public health has been best served when we don't permit a manufacturer to promote a product as safe and effective until it's proven safe and effective. Thalidomide is just one example that springs to mind. So I think that this is a law that has served the public well and we have good evidence of that.

DR. THROCKMORTON: Great. Thank you.

Are there other questions that any of the panelists have?

(No audible response.)

DR. THROCKMORTON: Otherwise, thank you very much. Thank you for flexibility for moving up before lunch. Let's see, we have 12:00. I'm going to say why don't we reconvene at 1:15 and we'll start the afternoon session. Thank you very much.

(Lunch.)

DR. THROCKMORTON: Mary, do I understand that

we're starting with someone with a discussion from someone from before lunch or a presentation from Irfan Dhalla?

MS. GROSS: Right.

DR. THROCKMORTON: Okay. Go ahead. Whenever you're ready.

DR. DHALLA: (By video.) Hi. My name is Irfan Dhalla. I'm a general internist at St. Michael's Hospital in Toronto and also an Assistant Professor at the University of Toronto. I'm sorry I can't be with you in person today, but I do want to say thank you to the FDA for providing me with the opportunity to present via recorded video.

These are my financial disclosures. I don't receive any payments or research funding from the pharmaceutical industry.

I thought I would start with this slide. These data from the CDC are no doubt well known to everyone in the room, and I'm sad to say that we have observed a similar increase in opioid overdose deaths over the last decade in Canada as well. I think it's fairly well accepted now that opioid-related deaths are

a major problem in both of our countries, and although the numbers aren't as clear cut, I think it is also accepted that addiction to prescription opioids has become much more common than it was a decade ago. This, too, is a major problem.

Of course, prescription opioids are not the only substance people can become addicted to, but what separates opioids from heroin, cocaine, tobacco, or alcohol is that prescription opioids are licensed pharmaceutical products produced by pharmaceutical companies distributed to pharmacies and hospitals, prescribed by physicians, and ultimately used by our patients.

So when we look at a slide like this, one of the key questions we should ask ourselves is, is there a relationship between opioid prescribing and opioid overdose death? The answer, of course, is yes.

Here, for example, is a figure from a recent article in JAMA. The three lines represent opioid overdose fatalities, opioid sales, and treatment admissions to opioid addiction programs, and you can see that all three lines basically increase in

lockstep.

In addition to the temporal correlation, we have also observed geographic correlations. In parts of the world where opioid prescribing is frequent, opioid death rates are higher than average with observed geographic correlations not only when you look at different countries but also when you look at different states within the United States and when you look at different counties within Ontario.

My colleague, Tara Gomes, has also shown that risk of death increases with the dose that is prescribed, and Michael Von Korff and his colleagues in Washington State, who observed a similar phenomenon.

So we see temporal correlations, geographic correlations, and correlations with the dose that is prescribed.

Another important question we could ask ourselves when we think about whether the FDA should do anything about the label is whether people who die of opioid overdose are obtaining their opioids by a prescription. We've done some work to answer this question in Ontario. We've gone through thousands of

files at the Coroner's Office abstracting information about every opioid overdose death, and we have linked each death record to health care administrative data.

What we found is that people who die of opioid overdose are indeed frequent users of the health care system. Two-thirds of people who died of an opioid overdose saw a doctor within a month of death, and virtually everyone had seen a doctor within the year before death. The median number of doctor visits in the year before death was 15. To me, that's an astounding number. I would bet that very few people in the room have seen a doctor 15 times in the last year.

We also found that most people who die from an opioid overdose were recently prescribed an opioid by a physician. In our study, more than four out of five people who died had received a prescription in the year before death, and most people had received 10 or more such prescriptions. This doesn't exclude the possibility that some of these individuals were also obtaining opioids illegally, undoubtedly some were, but our data clearly indicate that physicians have an opportunity to reduce the number of opioid deaths by

prescribing opioids more carefully.

I should note that we are not the only researchers that have observed this phenomenon. Researchers in Utah, for example, have done a study of people who died of opioid overdose, and in their study they found that the primary source of opioids was health care providers in more than 90 percent of cases.

The other key question we have to ask when we think about what the FDA could do is this, how effective are opioids compared to other treatments in the setting of chronic non-cancer pain? Even in the most carefully selected and monitored patients -- i.e, those who are enrolled in randomized controlled trials -- opioids are at best only marginally better than placebo and probably no better than non-opioid treatments.

Here, for example, are the data from the Cochrane systematic review for opioids for osteoarthritis. The review authors concluded when they saw these data that opioids should not routinely be used even if pain is severe. Here are the data from the Cochrane review for back pain. The review authors

concluded that the benefits of opioids remained questionable.

In the real world, things look even less favorable for opioids than they do in RCTs. Opioids cause more falls and deaths than non-steroidal anti-inflammatory drugs in the elderly, up to one-third of patients who are prescribed opioids for chronic non-cancer pain meet criteria for opioid use disorder, what many people would call addiction, and functional outcomes in opioid users are worse than functional outcomes in NSAID users.

These studies, of course, are subject to all of the usual limitations we attach to observational studies. But I think it's safe to say that the preponderance of evidence supports the following four conclusions. Number one, prescription opioids do harm a lot of people. Number two, most people who are harmed by prescription opioids are in fact being prescribed the drugs. Number three, the evidence for the long-term effectiveness of opioids in the setting of chronic non-cancer pain is very weak. Number four, the current regulatory regime is not working. I'm therefore very

grateful that the FDA is holding these hearings and considering how it might change the situation. And I'm also grateful for the work that the FDA has done so far in addressing the prescription opioid problem, and I look forward to hearing what the FDA's next steps will be.

If anyone wants to contact me, please feel free. And thank you very much for listening.

DR. THROCKMORTON: Thank you. I'm sorry the slides didn't advance there the way we wanted them to.

UNIDENTIFIED FEMALE SPEAKER: It was the video.

DR. THROCKMORTON: Oh, it was the video, oh, in which we had no control. All right. In that case, I'll take back.

(Laughter.)

DR. THROCKMORTON: The next panel starts with Daniel Carr.

Daniel, please.

DR. CARR: Good afternoon. My name is Daniel Carr. I'm a Professor of Anesthesiology, Medicine, and Public Health at Tufts University School of Medicine,

where I am the founding director of its program on Pain Research, Education, and Policy. I'm a member of the American Society of Anesthesiologists Committee on Pain Medicine, in which capacity I am speaking today.

ASA supports the broad concept that high-dose opioids should in general not be used to treat chronic non-cancer pain. However, one of the basic facts that pain educators teach new students is that there is a wide variation between individuals in the intensity of pain experienced from the same surgical operations or trauma or from chronic medical conditions with identical pathology. Another basic truth is that there is substantial inter-individual variation in the response to analgesic agents, particularly opioids.

As a therapeutic class, opioids encompass a range of molecular structures whose interactions with an array of receptors and metabolic pathways are highly diverse. At present, translational research is dramatically advancing our knowledge of the genetic bases underlying diversity in every aspect of nociception, pain, and the response to pain therapies, yet, ironically, amidst this exciting progress, we find

ourselves today discussing a petition for uniform limits on doses and duration of treatment that ignores the importance and real therapeutic promise of individualized medicine informed by advances in preclinical science.

Because it ignores a complex reality, this proposal, if accepted, would immediately raise numerous practical difficulties for prescribers and patients.

First, as many others have pointed out, it can be difficult to define cancer versus non-cancer pain because treatments for cancer often lead to chronic pain. For example, is persistent pain from nerve damage deemed cancer related if it's incurred during chemo and radiation therapy?

Second, pain intensity is assessed as a patient reported surrogate for a subject of experience. Hence, the proposed wording would be unenforceable. Everyday clinical assessment of pain intensity typically employs a 0-to-10 scale in which moderate pain is identified with values of 4, 5, or 6. Imagine a physician telling a patient that because that patient reported his or her recent pain intensity as a 6 out of

10 -- i.e., moderate -- the new label would not support, nor might an insurer pay for, continuing chronic opioid therapy. On the other hand, had the intensity been reported as a 7 out of 10, there would be no problem doing so. How many patients might then say, "Well, on second thought, it actually was closer to a 7 than a 6"?

Third, the proposed wording is silent as to what proportion of the time pain would need to be reported as severe in order to justify prescribing of an opioid. I doubt the intent of the proposed wording is that it be 100 percent and hope it's not even the majority of the time.

I am certain that a clinical trial involving such an approach to pain therapy would never be approved by a human studies committee. This point relates back to a basic principle of pain management, that the treatment regimen should be designed to prevent pain from becoming severe.

Related to this same concept, it's very common for pain intensity to fluctuate during long-term treatment of chronic non-cancer pain. It would be

confusing for patients to be told never to take an opioid during intervals when their pain moderate but only to do so when their pain is severe. To the contrary, clinicians commonly prescribe a short-acting opioid to be taken just before planned therapeutic activities, such as exercise, that normally worsen pain so that pain intensity remains mild or moderate and does not become severe. To restate the obvious, an optimal opioid or any other regimen is one in which dose and timing have been individualized so as to prevent pain from becoming severe.

Fourth, the population-based conversion factors used to calculate equivalent morphine doses in patients treated with non-morphine opioids differ from patient to patient and even in the same patient followed across time, as renal or hepatic function vary.

Fifth, opioids for moderate pain, high-dose opioids, or opioids taken for longer than 90 days appear to be effective and well tolerated for certain patients and should continue to be a treatment option if clinically appropriate. An example would be for the

patient with a chronic painful condition who does not tolerate NSAIDs or for whom they are contraindicated and for whom other non-opioid treatments have been inadequate. One cannot use population-based aggregate epidemiological findings to dictate mandatory thresholds or cutoffs that apply to every patient given the wide intra-individual differences in pathophysiology and opioid responsiveness of seemingly identical chronic non- cancer pain conditions.

Finally, pain treatment physicians care for complex patients who, by definition, are selected outliers whose problems have persisted or worsened during non-specialist care. These patients have not adequately responded to routine treatment approaches derived from population-based studies. Mandating rigid across-the- board limits on opioid dosing and duration would add difficulty to the already challenging task of caring for this subgroup of outlier patients. Others presenting at this workshop address advances in formulation technology that mitigate the undesired societal consequences of opioid diversion and misuse, for example, by making opioid products more resistant

to tampering.

My comments today reflect a physician speaking on behalf of patients with pain and the clinicians, not only specialists, but any prescribers who will find the proposed wording confusing, impractical to implement, and an impediment to their best efforts to provide care for this already stigmatized population.

We look forward to continue working with the FDA and will be submitting a written comment letter that provides further detail on these important issues.

Thank you very much.

DR. THROCKMORTON: Thank you.

Dr. Von Korff, I believe you're next?

DR. VON KORFF: Hi. I'm Michael Von Korff, from Group Health Research Institute. I appreciate the opportunity to provide relevant information.

There is a premise, which we just heard, that a label change would establish a maximum dose and duration for opioid prescribing. That was not the intent of the Citizen's Petition. Rather, the proposed label change is intended to convey that use of opioids

long term and at higher dosage levels is not supported by scientific evidence from randomized controlled trials establishing safety and effectiveness. Given rapid increases in opioid-related morbidity and mortality, it is time to ensure that the limits of scientific evidence regarding safety and effectiveness are reflected in the label.

My opioid research funding has come from NIH. I have funding for back pain research from pharmaceutical companies. And I'm a board member of PROP. So those are my disclosures.

Existing randomized trials of chronic opioid therapy, almost all less than 16 weeks duration, have reported only modest benefits for pain and function.

Relative to other classes of drugs used long term by millions of Americans, the number of person-years of observation in these randomized trials, trials of chronic opioid therapy, is sparse. For example, there are over 700,000 person-years of observation in statin trials, and over 100,000 person-years in NSAID trials compared to only 1,500 person-years in trials of opioid analgesics for chronic pain. There is little

trials experience with opioid doses exceeding 100 milligrams morphine equivalent dose. Given these small short-term trials, rigorous scientific evidence regarding the long- term safety and effectiveness of chronic opioid therapy is lacking.

The lack of adequate trials data is troubling given that we are experiencing a major epidemic of prescription opioid overdose and addiction. There are now over 16,000 fatal drug overdoses a year involving prescription opioids in the United States, and over 140,000 persons a year seek addiction treatment for non- heroin opioids.

This epidemic is having a major impact on the health of the U.S. population. For example, among white Americans with low levels of education, life expectancy has dropped by 4 years since 1990, with this decline attributable in part to increased prescription drug overdose deaths among younger adults.

As you've heard, our research and that of others has found increased risks of drug overdose among chronic pain patients receiving medically prescribed opioids. These studies have found that risk of

prescription opioid overdose among chronic pain patients increases markedly with opioid dose received.

Increased overdose risk with dose is not surprising, given high rates of problematic use by patients using medically prescribed opioids. In our survey of over 2,000 chronic opioid therapy patients, we found that in the last 2 weeks prior to the survey date, 12 percent reported having two or more drinks of alcohol within 2 hours of taking opioid analgesics. Thirty to forty percent of these patients were frequent users of sedatives. These patterns were observed among patients with and patients without a history of substance abuse.

In a survey of over 800 chronic opioid therapy patients in Wisconsin, Fleming found high rates of opioid misuse including increasing dose without medical guidance, purposeful oversedation, drinking alcohol to relieve pain, and patient report of motor vehicle accidents related to opioid use.

The volume of opioids dispensed and available for diversion in community medicine cabinets is related to chronic opioid therapy dose prescribed. In our

health plan, we found that 87 percent of the total morphine equivalents dispensed in a year were given to chronic pain patients using opioids long term while 60 percent went to patients receiving 50 milligrams a day or greater morphine equivalent dose.

Some have expressed concern that more selective and cautious opioid prescribing for chronic pain could leave millions of chronic pain patients experiencing needless pain. In fact, most patients using opioids long term at higher dose continue to experience substantial pain and pain-related disability. In our survey, we found that the large majority of chronic opioid therapy patients on higher dose continued to report moderate to severe pain, continued to report significant pain-related interference with activities, continued to report many disability days due to pain, most were currently unemployed, and most were clinically depressed. Over 70 percent of these high-dose patients had three or more of these unfavorable quality of life indicators, and only 14 percent had one or fewer. In our survey, relatively few chronic opioid therapy patients on high

dose were doing well in terms of pain, function, and quality of life.

In conclusion, overly broad opioid labeling does not adequately convey to prescribing physicians or to patients the lack of scientific evidence regarding the safety and effectiveness of long-term opioid use for chronic pain. This is of particular concern for prescribing of higher dose regimens associated with the greatest risks. Given epidemic levels of prescription opioid overdose and addiction, it is imperative that the opioid label convey that scientific evidence regarding safety and effectiveness is lacking for long-term and higher dose opioid use for chronic pain.

Thank you very much.

DR. THROCKMORTON: Thank you.

Ms. Gomes?

DR. GOMES: Hello. And thank you for inviting me to speak today to you about some of the research that I have conducted along with my colleagues in Ontario looking specifically at high-dose opioid use and the risks associated with that.

I am a researcher and scientist at Sunnybrook

Hospital and St. Michael's Hospital in Toronto as well as an Assistant Professor at the University of Toronto at their Faculty of Pharmacy and as well lead the Ontario Drug Policy Research Network.

In terms of my financial disclosures, all of the research that is presented here today is funded by a grant from the Ontario Ministry of Health and Long-Term Care. And I do not receive funding from any for-profit entities or pharmaceutical companies.

So I mentioned the ODPRN. This is a research network that is funded by the government, and a lot of the work that we've done over the past several years has been geared towards informing the province's narcotics strategy, and as a result, it has focused on a variety of areas related to opioid use, but for the purposes of the presentation today, I wanted to focus on the research that we've done looking at high-dose opioid prescribing as well as the risks associated with high-dose prescribing.

So just to put this into context because this research was conducted in Ontario, Ontario is the largest province in Canada with a population of

approximately 13.5 million residents, and these residents have universal access to hospital and physician care services as well as those aged 65 years and older, as well as those receiving social assistance, receive government coverage for their prescription drug costs, and as a result, the research that I'll present today is focused on a population aged less than 65 since we have found in our population that very few people are receiving opioids over the age of 65, the vast majority of use is in this younger population. And we restricted to those individuals with no past cancer diagnoses or palliative care services to try and restrict this to a population of individuals receiving opioids for chronic non-cancer pain.

So a few key issues have come up as we have been working on this research, and I think really the questions that are most relevant to the discussions today are related to the prevalence of high-dose opioids when used in the general population as well as what these risks might be.

So this is a study that we conducted that was

published in Open Medicine looking at the prevalence of high-dose opioid prescribing based on a dose threshold of 200 milligrams of morphine or equivalents, which is a dose threshold used quite often in clinical guidelines, and you can see that by 2008 approximately a third of individuals who were being treated with long-acting oxycodone as well as approximately 20 percent of those being treated with other long-acting opioids were receiving daily doses of these opioids that exceed this 200 milligram of morphine or equivalents dose threshold.

If we then extend this to looking at 400 milligrams of morphine or equivalents, which most people would agree is a very high dose of opioids, you can see that there still remain between 10 and 14 percent of long-acting opioid users who are receiving a daily dose of these medications that exceed that threshold, and specifically if you look at those individuals receiving prescriptions for long-acting oxycodone, their median daily dose was over 600 milligrams of morphine or equivalents.

As my colleague, Dr. Dhalla, mentioned in his

prerecorded presentation, we have extracted opioid-related deaths in Ontario from the Chief Coroner's Office over the past several years, and we have seen a marked rise in opioid-related mortality rates over this time. In 2006, there were over 400 deaths annually in Ontario, and by 2010 and recently extracted data, we have seen that this now exceeds 500 deaths annually. This is of particular concern because the vast majority of these deaths are accidental and occur in a young population, the median age of deaths in 2006 was 45 years of age, so this represents substantial years of life lost as well as the fact that these overdose deaths often come along with a lot of concomitant use of sedatives and alcohol.

So when we overlay rates of opioid prescribing with rates of mortality, you can see that in Ontario there is a strong correlation between these two variables, but what we wanted to look at was what the relationship was with dose and opioid-related mortality, and so we conducted a study looking at exactly this association, and what we found in the study was that individuals prescribed over 200

milligrams of morphine or equivalents were at a threefold increased risk of dying of opioid-related causes, and even those who were being prescribed between 50 and 200 milligrams of morphine equivalents were at a doubled risk of dying of opioid- related causes compared to those who were being prescribed less than 20 milligrams of morphine or equivalents.

We then wanted to replicate this study within a population of -- sorry. There we go. We wanted to look at the outcome of road trauma, and we specifically wanted to look at this outcome as well because there have been some driver simulation studies that have indicated that opioids can influence reaction time and concentration. And what we found in this study was that the dose of opioid was significantly associated with risk of drivers being injured in motor vehicle accidents. And you can see at the bottom of this slide where that dose-response relationship occurs, and we found that risk to be between approximately a 21-percent and 42-percent increased risk of being injured in a motor vehicle accident compared to those being treated with less than 20 milligrams of morphine or

equivalents.

So in conclusion, although, of course, these data are subject to the limitations that come along with observational study designs, I think that these provide very important contextual findings relating to the use of opioids at high doses at a population real world setting. And of particular concern and of particular note for the FDA is that even doses that many people would consider to be a moderate opioid dose -- so, for example, 15 milligrams of morphine or equivalents -- were associated with considerable risks, including opioid-related mortality as well as injuries in motor vehicle accidents.

Thank you. And please feel free to contact me if you have any questions.

DR. THROCKMORTON: Thank you.

And, Greg Terman.

DR. TERMAN: Good afternoon. And thank you for allowing me to speak today. By way of introduction, let me first say that the tragedy of prescription drug overdoses cannot be overstated and must be minimized by every resource available. That is

why in recent months I have traveled repeatedly from --

Whoops. It seems to have a mind of its own. I need to restart that. The random signal generator is not working.

(Laughter.)

DR. TERMAN: Whoa, I'm back. Okay.

DR. THROCKMORTON: Help is on its way.

UNIDENTIFIED MALE SPEAKER: Can you just call out and we'll take care of it?

DR. TERMAN: You bet. No problem.

Next slide. Next slide.

In recent months, I have traveled repeatedly from that Washington to this Washington, sometimes on behalf of the American Pain Society, to speak at meetings advocating wider distribution of the opioid antagonist naloxone, educational REMS for prescribers, improving drug take-back effectiveness, and expansion of state prescription drug monitoring programs, several of which are scheduled to go out of business this year due to budgetary constraints, by the way.

In my laboratory, for more than 3 decades we have studied the mechanisms underlying side effects of

opiate analgesics, including hyperalgesia, tolerance, addiction, itching, and respiratory depression. I am not a zealot for opiate prescribing and never have been.

On the other hand, as a fellowship-trained pain management physician, I have observed a considerable number of patients with chronic pain whose lives seem to be improved by prescription opioids, even after many years. It is from this somewhat conflicted perspective that I will comment on the opiate labeling changes recently proposed to guide indication, dosage, and duration of treatment.

Next slide.

One proposal that we have heard is that we should eliminate moderate pain from the current moderate- to-severe pain indication for opiate prescriptions. I don't have a scientific argument against this proposal, but I am also not sure what the scientific evidence for it is either. In fact, as a pain doctor, I am not totally convinced that there is such a thing as moderate pain.

Next slide.

Who comes to the clinic asking for pain care complaining that their pain is so moderate?

(Laughter.)

DR. TERMAN: Moderate pain may have been invented by researchers such as myself to add another data point on the mild-to-severe pain scale to help demonstrate analgesic efficacy.

Next slide.

For instance, this figure from the Web is a pretty standard approach for treatment based on pain report. As you can see, it suggests that exclusively moderate pain resides in -- next pain -- or next slide.

(Laughter.)

DR. TERMAN: -- this small area of a 0-to-10 pain scale between 4 and 5. Is this little area really what we're here to discuss this week? If we stop giving opiates to people who have pain of exactly this severity, would people really stop dying of overdoses? Conversely, should we just keep piling on opiates to the many patients who come to me rating their pain up here?

Next slide.

Proper evaluation of patients in pain involves an assessment of pain, of course, but also of mood and function. I'm concerned about the mood of someone who reports a pain of 12 on a scale from 0 to 10, and I advise against simply prescribing more opiates for this patient's severe pain no matter what the labeling says.

Next slide.

Thus, if dropping "moderate pain" from an opiate's labeling is neither necessary nor sufficient for determining who can be safely prescribed chronic opiates, what is the reason for the proposed change?

Similarly -- next slide -- a change in opiate labeling suggesting that drug dose be limited to 100 milligrams of morphine equivalents per day is also not helpful in determining which patients should be prescribed opiates and how much.

Next slide.

I served on the Washington State Panel, which published guidelines in 2007 suggesting that prescribers should get expert advice before prescribing doses over 120 milligrams MED. We chose this dose for

the guideline anecdotally at best and arbitrarily at worst. However, in the ensuing years there have been several studies -- next slide -- indicating that patient risk increases significantly at just about this opiate dose. Some might say that it's not surprising that like most drugs, opiates are riskier at higher doses, but my major criticism of these epidemiology studies is that there is no assessment of benefit. Clinically, the more the benefit, the more risk one is willing to tolerate.

Next slide.

Again, it is the prescriber's responsibility to assess pain, mood, and function, and be certain that the benefits outweigh the risks. That responsibility begins with milligram 1, not 100. At higher doses, a prescriber may benefit from a consultant to help weigh risks and benefits, as suggested in our guidelines, but the idea that we should label opiates as safe up until some specific dose and that after that they are too dangerous represents a misunderstanding of responsible prescribing and runs the risk of prescribing opiates too liberally in most patients and too conservatively

in others.

Next slide.

Finally, the proposal that up to 90 days of opiates is okay but not 91 also strikes me as more restrictive than responsible and could even lead to patients being prescribed 90 days of drugs when they don't need them. It is true that there is a lack of studies demonstrating the efficacy of opiates for more than 90 days. Nonetheless, as Dr. Twillman mentioned earlier, the absence of evidence of efficacy does not provide evidence of an absence of efficacy.

I know of no known or theoretical mechanism that would cause opiates to lose their efficacy or suddenly become more dangerous in all patients at 91 days. The known mechanisms of opiate tolerance, for instance, occurred largely within just a few hours or at most a few days. And, of course, there may be mechanisms that are completely unstudied at present, but I would caution against regulations based on such speculation.

I have already experienced an era in which experts' opinions discounted the animal studies of many

of us concerning opiate tolerance opining that tolerance does not occur in patients and thus need not be considered when treating patients with chronic opiates. Now that we find this opinion was probably wrong, I encourage FDA and prescribers everywhere to not allow similarly loud, though diametrically opposed, expert opinions to create arbitrary restrictions on opiate prescribing, affecting even patients who are currently benefiting from these drugs.

When the pendulum of medical opinion swings wildly without research data to guide it -- next slide -- patients can get hurt.

Thank you very much.

DR. THROCKMORTON: Thank you. FDA Questions

DR. THROCKMORTON: Do members of the panel have questions for any of the speakers that we've just heard?

Judy?

DR. STAFFA: This is Judy Staffa. I have a question for Dr. Gomes. Your work with the Ontario data, should I assume that's the claims data, administrative claims data, you've been using?

DR. GOMES: Yes, that's the case. And so the data presented for those less than 65 represents those who are eligible for public drug coverage, which represents people of low socioeconomic status in general.

DR. STAFFA: So can you just briefly, without going into too much detail, just help me understand the assumptions you had to make to calculate the dose based on those data?

DR. GOMES: Absolutely. It depended a little bit based on the study design, but in general, for example, in the opioid-related death analysis, we looked at the date of death and looked at prescriptions that were prescribed that overlapped that date of death, and so it was restricted only to those patients for whom we had data, so who were eligible for public drug coverage, but we looked at the converted morphine equivalents for prescriptions that overlapped with that date of death and summed them up.

DR. THROCKMORTON: I have a follow-on question, and maybe I missed it in the slides. How did you determine something was considered opioid related,

since I think a lot of them were unanticipated, if I remember?

DR. GOMES: Yeah. So what we did was we actually went into the Chief Coroner's Office and reviewed all of the files for drug-related deaths since 1991 and looked at the toxicological screens as well as any other information gleaned during the coroner's investigation for those deaths to see whether or not opioids were present at such a level as to cause the death on their own or in combination with another product such that neither product alone would have caused the death but the combination of the products led to the death.

DR. THROCKMORTON: Thank you.

DR. HERTZ: This is Sharon Hertz. So do you have described somewhere what the absolute levels of opioids that you consider lethal that were used in the study?

DR. GOMES: Legally prescribed as opposed to --

DR. HERTZ: Not the prescribed amount, but the levels used from the coroner data?

DR. GOMES: We don't have the levels specifically from the blood toxicological screenings. We have extracted that data, but that wasn't what we used for determining the relationship with prescribed dose for our studies.

DR. HERTZ: So I'm sorry, perhaps I misunderstood. So when you decided to make the attribution that there was an opioid-related death, that was based on the prescribed dose?

DR. GOMES: No, sorry. Okay. Sorry, I misunderstood your question. Yes. So it was based on the levels in the blood of the opioid, the various opioids, as well as we also were able to look at alcohol levels and other medications such as sedatives.

DR. HERTZ: And is that reported somewhere, like what your criteria were?

DR. GOMES: In the publication by Dr. Dhalla in 2009 in CMAJ he goes into detail as to exactly how that determination was made.

DR. HERTZ: Great. Thank you.

DR. GOMES: Thanks.

DR. THROCKMORTON: John?

DR. JENKINS: Let me first introduce myself. I'm John Jenkins. I'm the Director of the Office of New Drugs in CDER at FDA. I apologize I wasn't able to be here this morning.

We heard a couple of presentations from our colleagues from Canada, so I was interested in understanding, are you aware -- I guess this would be for Dr. Gomes -- are you aware of any substantial differences in the labeling for these drugs in Canada versus the current labeling in the United States?

DR. GOMES: I'm not aware. As far as I know in Canada, at least for Ontario, there are no maximum doses that are on the labels for opioids as well as no restrictions on duration as well.

DR. JENKINS: Okay. And one other question, for Dr. Terman. You mentioned several of the programs you think can be very useful such as wider use of naloxone, take-back programs, prescription drug monitoring programs, and you also commented on the aspects of the petition that you don't agree with. Are there aspects of the current approved labeling that you think should be changed independent of the ones that

you commented on in your presentation? So do you see anything in the current label that you would recommend changing?

DR. TERMAN: So I think there is nothing wrong with an honest approach. I'm not an expert on labeling and I don't pretend to be that, but if there is a lack of evidence, then saying that seems like a reasonable thing to do. But, again, I've probably never read any of the labels of the things that I've ever prescribed.

(Laughter.)

DR. JENKINS: At least you're honest.

UNIDENTIFIED MALE SPEAKER: There's that honesty.

(Laughter.)

DR. JENKINS: When you say the lack of evidence, are you referring to the lack of data on long-term benefit beyond I think 12 weeks is --

DR. TERMAN: Well, if there is a limitation on the data, then saying that there is a limitation on the data seems like the most straightforward approach. I think I made it pretty clear that setting arbitrary

numbers isn't necessarily going to even reduce opiate prescribing. It certainly isn't the direction I'm trying to push my prescribing colleagues in, which is paying less attention to the numbers and more attention to the patients and function.

DR. THROCKMORTON: Other questions?

(No audible response.)

DR. THROCKMORTON: If not, Mary, I was going to suggest that we continue on with the next couple of sessions and see if we need to take a break in between them maybe. So if the next group -- Stephen Wood, Matt Ervin, Kevin Zacharoff, and Jody Green -- and then the last four groups could just come to the table, that would be appreciated, and we'll see how that goes.

And the first person is Stephen Wood, whenever you're ready, sir.

MR. WOOD: My name is Steve Wood, President and CEO of Covectra, a company based in Massachusetts. Today I'll be speaking with you about the subject of traceability for opioids. Traceability is the practice of establishing a link between the prescribing physician, the pharmacy, and the patient, as well as

the payers.

Next slide, please.

First of all, the current landscape. I'm sure most of you have heard about the ongoing initiatives, including REMS programs, reformulation of opioids, and education, are in fact positive first steps, but despite these initiatives, opioid diversion, abuse, and misuse is increasing.

If we take a look at the stakeholders involved with this problem, I would like to make a few comments on each of those stakeholders. First of all, some patients, as we heard sadly this morning, have become addicted unintentionally and sorely need adherence monitoring and support. Some of you may have seen recent reports about patients' homes, homes of patients who are known to be using opioids for whatever reason are now being targeted by diverters and these medications have actually been robbed.

The physicians are having difficulty monitoring patient adherence and some live in fear of losing their DEA license.

The pharmacies are on the front line of

diversion and are susceptible to theft or even bodily harm by people coming into the pharmacies demanding opioids at either gunpoint, knifepoint, or bomb threats. The pharmacists whom we've talked with are often aware of possible diversion or abuse by people coming in for their medications, but they have limited tools to actually verify whether that's the case.

The payers are telling us that there are extremely high costs of treatment, we've seen some of those data this morning, and they can often detect incidents of diversion by looking at prescribing patterns, but they don't have enough data to really confirm that.

In terms of the supply chain, you've all heard about recent legislative activities in either California or at the U.S. Congress and other states about the subject of e-pedigree, or electronic pedigree, but it is doubtful that effective e-pedigree legislation will be enacted down to the actual unit of dose.

Current patient prescription monitoring programs are in effect in 40 states, however, it is

very difficult for one state to share the data with the other state, and in a number of states participation by the physicians in these prescription monitoring programs is voluntary.

Next slide, please.

I would like to quote Mr. Gil Kerlikowske, who is the Director of the White House Office of National Drug Control Policy. He said at one conference that the most cost effective and efficient way to stem our nation's prescription drug abuse epidemic is by stopping abuse before it ever starts.

And what I would like to tell you about today briefly is something called serialization, which is in effect putting a serial number on each unit of use, each unit dose, or at a minimum, each primary carton, but for opioids we recommend each unit of use or unit dose. It's essentially putting a license plate on a unit dose package. It would be a blister pack dose or perhaps a foil pouch containing an oral thin film.

The serial numbers are put on at the point of packaging and they are scanned as the packages go from one package level to the next and sent to a database,

and these serial numbers can be accessed by various stakeholders that we mentioned earlier. The physicians can use these serial numbers to monitor adherence and also to bring in other stakeholders into this effort for traceability, including the pharmacies and the payers. With minimum disruption, the physicians and the pharmacies can create patient profiles, and then the patients are held accountable by periodic medication dosage checks by the physicians or the physicians' staffs, and this system can even detect substitution. Occasionally when physicians do require their patients to come back for essentially checking to see how many unit doses are left compared to how much there should be, we can even tell them which serial numbers should be remaining in that package.

Now, this data flow enables a team approach toward diversion prevention and also gives law enforcement a tool for determining who the patient of record was if this medication is found on the street.

Next slide, please.

What can the FDA do? These are some recommendations that we think are very worthy of

consideration. First of all, we are aware that there are initiatives going on within both houses of Congress, also the DEA and the FDA and various government agencies such as SAMHSA and NIDA, and we encourage a cross-agency or collaborative effort to try to determine how track-and- trace can stem this tide of opioid diversion and misuse. Prior to review, for those new drug applications that do include a track-and-trace capability, also to consider granting orphan drug status for those opioids that do have a track-and-trace. There are some pilot tests that are now being planned by several pharmaceutical companies, and then one other would be a classwide REMS for certain types of opioid products.

Next slide, please.

If anybody would like any further information, we have our contact information provided here. Thank you very much.

DR. THROCKMORTON: Thank you very much.

Mr. Ervin?

MR. ERVIN: Maybe I can try the clicker if it's around?

DR. THROCKMORTON: I think we've been doing, "Next slide." We had some clicker challenges earlier.

MR. ERVIN: Sure. Sure. I'll try to be efficient.

So next slide.

So I'm Matt Ervin, CEO of MedicaSafe, and we have received funding, several different grants, from the National Institute of Drug Abuse, to first conduct a pretty comprehensive study of opioid risk management, and then thereafter we actually have received funding to develop technologies that could provide an impact in this area with the goal of creating a balanced approach, meaning minimizing COT risk while maintaining and potentially improving pain management and access.

Next slide.

A couple preliminary observations that led us down this path. High-quality guideline-based treatments are hard to implement in practice, they're very labor intensive, and therefore are often really not followed. And ADF formulations are no magic bullet, they don't, for example, keep abusers from simply taking the drug in excess.

Next slide.

But we do think, this being the 21st century, there are technologies that could be brought to bear to what we now all recognize is a problem. And I should just say before I go forward, I'm not really pro or con any of the narrow considerations that are up for debate today around new indications, but I do think that any discussions of, I should say, new labeling changes should keep in mind that technology is progressing and in the not-too-distant future it might be possible to provide guidelines that are much more granular and address some of the issues that are being raised today.

In particular, we found some success and are starting some active pilots with an approach that combines a drug dispensing device -- consider it smart packaging -- with techniques, complementary techniques, for guiding and tracking patients that would yield valid data on actual medication usage, symptoms, and patient- reported outcomes, and conditions the patients for healthy, appropriate opioid use whether they're at risk or not to again hopefully head off some of the problems we're seeing.

Next slide.

Let me just quickly give you an overview of this particular device. This is something that would require an access code, it would come with the medication preloaded in it, you know, a packaged offering. It does require an access code to initiate treatment. The device thereafter is personalized to the prescription and the patient and therefore limits usage to an appropriate level again for that prescription and patient, along the way does display reminders and instructions on a display so that the patient does adhere. And it's inherently child-safe, there is a push-and-twist requirement in order to dispense.

Next slide.

Importantly, this physical technology would be part of broader treatment management approach. I mentioned there is an access code required to initiate treatment, but that code wouldn't necessarily be valid forever. In the pilots we're commencing, it's valid for about 10 days, well, for 10 days, because the concept is the patient will then go through a virtual

visit on a weekly basis in order to renew that access code, get a new access code, and during that virtual visit they are pushed through structured assessments, the four As, and provided with safe use education.

So, again, before they initiate treatment, they're provided with a baseline assessment and initial safe use education, and then every week they are assessed in an ongoing manner to see where in the risk stratification they lie, and they are provided safe use education in an appropriate manner. This is all conducted via phone or via the Web, whichever is most convenient for the patient. And feasibility studies indicate that actually the phone is a little more popular.

Next slide.

Easy for the physician, right? This is a practical thing. They just write a prescription, check off a few boxes. For example, what is the limit of usage? What should be the dosage limit for this particular patient, the max usage?

Next slide?

And the physician gets an actual report,

actual data, daily usage, and data on assessments, presented in a longitudinal manner, so they can see patterns. And, importantly, this invokes a Hawthorne effect, meaning the patient is more likely to be responsible because they know the doctor knows what's going on. This report might end up being blank because the patient took a hammer and cracked this thing open, but then the doctor is going to see that the report is blank because the patient took a hammer and cracked it open, so it does tend to lead to positive behavior.

Next slide.

And what we think, more broadly speaking, that technology can do is narrow the gap between guidelines and labeling and actual clinical practice and also potentially fill in some gaps that are impractical right now in the guidelines and labeling.

Next slide.

Skip. This is just current guidelines as they are.

Next slide.

Where do the gaps exist? Well, monitoring, safe use education, and safe storage.

Next slide.

So with monitoring, it is, of course, a good idea to assess the patient on a regular basis. This is impractical for the physician today. They cannot call a patient on a daily or weekly basis. Technology does make this possible. This approach does make this possible and should be considered in the future as part of a treatment guideline.

Next slide.

UDTs actually research indicates tend to be less effective than they could be today because they're truly not conducted randomly. Physicians generally conduct these UDTs when the patient comes to the office, the patient knows when they're going to come to the office, as long as they're good 3 days prior, a quantitative urine drug test won't show anything unusual. We can invoke UDTs on a random basis with this technology, just at some point they're alerted or called and say it's time, and if they don't follow through within 3 days the device can lock, so we can escalate management and monitoring of the patient. By the way, if our device indicates they're abusing the

drugs and the UDT screen indicates there is no opioids in the system, we've potentially identified a diverting patient.

Next slide.

There are no guidelines for monitoring medication usage in a granular manner because it's just not practical today. The best you can do is pill counts. Again, technology like this does make this possible.

Next slide.

Safe use education, while suggested, again isn't practical. Physicians and pharmacists don't have the time. It can be made. The program I mentioned builds that in inherently.

Next slide.

Safe use storage, again, inherent in a device like this, requires a pass code, the patient can set their own PIN thereafter if they desire. It's a lockbox in and of itself and doesn't require the patient to do anything. In practice, they rarely do.

Next slide.

So the conclusion I'm getting to is that COT

guidelines may not be that bad as they are, and not to discourage tweaks thereto, but there are big gaps between the guidelines and actual practice, and what I would suggest is that, again, in thinking about how to modify labeling today, you keep in mind that technologies will be available in the future that could enable a prescriber to have much more granular control over the treatment and over risk gratification of the patient. This is just one example that's relatively inexpensive, easy to use, and again does enable implementation of current treatment guidelines and any modifications thereto.

Thank you.

DR. THROCKMORTON: Thank you.

Kevin Zacharoff.

DR. ZACHAROFF: Hi. And thank you.

First slide, please.

So I'm speaking to the panel today as really three different people. Primarily I'm here as the Vice President of Medical Affairs at Inflexxion, and I am going to be presenting some data as requested by FDA with respect to this issue, but I'm also a clinician

with over 20 years of experience in anesthesiology and pain medicine, and I'm an educator at a medical school in New York. And one of the things that I teach my students is that pain is one of the few conditions where a patient actually gets to have a say in what a positive outcome is, and that makes it a little bit different than other medical conditions that we think about. And when we think about labeling for these medications, we need to take that into account.

And, secondly -- and I've heard this many times throughout the course of the day -- pain seems to be being reduced to a score and a number -- and anybody who has experience and the colleagues and clinicians who have spoken before me have scratched at this -- but it is way more than just a score on a scale of 0 to 10. There are a lot of different things that need to be looked at in terms of efficacy, such as function and what the patient is able to do versus not to do, and I find it upsetting to even have it be in someone's slides that it's a non- progressive condition. Untreated, it is an extremely progressive condition.

Moving on to the topic of standardization,

it's worth asking the question, being an anesthesiologist, is, why is anesthesia safer today than it was 50 years ago? And that's because standardization has been applied to the practice of anesthesiology. If you look at the death rates 50 years ago versus now, it's significantly safer. There have been technological improvements. But the process of getting anesthesia has been standardized. And my case would be that standardization is widely considered an important component in pain management as well. It's worth mentioning that education has to take place as a foundation before standardization could be implemented, and drug labeling certainly plays a critical role in standardizing pain treatment and pain management, but the impact of labeling alone may very well be limited. There are other practical ways to enhance safety and efficacy which should be considered.

Next slide, please.

Now, this includes systematic assessment of patients' risks for engaging in aberrant drug-related behaviors long before the prescription is ever written. There is a lot that needs to take place before the pen

goes to the paper or the keyboard is accessed to write that prescription. It's a key component of an overall strategy to reduce risk of chronic opioid therapy, and anything less oversimplifies it. Patient risk assessment should not be overlooked as policymakers seek to improve prescription opioid prescribing practices.

Next slide, please.

Now, there are practical validated tools that exist to establish patient risk level, none of which have been mentioned here today. We haven't really heard a lot about how you might predict whether or not a patient is going to exhibit an aberrant drug-related behavior when you're considering whether opioid are appropriate candidates.

Systematic use of these tools may significantly benefit safe and effective pain care. There are tools like the ORT and the SOAPP and the COM (ph) that are out there that have been validated that just aren't being used or aren't being promoted. Effective integration of tools like this into clinical practice could be more difficult than people think.

Just presenting them to the clinicians doesn't do it, and that's some of the data I'm going to present. We have a number of institutions that have incorporated our SOAPP and COM into clinical practice, but yet when we did chart reviews we only found that even though the institution made a decision to use them, they were being used sometimes less than one-third of the time.

So we hypothesize that possibly creating electronic versions of these tools that could integrate with the electronic medical record might make a difference, and on the next slide we can take a look at what we found in a small pilot study.

We did a retrospective chart review to look at in institutions that had made the decision to use tools like these, and we found that only 40.9 percent of the time did the charts contain any evidence of a formal opioid risk assessment being done. After utilizing our electronic tool, that went up to 79.5 percent in workflow that they considered to be clunky and needing improvement.

When we looked just at SOAPP-R utilization, which is screening at the time that an opioid is being

considered, it was only used 30.3 percent of the time. That went up to 76.9 percent of the time after the intervention with an electronic form, and when we looked at the follow-up correlating risk assessment, the COM, it went from 4.5 percent to 43.6 percent. This was under duress, it still went up.

Next slide, please.

So final impressions? Well, introducing electronic standardized risk assessments that work with electronic medical records as everybody moves towards these tools, we've shown in a pilot study -- we are doing further studies -- increased utilization of risk assessments. Impact on practice patterns, patient outcomes and rates of aberrant medication-related behaviors remains to be evaluated, but policy efforts to standard pain treatments and pain management should encourage use of new assessment and technical advances to impact clinical practice especially when chronic opioid therapy is an appropriate component of care.

And with respect to Dr. Jenkins's question on label, when we're all done, I do have some suggestions on the label if you're interested.

Thank you very much.

DR. THROCKMORTON: Thank you.

And, Jody Green.

DR. GREEN: Good afternoon. I'm Jody Green. I'm Director of Research Administration at the Rocky Mount Poison and Drug Center and Assistant Professor at the School of Nursing at Vanderbilt University Medical Center.

Next slide.

So the RADARS System is a network of programs that monitors the abuse, misuse, and diversion of prescription drugs. Since 2006, RADARS System has been independently owned and operated by Denver Health and Hospital Authority, a political subdivision of the State of Colorado. We are committed to running national scientifically rigorous programs based on strong epidemiological principles and best practices.

Funding for the RADARS System comes from our data subscribers, namely, pharmaceutical companies, that produce prescription opioids and stimulants. Subscribers are essentially end users of the data and do not have authority or decision-making power in

regards to the program methodology, data collection, or publications.

Next slide.

So the RADARS System is composed of four different programs -- I'm sorry, five different programs. We have 53 of the 57 regional poison centers of the United States are included in our RADARS System Poison Center Program. This covers approximately 90 percent of the U.S. population. Our drug treatment programs include 73 opioid treatment programs, both public and private, from 33 different states. We have 280 drug diversion units that we work with nationally to collect data. Through online surveys, we collect information from 6,000 college students annually, and also from a national distribution geographically stratified by region, and we also have a website that uses cloud sourcing methodology to monitor the street value of illicit and prescription drugs.

Next slide.

So I would like to share the following three key points with you today, the first being that all prescription opioids are abused to some degree,

immediate-release, extended-release, and in some cases, immediate-release opioids are just as highly or more highly abused than extended-release products. Secondly, abuse and diversion of specific opioid products has been reduced with abuse deterrent formulations, and I'll share data with you on that today. And also that the proposed prescription limits must ensure continued access to these important therapies for legitimate pain patients, I think a common theme that we've heard from many presenters today as well.

Next slide.

While this is a busy slide, I will summarize it very briefly for you. All prescription opioids are abused to some degree. Again, immediate-release, extended-release, single-entity, combination products. This chart illustrates the disparity in intentional exposure rates reported to our RADARS System Poison Center Program after accounting for drug availability. The heavy black dotted line is the long-acting or extended-release opioid group, as a product grouping. The other lines represent products that are broken out

by active pharmaceutical ingredient and by immediate- or extended-release. We have seen many are far above and below the line for the LA/ER group, indicating that not all opioids are created or abused equally.

Next slide.

The FDA has widely noted that the most common route of abuse, the oral route of abuse, continues to be an issue that is not addressed in the current technology for abuse deterrent formulations. There is hope that the proposed prescribing limits discussed today will help address oral route of abuse until such technology becomes available as long as legitimate pain patients do not suffer unnecessarily. Meanwhile, we do have data to support that the currently available abuse deterrent formulations can have a significant impact on abuse and diversion of prescription opioids.

The abuse rate reported to RADARS System Poison Centers, based upon population, illustrates a 40-percent reduction in abuse of ER oxycodone following the launch of the reformulation in 2010. This reduction was seen during a period of time in which there was actually a 5- percent increase in abuse

involving all other opioids. A significant decrease in the abuse rate is also evident after adjusting for drug availability. That data is not illustrated here for simplicity purposes, but we would be happy to talk about that at a later time.

Next slide.

A significant decrease was also found in the RADARS System Drug Diversion Program with a 50-percent decrease in cases involving ER oxycodone since the reformulation while cases involving all other opioids remained stable.

Next slide.

Abuse deterrent ER oxymorphone was launched just 1 year ago. The intentional abuse reports to RADARS System Poison Centers decreased by 63 percent in the first 9 months on the market. During the same period, all other opioids decreased by about 6 percent.

In January of this year, generic ER oxymorphone entered the market without the requirement of abuse deterrent technology. Within days, the internet chatter posts began describing in detail and with pictures the ease of which these drugs can be

crushed and injected, specifically a picture on how clear the drug appeared in the syringe. We recognize that these initial reports are anecdotal and plan to monitor the abuse and diversion of these products through ongoing national scientific programs.

Next slide.

So in summary, many IR products and nonabuse deterrent products have high and continually rising rates of abuse. RADARS System data have detected significant reductions in abuse and diversion for products with abuse deterrent properties. Limiting prescriptions may be a reasonable strategy to help reduce risk as long as it does not prevent appropriate treatment for patients in pain. This will be difficult to quantitate and careful thought should be given to the definition and measure of success with prescribing changes as well as with any other intervention aimed at addressing this very complex issue.

Thank you.

DR. THROCKMORTON: Thank you. FDA Questions I look to my colleagues to see if there are questions.

Judy?

DR. STAFFA: My first question is for Dr. Zacharoff. With regard to the tools that you're talking about that can actually try to predict or help predict whether a patient might run into abuse issues before prescribing an opioid, have those actually been validated as being correlated with patient outcomes that they really can predict?

DR. ZACHAROFF: We are just starting the validation with patient outcomes, but they have been validated for use in chronic pain patients to predict the likelihood of displaying an aberrant drug-related behavior.

DR. STAFFA: Okay. Thank you.

And then I have a question for Dr. Green. I was wondering if you could comment on the nationally representativeness of the sample of the Poison Control Centers. I believe you said you have data from 53 out of the 57?

DR. GREEN: Right. So the American Association of Poison Control Centers includes 57 regional poison centers throughout the United States, and they collect a very standardized dataset. With the

RADARS System Poison Center, we collect that same standardized dataset plus all the case notes so that we can read through every case and verify the product that was involved, the route of exposure, the reason, and the outcome, and so for that reason, we have to work directly with the regional poison centers. So currently 53 of those regional poison centers participate in our program specifically. The other four that don't are generally around institutional policies and IRB challenges, but we do have representation of about 90 percent of the U.S. population that's covered by those poison centers.

DR. STAFF: Okay. Thank you. And then just one last question. On the graphs that you showed around the reformulation of both the OxyContin and I believe the oxymorphone, there was a huge drop in one quarter, and I just find that a little surprising given that there wasn't a recall of the old formulation, so both formulations would have been out there during that time. I guess I might have expected to see the drop be a little more gradual. Do you have any ideas of what might be causing such a precipitous drop?

DR. GREEN: Well, I think if we can go back to the actual slides, I don't know if you can do that or not in the short period of time, but it's an interrupted time series model, and so you'll see there that there is a little gap in between the two lines to allow for some of the product to be put through the system as well. For the oxycodone, you're right, it was a switch basically, manufacturing one day, the old formulation went out the next day, the new formulation went out, and then for the oxymorphone, I believe there was also a large recall or a manufacturing issue prior to the new formulation, so there was a little bit more of a gap between the distribution of the old product and the new product, which actually was I think real helpful in monitoring the data.

DR. THROCKMORTON: Mike?

DR. KLEIN: This is also for Jody Green. Are you collecting data on routes of administration for the different formulated products?

DR. GREEN: Yes. And so for the evaluation, particularly for the abuse deterrent formulations, it is important to look at the route of abuse because that

is the intention of those interventions, that technology, is to prevent the tampering and whatnot. And so we see even more dramatic difference when we look at the route of administration.

DR. JENKINS: A question for Mr. Wood. You mentioned as one of the incentives that people, companies or sponsors, who developed the serial number approach would be granted orphan drug status or orphan drug exclusivity. I was confused by that because how would they meet the criteria that are in the law for treating a disease that affects less than 200,000 patients? So the use of opioids is much broader than that. So what am I missing of how they would qualify for orphan drug exclusivity?

MR. WOOD: In other words, we think it would be worthwhile considering an opioid product for a new indication that is serialized would be granted the orphan status.

DR. JENKINS: Okay. So presumably you're talking about some sort of a statutory change because it wouldn't fall under the current criteria for orphan drug status.

MR. WOOD: In other words, if there were an indication that is not currently being treated, and this indication is for a new product that is an opioid, then we would ask that this may be considered for another reason to grant it orphan status.

DR. JENKINS: Okay. And, Dr. Zacharoff, I have to follow up on your offer to give your thoughts about current labeling and changes that might be warranted.

DR. ZACHAROFF: Thank you. Yeah, basically two things. First and foremost, stronger wording about what to do with an unused portion of medication. This is not a discussion that's going on out there in the real clinical world. Clinicians do not prescribe these medications and instruct patients with this sentence, "Here is what I want you to do with the medication you don't use," and it ends up staying in the medicine chest and everybody considers that to be the norm. I think that much stronger wording about that could appear in the label in terms of encouraging that discussion between health care provider and patient.

And secondly -- and I'll only address this to

some of the data that was presented earlier in the day with respect to Erin Johnson's work in Utah. We worked with Erin Johnson when she was doing that work looking at opioid-related deaths in the state. It's worth mentioning that opioid-related in that context meant that there were opioids in the bloodstream of these patients who died. They did virtual autopsies and looked at these patients, and in almost every scenario there were other medications in the patients' bloodstream.

So wording in the label making much stronger concomitant use of other medications along with opioids could go a long way in my mind. I think that people don't realize that combining these with other medications is a major problem, and in almost all of the data that we've seen here today, opioid-related means that opioids were involved, but in most of the situations, other medications and other substances were involved as well.

DR. KLEIN: And for Mr. Ervin, is there any clinical experience using your device in patients being treated with chronic pain to see how it's accepted by

the patients, the prescribers, the pharmacists, so that we have actual practical clinical experience?

MR. ERVIN: Yeah. We've been through a feasibility study but with placebo, not with opioids, and now there is a fully funded randomized clinical trial funded by NIDA to use this in live patient settings, four different sites, and there will be assessment data from both the clinicians and patients at various endpoints to indicate whether at the end of the day there is less misuse than there otherwise would have been.

DR. KLEIN: So from the feasibility study, can you share anything about how well was the device accepted by the various parties involved?

MR. ERVIN: Yeah. In plain English, the doctors love it because it takes a burden away from them -- right? -- that suddenly some other system helps them stratify patients into risky or not risky. The patients, oddly enough, honestly really liked it once it worked. When it didn't work perfectly initially, they did not like it so much, but once it worked well, because they felt like they were being cared for more

intensively, they liked the fact that the doctor was going to review the report.

Remember, these were opioid patients, these were patients on chronic opioid therapy, just there was placebo in the device. But they were patients that were at risk or potentially not at risk, they weren't active addicts. So people in those categories that haven't yet gone to the worst extreme like the fact that there is monitoring of their treatment.

DR. THROCKMORTON: Dr. Zacharoff, I have a follow-up question to your comments about the risk models and the use of tools to predict what patients what might abuse opiates, and other speakers have talked about using either dose or duration of therapy as risk factors as ways of identifying patients that are at risk of misuse of the medicines, abuse of the medicines. I recognize the limitations of the data here. Have you tried to decide whether your tools would be more or less powerful than the data using dose and duration?

DR. ZACHAROFF: We have data to show specifically the current opioid misuse measure along

the continuum of care, and it certainly is a single item, it can't make your case by itself, but along with other information, it can support your decision. And one of the things that we found is that many consider opioid risk to be a static phenomenon when in actuality it's very dynamic and a patient's level of opioid risk could change 12 months into treatment due to outside stressors, different things that happen to the patient. So it's incredibly important, along with a clinical interview, and using all of the tools that you have available to factor that in, but a lot of the discussion we were hearing, it just seemed, "Do I prescribe or do I not prescribe?" It's just not that simple.

DR. THROCKMORTON: Thank you.

And then, Ms. Green, I have a question for you. You had raised the issue of access, and so that gives me my opportunity to ask the same question I asked this morning. Your system is obviously poison control-based, and so on surface that's probably not a great place to ask questions about access, but then you mentioned your street Rx thing, which seemed to be a

slightly different kind of a tool. I mean, are you exploring ways of measuring access, appropriate access, to medicines by some other means or other tools?

DR. GREEN: Sure. So the streetrx.com actually monitors street price that people are paying for black market drugs, both illicit and prescription, so it doesn't -- I guess we haven't thought yet about that being a surrogate of availability through legitimate distribution channels. I think that's probably a stretch. We don't currently have a way to monitor that as far as number of patients in pain that cannot get adequate medications.

DR. THROCKMORTON: Thank you.

Other last questions?

(No audible response.)

DR. THROCKMORTON: Otherwise, we'll move to the last panel if everybody is okay with that, we'll forego the break for now, and if people need to stand up, obviously, please do so.

Mr. White I believe is the first one next.

MR. WHITE: Thank you very much for allowing me to speak to you guys today. I am very honored to be

here. I am going to be talking to you today about the effect of opioids on the worker's compensation industry particularly dealing with my company. I was hired by Accident Fund Holdings, which is located in Lansing, Michigan, 2 years ago as Director of Medical Management Practices and Strategy particularly because of my experience with data analytics and predictive modeling and health care background.

Next slide, please.

Accident Fund Holdings is a company that is over 100 years old. We have four companies across the country licensed and insured in all 50 states. We're the thirteenth largest worker's compensation insurance company and the largest monoline worker's compensation company in the country. We're a subsidiary of Blue Cross Blue Shield. We insure over 46,000 employers representing over a million lives and working with over 70,000 treating providers across the country.

Next slide, please.

So in my position, I'm expected to look at the databases inside the organization and give an understanding of medical trends to identify opportunity

for us to improve the outcome for injured workers, to get them back to work, and contain our medical costs. What you're seeing up here on the screen is the trajectory of the types of injuries we've seen over the last 10 years represented as a percentage of total for each one. As you can see, we consistently see over the last 10 years similar types of injuries dominated by strains, lacerations, contusions. Many of these injuries, at least 40 percent of them, lead to surgery and physical therapy, and when they're out of work, they can last up to 115 days, and typically results in chronic pain.

Next slide, please.

Although the injuries have pretty much stayed the same over the last 10 years, provider treatment patterns have changed drastically. Prescription patterns have migrated, and we have recognized about a 1-percent growth of use of opiate agonists over the last 10 years. Opioids now account for 3 percent of our medical spend and 46 percent of our scripts by volume. Interesting to note is that of all the injured workers that are part of our pharmacy benefit management

system, 70 percent of them have received at least one opioid in the duration of their treatment.

Next slide.

Of another interest to us is what are the distribution pathways and supply chains of which our injured workers have access to opioid prescriptions. We would hope that more would go through our pharmacy benefit management solution as we have controls in place, particularly formulary controls, to help us understand when it's indicated. We also have safety programs that we have developed that allow us to look for aberrant utilization of opioids. One of the challenges we have, though, is that 24 percent -- so almost one out of every four -- scripts are dispensed directly out of the physician's office. These come to us generally by paper form several weeks after and bypass our safety programs.

Next slide, please.

Since I originally did not come from the work comp industry, a lot of the people inside our company were a little bit suspect about my research. I decided to team up with Johns Hopkins University, Dr. Edward

Bernacki from Johns Hopkins University School of Medicine, and we did a retrospective study of 12,226 claims, particularly in the State of Michigan, all indemnity claims over the last 4 years from 2006 to 2010, so claims that were opened and closed in that timeframe.

Next slide, please.

We wanted to just simply take a look at what is the difference on claim cost when opioids were used, looking first at what is effective a claim with no prescriptions and then bucketing any other type of prescription other than opioids, then looking at when only short-acting opioids were used, and then whenever a long-acting opioid was used. So if you look at the table on the right, on some summary statistics around those types of claims, you can see that a short-acting opioid is defined by NDC was on an average 3.6 times more expensive than a claim with no scripts. Whenever a long- acting opioid was used on the claim, we were looking at an average claim cost of 11.8 times that of a claim without scripts. And when we adjust for using multivariate logical regression, adjusting for age,

gender, lost time days, complexity of the injury, and any legal involvement, we see short-acting opioids increased the odds of a claim exceeding $100,000 by 1.76 and long- actings by 3.94.

Thank you very much.

DR. THROCKMORTON: Thank you.

Mr. McClure?

DR. McCLURE: Yes. I'm Leland McClure. Thank you for the opportunity to speak today. I am a board- certified forensic toxicologist with Quest Diagnostics, and my role is Director with National Testing Operations for Corporate Operations for Quest Diagnostics. I also serve as a scientific inspector consultant with the National Laboratory Certification Program for Federally Regulated Testing, and I serve of a broad variety also of other agency groups as a consultant, including CDC.

If we could go to the next slide.

Quest Diagnostics is the world's leading provider of diagnostic information services. We're a Fortune 500 company with a New York Stock Exchange listing based in the United States with worldwide

presence and we employ approximately 42,000 people. We provide comprehensive diagnostic testing solutions, and we test more 500,000, half a million, patients every day in our facilities. We touch the lives of patients 145 million times per year, and we service half of all the hospitals and physicians in the United States, and we're a pioneer in developing innovative tests.

Our advanced technology solutions provide physician connectivity solutions that are used by more than 200,000 physicians across the country, and we also provide patient mobile health apps so that they can empower themselves to be able to retrieve their own personalized health information.

If we can go to the next slide.

The background on why we're here today is the rising rates of drug overdose and accidental death indicate that medicine opioids that are utilized for palliative care can be misused and abused, and our overall goal on here is to reduce the abuse of and the overdose from opioids while ensuring that patients with pain are safely and effectively treated. It's very important on that.

When we look at some of the limitations out there, in particular, with the FDA labeling topic Number C, talking about limiting opioid prescription and use, it's directly related to but it does not address all of the limitations that are inherent with physician screening and surveillance of the opioid-prescribed patients. Many of the tools -- and we've heard this today -- that physicians utilize to evaluate patients, they're subjective in nature, including patient history, patient self-reporting, screening tools, like the Opioid Risk Tool, the Screener and Opioid Assessment for Patients with Pain, the SOAPP, or the SOAPP-R for the revised, but the bottom line on this is that patients may lie to physicians about their drug use.

If we could go to the next slide.

As an industry thought leader, Quest Diagnostics utilizes data to transform health care decision making. We have the largest private clinical laboratory data warehouse in the United States, and our health trends reports are designed to identify and track disease and wellness benchmarks, and we do this

for really three purposes out here; it's to inform patients, health care professionals, and policymakers on the current status of what's happening with the nation's health.

We have over 1.5 billion patient encounters that we have on record now in our data files that we can analyze since January 2000. Some of the reports that we have has been Allergies Across America, which is the single largest study of its type on allergy and asthma testing, but we touch on topics of pregnancy, various chronic diseases, including cardiovascular disease, Type 2 diabetes, chronic kidney disease, and the list goes on and on. But in particular we're talking about prescription drug monitoring here today.

If we go to the next slide.

In 2010, we started the program for prescription drug monitoring at Quest Diagnostics, and we analyzed our analytics from 2011 and produced them last year in a report. Our Health Trends report from last year entitled, "Prescription Drug Misuse in America: Laboratory Insights Into the New Drug Epidemic," is listed out on our website, and it's fully

retrievable.

But when we looked at the information and we did our analysis, we saw five key findings that were important to communicate to health care professionals, and this was in regards with urine prescription drug monitoring testing. We saw that the majority of patients tested misused their prescription medications.

And what's important about this information is that in our study we excluded any patients that had any designation for ICD-9 codes or treatment codes that there would have been any kind of rehab or any kind of drug treatment program. Those types of patients have been excluded from this study. These are patients where physicians have indicated that they prescribed a drug, they provide the information to us, and we are able to test that.

What we saw was that many patients took drugs or combined drugs without physician oversight. The physicians indicated those drugs were not prescribed. And we also saw a large number of patients that showed no drug in their specimen. What we saw overall is that anyone is at use (sic) for misuse. When we looked at

socioeconomic factors and we looked at what was occurring with sex-based information, and we looked at ages, we saw across the boards on there that there was misuse of medications, and in particular we've listed here that with the Medicare, Medicaid, and the private payer groups, we saw that misuse was occurring at a rate of 72 percent in Medicaid patients, 61 percent with Medicare patients, 62 percent private payer. We did see that repeat drug testing more than 30 days after the first test was associated with a lower prescription drug misuse. It's a modest but yet still statistically significant 10-percent improvement.

Overall, urine drug testing is an objective tool that provides definitive analysis of the patient's most recent drug use. It also helps to identify which metabolites are prescribed and illicit drugs may be in a sample, and it provides a measurable and a more reliable objective method of monitoring for medication adherence or misuse than other subjective monitoring efforts.

Associations such as the American Medical Association, American Pain Society, American Academy of

Pain Management, and the American Society of Interventional Pain Physicians all recommend urine drug testing as an effective tool in pain management and prescription drug monitoring. We ask that when we look at labeling information, incorporating urine drug testing as a monitor of patient compliance. It helps to provide the physician with objective data to better manage prescribing practices, patient access to pain medication, and patient pain control, and also better manage abuse and misuse of the opioid medications.

We would like to thank you again for the opportunity to speak, and if we can provide any other information, I can follow up if you contact me.

DR. THROCKMORTON: Thank you very much.

Dr. Alexander?

DR. ALEXANDER: Thank you, and good afternoon. I'm a practicing general internist and pharmaco- epidemiologist and an Associate Professor of Medicine in Epidemiology at the Bloomberg School of Public Health, where I also co-direct at Johns Hopkins Center for Drug Safety and Effectiveness. My research focuses on the determinants and quality of drug use in

the United States, and the opinions expressed here are my own and do not necessarily reflect the views of the Johns Hopkins University. I'm a consultant for IMS Health and funded through grants from ARC and NHLBI but receive no industry funding.

The epidemic of prescription opioid addiction and abuse is one of the most complex issues in policy that our country has faced, and I think all of you recognize that, and there are a lot of reasons for this, but one of the major ones is that historically we've done quite poorly as a society treating pain, and this is important because, as you've heard, chronic pain affects tens of millions of Americans, and it's one of the most common reasons people seek health care. In addition, the growing awareness of the prevalence and disability associated with pain has prompted initiatives to improve its identification and management and indeed one of the key concerns that lead many to oppose changes such as those considered today is that such restrictions will stifle access to care.

As a public health professional and expert in drug utilization, I do not believe there is a conflict

between reducing prescription opioid-related addiction, either morbidity and mortality, through changes to the drug label and improving the quality of care for patients with pain. I would like to spend the rest of my time discussing research that my team has recently completed that supports this assertion.

Since escalating rates of addiction and death have occurred in the context of efforts to improve pain management, we examined the diagnosis and management of nonmalignant pain among adults in office-based settings in the United States between 2000 and 2010. To do so, we used the NAMCS, or the National Ambulatory Medical Care Survey. As you may know, this is a nationally representative audit of office-based providers that's rigorously conducted and designed by the National Center for Health Statistics.

In our main analyses, we examined visits with a primary symptom or diagnosis of pain. We also examined new musculoskeletal pain, since this represents a more restricted population of individuals presenting for the first time with a new pain complaint. In some analyses, we examined the use of

select non-opioid analgesics, such an anticonvulsants, tricyclic antidepressants, and in the case of musculoskeletal pain, muscle relaxants, injectable and topical treatments, and non-pharmacologic therapies such as acupuncture or physical therapy. We performed several analyses that support the robustness of our results and their substantive interpretation including examining different populations of patients and different groupings of symptoms, diagnoses, and medications. There were three main questions that we examined. First, we were interested in whether symptoms and diagnoses of pain have changed over the past decade. In fact, patient-reported pain consistently comprised 17 to 19 percent of visits, whereas provider diagnoses increased nearly 50 percent from 2000 to 2010. However, since there is overlap in patient symptoms and provider diagnoses, the proportion of visits with a primary symptom or diagnosis of pain consistently represented one-fifth of visits varying less than 2 percent in absolute terms over the period examined.

So limitations in the data notwithstanding,

these results suggest that at a national level, ambulatory non-malignant pain in adults poses a similar burden as it did a decade ago when opioid utilization was a fraction of current levels.

Second, we explored whether treatment rates have improved during this period. We were really surprised to find that we found modest to no improvements in the proportion of pain visits resulting in any analgesic treatment. For example, among all visits with a primary symptom or diagnosis of pain, the proportion associated with either an opioid or a non-opioid analgesic increased only modestly from 39 percent to 47 percent of visits.

More remarkable still, among visits limited to new musculoskeletal pain, about one-half in a given year were associated with analgesics: in 2000, 53 percent of visits; decreasing to a low of 47 percent in 2004; returning to 53 percent by 2010. So this is noteworthy because it suggests that large increases in opioid sales, 400 percent from 1997 to 2007, have not been associated with substantial improvements in the rates of treatment among this nationally representative

sample.

Third, we were interested in how pain treatments have been balanced among opioid and non-opioid therapies. Among all pain visits, opioid use nearly doubled from 11 percent to 20 percent, whereas use of non-opioid analgesics remain unchanged at 26 to 29 percent of visits over the decade. And although one-half of new musculoskeletal pain visits resulted in pharmacologic treatment, the use of non-opioid treatments actually decreased over this period from 38 percent of visits in 2000 to 29 percent of visits in 2010. Most of this was due to reductions in the proportion of visits treated with NSAIDs rather than other non-opioid analgesics. This is important because it suggests that despite large increases in opioid use, there were not similar increases in the use of NSAIDs, acetaminophen, or other therapies that may serve as alternatives to prescription opioids.

So in summary, using nationally representative data on ambulatory practice, we found that rapidly rising rates of opioid use have not been accompanied by large improvements in the proportion of

patients treated for pain, nor have large increases in opioid use been accompanied by similar increases in non-opioid analgesics. Although I have insufficient time to discuss the comparative effectiveness and safety of opioid versus non-opioid analgesics, suffice it to say that clinicians have a large number of therapies to choose from and that, as we have heard, opioids have been widely used at tremendous cost to the public health far beyond the evidence base regarding their comparative effectiveness and safety.

So I would just like to thank you again for the opportunity to speak today and for your important work on behalf of the public good.

DR. THROCKMORTON: Thank you.

And, Dr. Von Korff, are you -- I think you're speaking last?

DR. VON KORFF: That's right. Dan Solomon was unable to make it down to D.C. today. He asked me to read his prepared remarks for him.

This work of Dr. Solomon and his colleagues was undertaken as part of an ARC grant on comparative safety on analgesics in older adults with arthritis.

Dr. Solomon is a practicing rheumatologist who runs the Clinical Research Group in Rheumatology at Brigham and Women's Hospital. He is a Professor of Medicine at Harvard Medical School.

Opioid prescribing for chronic pain has increased in the wake of cardiovascular and other safety concerns raised about NSAIDs and COX-2 inhibitors. Dr. Solomon's research concerns opioid safety signals that have received less attention than opioid overdose, addiction, and diversion.

Next slide, please. Oh, wait. Let's see, can you go back to the disclosures slide? There we go. Thank you.

Dr. Solomon's research is funded by NIH, ARC, foundations, and the pharmaceutical industry. He has no personal relationships with industry. He was recently appointed as a member of the FDA Arthritis Advisory Council.

Next slide.

Several opioids have a known relationship with changes in cardiac conduction resulting in excess cardiovascular risks. However, the cardiovascular

safety of opioids in general has not been carefully studied. In addition, there have been many prior reports of links between opioids and fractures, but this topic requires further study because of the considerable risk that fractures pose to older adults with arthritis.

Next slide.

Dr. Solomon's research estimates incidence rates and adjusted relative risks of important adverse events comparing commonly used analgesics among patients with osteoarthritis and rheumatoid arthritis.

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Comparative safety studies pose many methodologic challenges. In the absence of large scale randomized trials, epidemiologic methods can be used to compare the safety of different commonly used analgesics. Such studies pose significant methodologic challenges that Dr. Solomon and colleagues have worked on for many years. This study employed novel methods to control for differences between patients using different analgesics.

Next slide.

Imbalances in measured and unmeasured patient characteristics can confound comparative safety studies. Dr. Solomon and colleagues employed a multiple matching propensity score that balances measured patient characteristics, minimizing confounding bias. This table shows selected baseline characteristics across the three matched cohorts. Each group included new users of nonselective NSAIDs, COX-2 inhibitors, or opioids.

Next slide.

Prior work has found an increased risk of fracture with opioids, potentially related to an increased risk of falls and/or ineffective opioids on bone metabolism through androgen suppression. This event rate curve shows the cumulative risk of hip, forearm, and humerus fracture experienced in the three matched cohorts. As expected, nonselective NSAIDs and COX-2 inhibitor users experienced similar fracture risk. However, the risk of fracture among the opioid users was significantly elevated. This was apparent early after initial exposure. By 6 months, the risk difference was 4.3 percent, which translates into a

number needed to harm of about 25. In other words, if 25 persons received an opioid, who could have received an NSAID or COX-2 inhibitor for arthritis, these results would predict one excess fracture in the opioid group.

Next slide.

This figure breaks out the fracture risk by commonly used opioids. Tramadol had the lowest risk while others had similar risks. I note that propoxyphene was included in the study although it is no longer marketed.

Next slide.

This is a similar curve for cardiovascular event risk. Dr. Solomon found that nonselective NSAIDs had the lowest risk, COX-2 inhibitors had slightly higher risk, but that opioids had the highest cardiovascular event risk. They observed 2.5 percent excess risk over the first 6 months of use comparing opioids to nonselective NSAIDs.

Next slide.

The number needed to harm for opioids compared with nonselective NSAIDS was 17 for

cardiovascular events. This points out that these adverse events are not rare in older adults with arthritis who use analgesics long term. Thus, even comparatively small relative risks can be clinically important.

Next slide.

In conclusion, in Dr. Solomon's research, opioids were associated with increased risk of several adverse events relative to nonselective NSAIDs and COX-2 inhibitors; notably, risk of fractures and cardiovascular events. These excess risks appear to be clinical significant in that relatively few patients need to be treated to observe excess adverse events based on the results of this study.

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If clinicians and regulators are confused by the data and the lack thereof, the situation is even worse for patients. Regulators can help clarify these issues with clear statements about what is known and what is not known about opioid safety and effectiveness.

Thank you very much.

DR. THROCKMORTON: Thank you. FDA Questions Let me ask the panel if there are questions. Perhaps I could just start by, Dr. Alexander, and I'm picking up on what Dr. Von Korff just said. So to the extent that there are recommendations you or Dr. Von Korff might see for the labeling to describe these differences in terms of the uses or the safety of the nonsteroidals versus opiates, I wonder if you had any recommendations.

DR. ALEXANDER: Well, I would strongly support label changes consistent with what's been recommended by PROP, if that's your question.

DR. THROCKMORTON: Well, you made suggestions of differences in practice pattern, changes in practice pattern. You didn't talk about what caused that, what was it that resulted in those changes in practice pattern? To the extent you think labeling had a part in that, it would be useful to hear.

DR. ALEXANDER: Yeah. I mean, what we are describing are trends over 10 years, and our study wasn't designed to examine using quasi-experimental methods, the impact of any particular regulatory or

other policy change that may have impacted those patterns. Nevertheless, we think it's noteworthy that despite soaring rates of opioid sales and the morbidity that we've heard about that we don't see similar improvements either in the proportion of patients with pain receiving some analgesic treatment or, for that matter, in the use of non-opioid therapies, and in fact, as I mentioned among patients with musculoskeletal pain, we actually see declines in the use of those alternative therapies.

You know, I think with respect to the comparative safety, the devil is in the details here, and it depends on the outcomes examined, and perhaps our last speaker wants to speak more to that.

DR. THROCKMORTON: Thank you.

DR. HERTZ: Dr. Von Korff, do you know when this work from Dr. Solomon will be published?

DR. VON KORFF: It is published.

DR. HERTZ: Oh. Can you give us the --

DR. VON KORFF: Yeah. I've got copies here, the Archives of Internal Medicine.

DR. THROCKMORTON: Other comments/questions?

Judy and then John.

DR. STAFFA: I have a question for Mr. White. I was wondering if in your analysis, I saw that you adjusted for some things, but I'm wondering if severity of the injury was adjusted for because that might be a reason to prescribe longer acting opioids.

MR. WHITE: It is, and typically that's the first question we get. In the literature, most of the people that have done research in this area have used ICD codes to determine a proxy for injury complexity and severity. We use previous used methods for doing that. So the results we're showing are results that have been adjusted for injury complexity.

DR. STAFFA: Thank you.

And, Dr. Alexander, thank you for sharing your analyses with us. Can you remind me of the NAMCS sample? Are all specialties included in that, such as dentists, surgeons, or is it limited in its scope?

DR. ALEXANDER: Sure. I don't want to misstate the sample. Our study was limited to office-based providers, and we did not use the NHAMCS, the National Hospital Ambulatory Medical Care Survey, which

although we're studying that now, but that provides analysis of practice in emergency departments and in hospital-based outpatient departments. I do not believe the NAMCS includes dentists and other licensed prescribers such as physician assistants, although it does allow for some analysis of whether or not a visit included non-physician health care personnel. So we were able to examine, for example, whether visits that had both a nurse and a physician resulted in an opioid more commonly than visits that only involved a physician.

DR. KLEIN: This is for Mr. White. Do you have the individual drug product data to break down the long- acting agonists as well as the short-acting agonists? Is that information available?

MR. WHITE: Yeah, we could probably make that information available. Everything comes from our transactional database, and so we have everything by NDC and (inaudible) and everything like that. So yes.

DR. THROCKMORTON: I am not seeing other questions then. I guess what I do at this point is thank the audience for their time and their comments

today. We have heard valuable comments from a variety of speakers on the three main sets of questions that we posed in the FR Notice. We started obviously with individuals with powerful and often tragic stories of the use of opioids. We have also heard expert comments on the available data, its value, the things that are lacking in those data, as well as some comments about potential impacts of changes to labeling that have been suggested by a variety of individuals.

This afternoon we heard some other approaches to risk management, storage solutions, and the like, and most recently we heard some discussion of ways to predict risk, whether through tools or other means. I look forward to the discussion tomorrow morning.

Again, the focus of this meaning is intended to solicit comment related to the questions that we posed in the Federal Register Notice, and while we are obviously incredibly interested in all aspects of improving the use of opioids, those questions are very important for us as we're working on the various policies related to opioid use, and I look forward to any comments that specifically target those questions.

I have looked at the weather -- or I've been told, others looked at the weather -- that the weather looks good for the D.C. area tomorrow, and I look forward to seeing everyone at 9:00 tomorrow morning.

Thank you so much.

(Whereupon, at 4:17 p.m., the meeting of the Impact of Approved Drug Labeling on Chronic Opioid Therapy, Part 15 Public Hearing was adjourned.)

CERTIFICATE OF COURT REPORTER

I, ERICK MCNAIR, the Court Reporter before whom the foregoing proceeding was taken, do hereby certify that the proceeding was recorded by me; that the proceeding was thereafter reduced to typewriting under my direction; that said transcript is a true and accurate record of the proceeding; that I am neither related to nor employed by any of the parties to this proceeding; and, further, that I have no financial interest in this proceeding.

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ERICK MCNAIR
Digital Court Reporter

CERTIFICATE OF TRANSCRIPTION

I, DEBORAH ARBOGAST, hereby certify that I am not the Court Reporter who reported the following proceeding and that I have typed the transcript of this proceeding using the Court Reporter's notes and recordings. The foregoing/attached transcript is a true, correct and complete transcription of said proceeding.

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Date DEBORAH ARBOGAST
Transcriptionist

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