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Impact of Approved Drug Labeling -- Part 15 Hearing 02-07-2013

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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  
5151 Pooks Hill Road  
Bethesda, Maryland 20814

Reported by: Erick McNair

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1 Meeting Roster

2 Mary Gross, CDER, FDA

3

4 Sharon Hertz, MD, Deputy Director, Division of  
5 Anesthesia, Analgesia, and Addiction Products, CDER,  
6 FDA

7

8 John Jenkins, MD, Director, OND, CDER, FDA

9

10 Michael Klein, PhD, Director, Controlled Substance  
11 Staff, CDER, FDA

12

13 Bob Rappaport, MD, Director, Division of Anesthesia,  
14 Analgesia, and Addiction Products, CDER, FDA

15

16 Judy Staffa, PhD, RPH, Acting Director, Division of  
17 Epidemiology, CDER, FDA

18

19 Douglas Throckmorton, MD, Deputy Center Director,  
20 CDER, FDA

21

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

2 Presiding Officer Opening Remarks

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

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

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

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

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

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

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

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

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

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1 Analgesia, and Addiction Products.

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

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

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

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

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

19 A couple of other items. We have a total of  
20 55 speakers that are scheduled to present. I have  
21 asked to go over a few ground rules just so that those  
22 presentations are able to go as smoothly as possible.

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

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

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

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1 panels.

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

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

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

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

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

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

11           Elizabeth? Mary? All set? Okay.

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

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

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

19           UNIDENTIFIED FEMALE SPEAKER: Exactly.

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

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

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

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

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

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

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

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

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

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

22           We live in a society where doctors are



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

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

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

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1 a thing of the past.

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

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

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

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

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

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

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

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

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

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

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1 1972 Controlled Substance Act and how it could be  
2 strengthened to enforce the laws of prescribing these  
3 highly addictive drugs to patients who can easily fall  
4 into the black holes of addiction and succumb to the  
5 effects of these addictive drugs. I am not the first  
6 parent to lose a child, but I certainly want to be  
7 among the last.

8 Thank you.

9 DR. THROCKMORTON: Thank you.

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

12 MS. GUIDICE-TOMPSON: My name is Ada Guidice-  
13 Tompson. I live in Ontario, Canada. Thank you for the  
14 opportunity to speak to you today. I am a bereaved  
15 mother of a wonderful young man, Michael, who died in  
16 2004. Could we get his slide up? Oh, there he is.

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

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1 based prescribing.

2           The focus on business and financial rewards  
3 has created unsafe medical practices. In 1992, almost  
4 90 percent of physicians recognized the very real risk  
5 of opioid addiction. Then came a shift in practice and  
6 opioids began to be prescribed widely for CNCP. This  
7 change was based purely on assumption. In a recent  
8 article review, pain expert Jane Ballantyne, M.D.,  
9 states, "The accuracy of that assumption has not been  
10 tested against accumulated evidence and the safety of  
11 opioids used long term has not been tested in clinical  
12 trials." Dr. Ballantyne highlights important  
13 epidemiological studies which document adverse safety  
14 events, especially death, and a reduction in the  
15 quality of life of CNCP patients on COT.

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

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

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

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

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

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

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

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

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



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

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

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

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

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

22 Medical boards, and not the FDA, govern this.

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

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

10 Thank you.

11 DR. THROCKMORTON: Thank you.

12 Mr. Israel.

13 MR. ISRAEL: Can we get the slide up?

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

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

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

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

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

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1 behind.

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

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

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

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

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

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

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

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

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

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

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

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

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

21           Thank you.

22           DR. THROCKMORTON: Thank you.



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1 Mr. Jackson?

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

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

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

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

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

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

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

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

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1 also provide substantial evidence of a drug's  
2 effectiveness.

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

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

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

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

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

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

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

18           Thank you.

19           DR. THROCKMORTON: Thank you, Mr. Jackson.

20           Ms. Foster? FDA Questions

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

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1 we've heard to date? I apologize.

2 (No audible response.)

3 DR. THROCKMORTON: Okay. Thank you.

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

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

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

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

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



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

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

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

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

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

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

11 Thank you.

12 DR. THROCKMORTON: Thank you, Ms. Foster.

13 Mary, I think we have a video testimony next?

14 MS. GROSS: Audio.

15 DR. THROCKMORTON: Audio?

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

17 DR. THROCKMORTON: That was Zxy Atiywariiii.

18 I think I'm saying the name more or less correctly.

19 Patricia McDonald is next, Mary?

20 MS. McDONALD: I live in Buffalo, New York.

21 I'm active with Save the Micheals of the World, a group  
22 dedicated to saving families from the devastation of

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

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

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1 blue she was when she was born.

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

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

22           You see, for 3 years prior, Adrienne was

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

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

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1 of other kids lost and their grieving families are the  
2 statistics. I am a statistic. Adrienne is a statistic.  
3 Why is it that the FDA, an organization designed to  
4 protect us, finds it acceptable that every 19 minutes  
5 in America someone dies from prescription pill-related  
6 deaths? Why is it that until now the FDA has found it  
7 acceptable that patients aren't sufficiently informed  
8 and warned of the dangers of prescription narcotics?  
9 Why has the FDA not previously acted on the fact that  
10 opiate prescriptions are just as dangerously addictive,  
11 even when taken as prescribed, as heroin? Why has the  
12 FDA put more faith in what the pharmaceutical companies  
13 have to say and the pain management societies, who are  
14 funded by the pharmaceutical companies, have to say  
15 than we, the American people, who have already been  
16 proven to be devastated by these drugs? Why has the  
17 FDA not acted sooner and more aggressively to save  
18 lives lost to unnecessary addiction to these drugs?  
19 Had the FDA acted sooner, when it initially  
20 became evident that lives are being lost at  
21 increasingly alarming rates to the prescription drug  
22 epidemic, I might still have my daughter, these

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

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

18 Thank you.

19 DR. THROCKMORTON: Thank you.

20 Mary, is there another speaker in this panel?

21 MS. GROSS: No. FDA Questions

22 DR. THROCKMORTON: Okay. And do any of the



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1 panelists have questions for any of the -- okay.

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

7           (Break.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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1 more helpful.

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

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

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

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

6 DR. THROCKMORTON: Thank you.

7 Ms. Abernethy?

8 Sorry. Ed, Mr. Manougian. Edward Manougian?

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

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

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

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



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

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

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

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

5           In 1987, it was discovered that the doctors  
6 were a big problem by not treating the patients  
7 adequately and were leaving them out to wander off for  
8 themselves and getting into trouble and wind up going  
9 to the emergency rooms frequently trying to get  
10 medications and found that a new name was provided in  
11 1987, a pseudoaddiction, and it's clear now that any  
12 statistics that has to deal with addiction has to  
13 consider whether or not pain was involved, in which  
14 case it most likely is pseudoaddiction and not  
15 addiction. Therefore, any statistics that only  
16 mentions addiction and comes up with numbers with a  
17 comment about pain is invalid.

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

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

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

20           DR. THROCKMORTON: Did we lose him?

21           UNIDENTIFIED FEMALE SPEAKER: I think that  
22 was the end.

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

3 Amy? Ms. Abernethy?

4 DR. ABERNETHY: I'm over here.

5 DR. THROCKMORTON: Oh, okay.

6 DR. ABERNETHY: Hi. How are you?

7 DR. THROCKMORTON: Thank you.

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

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

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

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

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

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

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

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

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1 focus on how to best take care of their families.

2 I don't think anyone would disagree that  
3 there is a public health imperative to address the  
4 scourge of prescription drug misuse and abuse.

5 However, we, at the

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

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

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1 for each specific case and individual person.

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

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



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

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

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

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

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

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

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

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

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

22 For example, many hospice patients have acute

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1 symptoms from non-cancer terminal illnesses and require  
2 more than 100 milligrams of morphine equivalents every  
3 few hours for sufficient pain and symptom control.  
4 Likewise, many palliative and hospice patients with  
5 non- cancer-related pain and other symptoms from  
6 serious or terminal illness experience these symptoms  
7 for periods of time much longer than, say, an arbitrary  
8 90-day maximum that some have suggested, if there is a  
9 90-day limit for non-cancer opioid pain management but  
10 we have to stop opioids in the last 10 days of life for  
11 a person dying of MS who happens to live 100 days  
12 instead of 90. Palliative and hospice care  
13 appropriately emphasize individualization, as I've  
14 highlighted, and I think we need to continue to do  
15 that.

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

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

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

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

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

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

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

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1 respect for the legitimate properties."

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

13           Thank you.

14           DR. THROCKMORTON: Thank you.

15           Mr. Argoff?

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

22           The first thing I would like to point out is

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

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

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



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

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

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

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

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

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

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

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1 In a long-term safety and tolerability study of  
2 tapentadol extended-release, 46 percent of patients  
3 completed that 1-year study. And I know that we've  
4 already said, there has already been a previous  
5 presenter stated, that headache is not a typical  
6 indication for chronic opioid use, but in the longest  
7 study ever done of this type published in Neurology in  
8 2004, of 160 patients who were started for intractable  
9 headache on daily scheduled opioids at the Michigan  
10 Headache and Pain Institute, after 3 years, 26 percent  
11 of those patients originally started continued on  
12 opioids with a greater than 50- percent reduction in  
13 their pain.

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

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

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

12 Thank you.

13 DR. THROCKMORTON: Thank you. FDA Questions

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

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

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

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

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

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

11 DR. THROCKMORTON: Thank you.

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

14 (No audible response.)

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

17 Mr. Michna?

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

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

3           The American Pain Society strongly agrees  
4 with the intent to promote responsible opioid  
5 prescribing and to reduce opioid-related harm.

6 However, the APS does not support the proposed labeling  
7 changes, as we perceive an insufficient scientific  
8 evidence base to support these recommendations.

9 Further, we're concerned about the implementation of  
10 these labeling changes, which would dictate  
11 indications, dosing, and duration of opioid treatment  
12 and will not accomplish the intended goals but instead  
13 have unintended negative consequences for patients  
14 including those not limited to untreated pain and a  
15 loss of access of individualized care.

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



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

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

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

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

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

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

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

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

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

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

5 Thank you.

6 DR. THROCKMORTON: Thank you.

7 Ms. Carr?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17 Thank you.

18 DR. THROCKMORTON: Thank you.

19 Ms. Herman?

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



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

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

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

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

8           The problem of substance abuse in America is  
9 vast but severely neglected, as are most mental health  
10 issues. According to SAMHSA, the Substance Abuse and  
11 Mental Health Services Administration, last year alone  
12 20 million people who needed substance abuse treatment  
13 did not receive it and an estimated 10.6 million adults  
14 reported an unmet need for mental health care. SAMHSA  
15 has also reported that the number of emergency visits  
16 involving attention deficit-hyperactivity stimulant  
17 medications more than doubled from 13,379 visits in  
18 2005 to 31,244 in 2010. Hospital emergency departments  
19 linked to Suboxone, a medication used to treat opioid  
20 addiction, increased substantially from 3,161 visits in  
21 2005 to 30,135 visits in 2010 with 52 percent -- that's  
22 15,778 in 2010 -- involving nonmedical use. According

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1 to the latest NIDA, National Institute on Drug Abuse,  
2 survey of teen drug use in 2012, 41.5 percent of 12th  
3 graders consumed alcohol during the previous 30 days,  
4 and 36.4 used marijuana. The figures for prescription  
5 drugs were Adderall, 7.6; Vicodin, 7.5; cold medicines,  
6 5.6; tranquilizers, 5.3; OxyContin, 4.3; Ritalin, 2.6.  
7 I am citing these statistics not as a means to advocate  
8 the relative merits of safety of one drug or another  
9 but to emphasize that substance abuse is a major health  
10 problem in this country and that it encompasses a wide  
11 variety of drugs.

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

22 Against this background, I would stress that

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

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

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

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

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1 different modes of treatment.

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

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

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

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

5 Thank you.

6 DR. THROCKMORTON: Thank you.

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

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

12 (Laughter.)

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

15 (Pause.)

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

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

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

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

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

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

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



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

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

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

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1 follow-up periods.

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

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

16           Population-based data have also shown  
17 substantial and increasing opioid-associated adverse  
18 outcomes, as you can see on this slide. More than  
19 16,000 people died of opioid analgesic-associated  
20 overdoses in  
21 2010.

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

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

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

22           As Mark Sullivan noted in the Archives of

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

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

13           A 90-day limit would also affect a minority  
14 of New York City patients taking opioids. Again, only  
15 7 percent of those who filled opioid prescriptions did  
16 so for more than 90 days consecutively in New York  
17 City. Substantial overlap exists between those using  
18 long-term and high-dose opioids. Forty-six percent of  
19 patients who filled more than 90 days of consecutive  
20 opioid prescriptions took at least 100 MMEs per day.  
21 While these limits would affect a small percentage of  
22 patients prescribed opioids, they would achieve

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

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

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

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

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

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

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

18           Thank you. FDA Questions

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

21           (No audible response.)

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

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

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

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

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

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

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

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



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

5 Thank you.

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

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

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1 formulation in that sense did not work.

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

4 DR. CARR: That's correct.

5 DR. THROCKMORTON: Gotcha.

6 DR. CARR: Right.

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

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

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

3 DR. THROCKMORTON: Thank you very much.

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

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

8 DR. KOLODNY: To the entire panel?

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

13 (Pause.)

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

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

22 Our request for striking the term "moderate"

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

10 Thank you.

11 DR. THROCKMORTON: Thank you.

12 Roland Gray, I believe, Mary, is next?

13 DR. GRAY: Good day. My name is Dr. Roland  
14 Gray, and I appreciate the opportunity to give this  
15 presentation before the FDA. I am a Fellow of the  
16 American Academy of Pediatrics and a Fellow of the  
17 American Society of Addiction Medicine. For the last  
18 12 years, I have served as Director of Tennessee's  
19 Physician Health Program and as a consultant to Renewal  
20 House, a long-term residential program for addicted  
21 mothers and their children, and the Davidson County  
22 Drug Court.

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

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

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

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

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

9 This is the data from one of our neonatal  
10 intensive care units in Tennessee. This is from East  
11 Tennessee Children's Hospital, has a neonatal intensive  
12 care unit, and I'll just very briefly show you that in  
13 2011 there were 135 admissions for neonatal abstinence  
14 syndrome; in 2012, there were 280 babies born with  
15 neonatal abstinence syndrome. Currently, at East  
16 Tennessee Children's Hospital, about once a day a baby  
17 is admitted for neonatal abstinence syndrome.

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

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1 and the average cost to deliver a TennCare baby is  
2 \$7,285. If you look at the babies -- and there were  
3 512 during calendar year 2010 who were born with  
4 neonatal abstinence syndrome, the average cost was  
5 \$40,931.

6 Another consequence of babies that are born  
7 with neonatal abstinence syndrome are the numbers of  
8 babies that get into the custody of Division of  
9 Children's Service of DCS within 1 year of birth. This  
10 was in calendar year 2010. Of the instance of the  
11 56,498 babies born in calendar year 2010 in our  
12 TennCare population, 754 wound up in the custody of DCS  
13 within the first year of life. This was just a little  
14 bit over 1 percent. If you look at the numbers of  
15 infants with neonatal abstinence syndrome, 95 of 512  
16 infants were in DCS custody within their first year of  
17 life. This was over 18 percent of those babies.

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

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

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



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

5           We currently, in the United States, have over  
6 2 million of our citizens incarcerated for drug-related  
7 crimes. Many of these children will wind up in the  
8 jails and institutions. And unfortunately now in the  
9 U.S., our jails and the criminal justice system have  
10 become holding cells for those with alcohol and drug  
11 problems and mental health issues.

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

19           Thank you very much.

20           DR. THROCKMORTON: Michael Baron is next.

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

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

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

9 In 2010, I was appointed to the Tennessee  
10 Board of Medical Examiners by Governor Bredesen for a  
11 6-year term. However, I am speaking to you today as a  
12 physician that treats patients in my office that have  
13 chronic pain and addiction, so I see and hear both  
14 sides of this issue regarding opioid prescribing and  
15 chronic pain.

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

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

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

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

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

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

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

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1 period of time.

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

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

17           Thank you for allowing me this time.

18           DR. THROCKMORTON: Thank you.

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

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

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1 MS. GROSS: Someone is going to present.

2 DR. KOLODNY: Oh, oh.

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

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

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

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

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

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

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

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

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

12 DR. THROCKMORTON: Great. Thank you.

13 Are there other questions that any of the  
14 panelists have?

15 (No audible response.)

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

21 (Lunch.)

22 DR. THROCKMORTON: Mary, do I understand that



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

4 MS. GROSS: Right.

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

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

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

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

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

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

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

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

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1 lockstep.

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

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

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

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

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

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

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

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1 prescribing opioids more carefully.

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

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

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

1 concluded that the benefits of opioids remained  
2 questionable.

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

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

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

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

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

11           UNIDENTIFIED FEMALE SPEAKER: It was the  
12 video.

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

16           (Laughter.)

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

19           Daniel, please.

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

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

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

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



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

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

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

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

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1 10 -- i.e., moderate -- the new label would not  
2 support, nor might an insurer pay for, continuing  
3 chronic opioid therapy. On the other hand, had the  
4 intensity been reported as a 7 out of 10, there would  
5 be no problem doing so. How many patients might then  
6 say, "Well, on second thought, it actually was closer  
7 to a 7 than a 6"?

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

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

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

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

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

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

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

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

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1 to tampering.

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

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

12 Thank you very much.

13 DR. THROCKMORTON: Thank you.

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

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

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

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

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

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

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

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

6           The lack of adequate trials data is troubling  
7 given that we are experiencing a major epidemic of  
8 prescription opioid overdose and addiction. There are  
9 now over 16,000 fatal drug overdoses a year involving  
10 prescription opioids in the United States, and over  
11 140,000 persons a year seek addiction treatment for  
12 non-heroin opioids.

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

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

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

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

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

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



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

6           Some have expressed concern that more  
7 selective and cautious opioid prescribing for chronic  
8 pain could leave millions of chronic pain patients  
9 experiencing needless pain. In fact, most patients  
10 using opioids long term at higher dose continue to  
11 experience substantial pain and pain-related  
12 disability. In our survey, we found that the large  
13 majority of chronic opioid therapy patients on higher  
14 dose continued to report moderate to severe pain,  
15 continued to report significant pain-related  
16 interference with activities, continued to report many  
17 disability days due to pain, most were currently  
18 unemployed, and most were clinically depressed. Over  
19 70 percent of these high-dose patients had three or  
20 more of these unfavorable quality of life indicators,  
21 and only 14 percent had one or fewer. In our survey,  
22 relatively few chronic opioid therapy patients on high

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

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

14           Thank you very much.

15           DR. THROCKMORTON: Thank you.

16           Ms. Gomes?

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

22           I am a researcher and scientist at Sunnybrook

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

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

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

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

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1 approximately 13.5 million residents, and these  
2 residents have universal access to hospital and  
3 physician care services as well as those aged 65 years  
4 and older, as well as those receiving social  
5 assistance, receive government coverage for their  
6 prescription drug costs, and as a result, the research  
7 that I'll present today is focused on a population aged  
8 less than 65 since we have found in our population that  
9 very few people are receiving opioids over the age of  
10 65, the vast majority of use is in this younger  
11 population. And we restricted to those individuals  
12 with no past cancer diagnoses or palliative care  
13 services to try and restrict this to a population of  
14 individuals receiving opioids for chronic non-cancer  
15 pain.

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

22           So this is a study that we conducted that was

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

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

22           As my colleague, Dr. Dhalla, mentioned in his

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

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

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

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

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1 equivalents.

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

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

16           DR. THROCKMORTON: Thank you.

17           And, Greg Terman.

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



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1 why in recent months I have traveled repeatedly from --

2           Whoops. It seems to have a mind of its own.

3 I need to restart that. The random signal generator is  
4 not working.

5           (Laughter.)

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

7           DR. THROCKMORTON: Help is on its way.

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

10          DR. TERMAN: You bet. No problem.

11          Next slide. Next slide.

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

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

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

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

13           Next slide.

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

22           Next slide.

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

3           (Laughter.)

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

8           Next slide.

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

13          (Laughter.)

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

22          Next slide.

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1 Proper evaluation of patients in pain  
2 involves an assessment of pain, of course, but also of  
3 mood and function. I'm concerned about the mood of  
4 someone who reports a pain of 12 on a scale from 0 to  
5 10, and I advise against simply prescribing more  
6 opiates for this patient's severe pain no matter what  
7 the labeling says.

8 Next slide.

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

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

18 Next slide.

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

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

11           Next slide.

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

1 in others.

2 Next slide.

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

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

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

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

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

13           Thank you very much.

14           DR. THROCKMORTON: Thank you. FDA Questions

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

18           Judy?

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

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

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

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

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



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

3 DR. GOMES: Yeah. So what we did was we  
4 actually went into the Chief Coroner's Office and  
5 reviewed all of the files for drug-related deaths since  
6 1991 and looked at the toxicological screens as well as  
7 any other information gleaned during the coroner's  
8 investigation for those deaths to see whether or not  
9 opioids were present at such a level as to cause the  
10 death on their own or in combination with another  
11 product such that neither product alone would have  
12 caused the death but the combination of the products  
13 led to the death.

14 DR. THROCKMORTON: Thank you.

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

19 DR. GOMES: Legally prescribed as opposed to  
20 --

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

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

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

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

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

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

20 DR. HERTZ: Great. Thank you.

21 DR. GOMES: Thanks.

22 DR. THROCKMORTON: John?

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

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

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

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

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

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

11 (Laughter.)

12 DR. JENKINS: At least you're honest.

13 UNIDENTIFIED MALE SPEAKER: There's that  
14 honesty.

15 (Laughter.)

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

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

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

6 DR. THROCKMORTON: Other questions?

7 (No audible response.)

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

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

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

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1 the payers.

2 Next slide, please.

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

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

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

22 The pharmacies are on the front line of

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

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

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

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

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

5           Next slide, please.

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

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

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



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

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

20           Next slide, please.

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

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

15           Next slide, please.

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

19           DR. THROCKMORTON: Thank you very much.

20           Mr. Ervin?

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

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

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

5 So next slide.

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

15 Next slide.

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

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1           Next slide.

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

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

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1           Next slide.

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

15           Next slide.

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

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

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

15           Next slide.

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

21           Next slide?

22           And the physician gets an actual report,

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

11 Next slide.

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

17 Next slide.

18 Skip. This is just current guidelines as  
19 they are.

20 Next slide.

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

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1 Next slide.

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

9 Next slide.

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



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

4 Next slide.

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

10 Next slide.

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

15 Next slide.

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

21 Next slide.

22 So the conclusion I'm getting to is that COT

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

13 Thank you.

14 DR. THROCKMORTON: Thank you.

15 Kevin Zacharoff.

16 DR. ZACHAROFF: Hi. And thank you.

17 First slide, please.

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

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

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

22           Moving on to the topic of standardization,

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

18           Next slide, please.

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

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

8           Next slide, please.

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

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

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

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

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

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

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

7           Next slide, please.

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

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

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1 Thank you very much.

2 DR. THROCKMORTON: Thank you.

3 And, Jody Green.

4 DR. GREEN: Good afternoon. I'm Jody Green.

5 I'm Director of Research Administration at the Rocky  
6 Mount Poison and Drug Center and Assistant Professor at  
7 the School of Nursing at Vanderbilt University Medical  
8 Center.

9 Next slide.

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

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



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

3           Next slide.

4           So the RADARS System is composed of four  
5 different programs -- I'm sorry, five different  
6 programs. We have 53 of the 57 regional poison centers  
7 of the United States are included in our RADARS System  
8 Poison Center Program. This covers approximately 90  
9 percent of the U.S. population. Our drug treatment  
10 programs include 73 opioid treatment programs, both  
11 public and private, from 33 different states. We have  
12 280 drug diversion units that we work with nationally  
13 to collect data. Through online surveys, we collect  
14 information from 6,000 college students annually, and  
15 also from a national distribution geographically  
16 stratified by region, and we also have a website that  
17 uses cloud sourcing methodology to monitor the street  
18 value of illicit and prescription drugs.

19           Next slide.

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

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

12           Next slide.

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

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

5 Next slide.

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

17 The abuse rate reported to RADARS System  
18 Poison Centers, based upon population, illustrates a  
19 40-percent reduction in abuse of ER oxycodone following  
20 the launch of the reformulation in 2010. This  
21 reduction was seen during a period of time in which  
22 there was actually a 5- percent increase in abuse

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

6 Next slide.

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

12 Next slide.

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

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

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

6 Next slide.

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

19 Thank you.

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

22 Judy?

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

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

13 DR. STAFFA: Okay. Thank you.

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

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

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

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

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

16 DR. THROCKMORTON: Mike?

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

15 DR. THROCKMORTON: Thank you.

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

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

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

13 DR. THROCKMORTON: Thank you.

14 Other last questions?

15 (No audible response.)

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

20 Mr. White I believe is the first one next.

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

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

9 Next slide, please.

10 Accident Fund Holdings is a company that is  
11 over 100 years old. We have four companies across the  
12 country licensed and insured in all 50 states. We're  
13 the thirteenth largest worker's compensation insurance  
14 company and the largest monoline worker's compensation  
15 company in the country. We're a subsidiary of Blue  
16 Cross Blue Shield. We insure over 46,000 employers  
17 representing over a million lives and working with over  
18 70,000 treating providers across the country.

19 Next slide, please.

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



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

13           Next slide, please.

14           Although the injuries have pretty much stayed  
15 the same over the last 10 years, provider treatment  
16 patterns have changed drastically. Prescription  
17 patterns have migrated, and we have recognized about a  
18 1-percent growth of use of opiate agonists over the  
19 last 10 years. Opioids now account for 3 percent of our  
20 medical spend and 46 percent of our scripts by volume.  
21 Interesting to note is that of all the injured workers  
22 that are part of our pharmacy benefit management

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

3 Next slide.

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

18 Next slide, please.

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

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1 Bernacki from Johns Hopkins University School of  
2 Medicine, and we did a retrospective study of 12,226  
3 claims, particularly in the State of Michigan, all  
4 indemnity claims over the last 4 years from 2006 to  
5 2010, so claims that were opened and closed in that  
6 timeframe.

7           Next slide, please.

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

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1 gender, lost time days, complexity of the injury, and  
2 any legal involvement, we see short-acting opioids  
3 increased the odds of a claim exceeding \$100,000 by  
4 1.76 and long- actings by 3.94.

5 Thank you very much.

6 DR. THROCKMORTON: Thank you.

7 Mr. McClure?

8 DR. McCLURE: Yes. I'm Leland McClure.

9 Thank you for the opportunity to speak today. I am a  
10 board- certified forensic toxicologist with Quest  
11 Diagnostics, and my role is Director with National  
12 Testing Operations for Corporate Operations for Quest  
13 Diagnostics. I also serve as a scientific inspector  
14 consultant with the National Laboratory Certification  
15 Program for Federally Regulated Testing, and I serve of  
16 a broad variety also of other agency groups as a  
17 consultant, including CDC.

18 If we could go to the next slide.

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

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1 presence and we employ approximately 42,000 people. We  
2 provide comprehensive diagnostic testing solutions, and  
3 we test more 500,000, half a million, patients every  
4 day in our facilities. We touch the lives of patients  
5 145 million times per year, and we service half of all  
6 the hospitals and physicians in the United States, and  
7 we're a pioneer in developing innovative tests.

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

14           If we can go to the next slide.

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

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

16           If we could go to the next slide.

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

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

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

15           If we go to the next slide.

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

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1 retrievable.

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

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

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



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

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

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

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

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

14 DR. THROCKMORTON: Thank you very much.

15 Dr. Alexander?

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

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

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

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

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

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

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

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

22                   So limitations in the data notwithstanding,

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

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

14           More remarkable still, among visits limited  
15 to new musculoskeletal pain, about one-half in a given  
16 year were associated with analgesics: in 2000, 53  
17 percent of visits; decreasing to a low of 47 percent in  
18 2004; returning to 53 percent by 2010. So this is  
19 noteworthy because it suggests that large increases in  
20 opioid sales, 400 percent from 1997 to 2007, have not  
21 been associated with substantial improvements in the  
22 rates of treatment among this nationally representative

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1 sample.

2           Third, we were interested in how pain  
3 treatments have been balanced among opioid and non-  
4 opioid therapies. Among all pain visits, opioid use  
5 nearly doubled from 11 percent to 20 percent, whereas  
6 use of non-opioid analgesics remain unchanged at 26 to  
7 29 percent of visits over the decade. And although  
8 one-half of new musculoskeletal pain visits resulted in  
9 pharmacologic treatment, the use of non-opioid  
10 treatments actually decreased over this period from 38  
11 percent of visits in 2000 to 29 percent of visits in  
12 2010. Most of this was due to reductions in the  
13 proportion of visits treated with NSAIDs rather than  
14 other non-opioid analgesics. This is important because  
15 it suggests that despite large increases in opioid use,  
16 there were not similar increases in the use of NSAIDs,  
17 acetaminophen, or other therapies that may serve as  
18 alternatives to prescription opioids.

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

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

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

14           DR. THROCKMORTON: Thank you.

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

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

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



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

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

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

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

19 Next slide.

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

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

7 Next slide.

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

12 Next slide.

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

22 Next slide.

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

10           Next slide.

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

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

6 Next slide.

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

12 Next slide.

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

20 Next slide.

21 The number needed to harm for opioids  
22 compared with nonselective NSAIDs was 17 for

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

6 Next slide.

7 In conclusion, in Dr. Solomon's research,  
8 opioids were associated with increased risk of several  
9 adverse events relative to nonselective NSAIDs and COX-  
10 2 inhibitors; notably, risk of fractures and  
11 cardiovascular events. These excess risks appear to be  
12 clinical significant in that relatively few patients  
13 need to be treated to observe excess adverse events  
14 based on the results of this study.

15 Next slide.

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

22 Thank you very much.

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

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

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

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

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

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

15           DR. THROCKMORTON: Thank you.

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

18           DR. VON KORFF: It is published.

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

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

22           DR. THROCKMORTON: Other comments/questions?

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1 Judy and then John.

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

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

14 DR. STAFFA: Thank you.

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

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



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

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

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

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

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

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

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

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

5           Thank you so much.

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

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1 CERTIFICATE OF COURT REPORTER

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

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ERICK MCNAIR  
Digital Court Reporter

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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.

\_\_\_\_\_  
Date

\_\_\_\_\_  
DEBORAH ARBOGAST  
Transcriptionist

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