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FOOD AND DRUG ADMINISTRATION (FDA)  
  
STANDARDS FOR FUTURE OPIOID ANALGESIC APPROVALS AND  
  
INCENTIVES FOR NEW THERAPEUTICS TO TREAT  
  
PAIN AND ADDICTION

PUBLIC HEARING

September 17, 2019

9:00 a.m.

FDA White Oak Campus  
10903 New Hampshire Ave, Building 31  
Room 1503, Sections B and C  
Silver Spring, MD 20993

JOB No.: 3401290

A P P E A R A N C E S

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(Continued)

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	C O N T E N T S	
		PAGE
1		
2		
3	Opening Remarks	8
4	Dr. Douglas C. Throckmorton	
5	Comments on Behalf of Authors of NASEM Consensus	13
6	Report on Pain Management and the Opioid Epidemic	
7	(2017)	
8	Prof. Richard J. Bonnie	
9	Prof. Margaret Riley	
10	FDA's Response to the National Academies 2017	23
11	Recommendations for a New Opioid Regulatory	
12	Framework: Woefully Inadequate in Substance,	
13	Devoid of Necessary Urgency	
14	Dr. Michael Carome	
15	FDA Opioid Drug Labels: A Disability Rights	31
16	Perspective	
17	Ms. Kristin McGarity	
18	Fed-Up's Opinion on Opioid Analgesic Drugs	39
19	Mr. Anthony LaGreca	
20	Benefit-Risk Assessment of Opioids: Oxymorphone	47
21	as a Case Study	
22	Dr. Janetta L. Iwanicki	

	C O N T E N T S	
		PAGE
1		
2		
3	Break	58
4	Role of Postmarketing Surveillance in Opioid	59
5	Approvals	
6	Dr. Richard C. Dart	
7	Opioid and Alternative Pain Management	75
8	Effectiveness and Obstacles	
9	Ms. Tasha Olson	
10	Standards for Future Opioid Analgesic Approvals	84
11	and Incentives for New Therapeutics to Treat	
12	Pain and Addiction	
13	Dr. Andrew Kolodny	
14	What Research Tells Us that Can Improve FDA	93
15	Approval Standards and REMS for Opioids	
16	Dr. Diana Zuckerman	
17	Incentives for New Therapeutics to Treat Pain	105
18	and Addiction: An Industry Perspective	
19	Dr. Danielle Friend	
20	Lunch	118
21	Barriers to Innovation	119
22	Mr. Matthew Iorio	

1	C O N T E N T S	
2		PAGE
3	FDA Supporting Innovation in Pain Therapeutics:	133
4	An Industry Perspective	
5	Dr. James N. Campbell	
6	Assessing the Value of Novel Opioid Analgesics	143
7	Dr. Judy Ashworth	
8	Opioid-Sparing Indication, a Pre-Approval	152
9	Incentive for New Therapeutics to Treat Acute	
10	Pain	
11	Dr. Chris Storgard	
12	Considerations for Accelerating the Development	163
13	of Non-Opioid Analgesics	
14	Dr. David J. Hewitt	
15	Abuse Deterrence and Other Novel Approaches to	181
16	Address the Prescription Opioid Epidemic	
17	Dr. Beatrice Setnik	
18	Break	188
19	Open Public Hearing	189
20	Concluding Remarks	197
21	Dr. Douglas C. Throckmorton	
22		

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

## OPENING REMARKS

1  
2  
3 DR. THROCKMORTON: Good morning everybody, and  
4 why don't we go ahead and get started? Welcome to the  
5 public meeting Standards for Future Opioid Analgesic  
6 Approvals and Incentives for New Therapeutics to Treat  
7 Pain and Addiction. My name is Douglas Throckmorton.  
8 I'm the Deputy Center Director for Regulatory Programs  
9 at the Center for Drug Evaluation and Research, Food  
10 and Drug Administration. I will serve as the presiding  
11 official at this hearing. Before we get started, I'd  
12 like to give some background and review some of the  
13 Part 15 materials, procedures and then get going.

14 On June 21st, 2019, FDA issued a draft  
15 guidance on the application of FDA's benefit risk  
16 assessment framework to applications for the approval  
17 of opioid analgesic drugs entitled, Opioid Analgesic  
18 Drugs; Considerations for Benefit Risk Assessment  
19 Framework. As explained in the FDA's Federal Register  
20 notice announcing today's public meeting, while the  
21 existing benefit risk assessment has been and continues  
22 to be a comprehensive and effective mechanism for



1 evaluating all new drug approvals, including opioids.  
2 Given the current opioid crisis, it is critical that  
3 the FDA explore every possible option for effectively  
4 responding to opioid misuse and abuse.

5           For this reason, and in connection with FDA's  
6 commitment under the SUPPORT Act, this public hearing  
7 is intended to receive stakeholder input, not only on  
8 the benefit risk guidance, but also on the approval  
9 process for new opioids and on how FDA might best  
10 consider the existing armamentarium of therapies for  
11 pain among other factors in reviewing applications,  
12 renewal opioid analgesics.

13           FDA also seeks input on potential new pre-  
14 approval incentives in addition to existing incentives.  
15 We are aiming to foster the development of new  
16 therapeutics to treat pain and new treatments for  
17 addiction. Before I begin -- we begin I want to make a  
18 few administrative announcements. First, please  
19 silence all of your cell phones and other mobile  
20 devices as they may interfere with the audio in this  
21 room. Second, we ask that all attendees sign in, in  
22 the registration. Those who are outside, hopefully you

1 did that. Third, the restrooms are down the hall  
2 behind you and past the coffee area and down the  
3 hallway. Finally, copies of the presentations today  
4 are available on request. The contact information for  
5 making this request is available at the registration  
6 tables and will be on the monitors during our breaks.

7 I would now like to ask the FDA panelists to  
8 introduce themselves. I already have done that, so  
9 I'll look to have...

10 DR. THANH HAI: Good morning. I'm Mary Thanh  
11 Hai. I am the Acting Director in the Office of New  
12 Drugs at CDER.

13 DR. STEIN: Good morning. I'm Peter Stein.  
14 I'm Director at the Office of New Drugs in CDER.

15 MR. DAL PAN: Good morning. I'm Gerald Dal  
16 Pan. I'm the Director at the Office of Surveillance  
17 and Epidemiology in CDER.

18 DR. THROCKMORTON: There are two other  
19 individuals we hope will be arriving, and we'll have  
20 them introduce themselves when they do so. Thank you.  
21 For media at this point, there's Officer Sandy Walsh.  
22 Sandy -- put her hand up maybe. There you go. Thank

1 you. If any members of the media are here today,  
2 please sign in. If you have any questions or are  
3 interested in speaking with the FDA about this public  
4 meeting, please contact Ms. Walsh. The hearing is  
5 intended to give FDA the opportunity to listen to  
6 comments from the presenters, so the panelists and  
7 other FDA employees will not be available to make  
8 statements to the media. Although there are no rules  
9 of evidence for this public meeting, there are some  
10 general procedural rules. No participants may  
11 interrupt the presentations of another participant, and  
12 only FDA panel members will be allowed to ask questions  
13 of the presenters.

14           There will be an open public hearing at the  
15 comment period at the end of the day once all of the  
16 presenters are finished. Public hearings are public  
17 administrative proceedings and are subject to FDA's  
18 policy and procedures for media coverage.  
19 Representatives of the media are permitted subject to  
20 certain limitations to video, film or otherwise record  
21 FDA's public proceedings including the presentations of  
22 the speakers today. This hearing will also be

1 transcribed, and copies of the transcript can be  
2 ordered through the docket or accessed on our meeting  
3 website approximately 30 days after the public hearing.

4           Today we have 16 presentations, each of which  
5 are allotted 10 minutes. After each presentation, 3  
6 minutes will be scheduled for the panel members to ask  
7 questions, if necessary. If a presenter finishes early  
8 or withdraws, or if the question from the panel do not  
9 take the fully allotted time, we intend to move  
10 directly to the next speaker. This means that the  
11 presenters may find themselves being called on to give  
12 their presentation before the time that's listed on the  
13 agenda. And although we may be adjusting the  
14 presenter's schedules as needed, we do hope to keep to  
15 our scheduled breaks. For the speakers, we have the  
16 timer lights to guide you, a green light -- green light  
17 will indicate when to speak and a red light when to  
18 stop. The timer will give you a 1minute yellow warning  
19 before the red light goes on.

20           If you do not conclude your remarks by the  
21 time of the end of the allotted time, we may ask you to  
22 do so or wrap your comments up quickly. If you did not

1 register to speak, but would like to present oral  
2 comments, you may do so during open public hearing  
3 which is currently scheduled to begin at 2:45. If  
4 interested, please sign up with the registration table  
5 outside the meeting room by 10:30 for an available 4-  
6 minute speaker slot.

7 We also strongly encourage you to submit your  
8 comments to the docket by November 18th, 2019. Please  
9 see the Federal Register for details on how to consent  
10 [sic] that. This hearing is being webcast live. This  
11 is not an interactive meeting. Again, only the FDA  
12 panel members are allowed to ask the presenters  
13 questions. In closing, I want to thank everyone  
14 including our panelists and speakers for participating  
15 today, and I'll look forward to a productive meeting.  
16 Thanks.

17 Dr. Bonnie, I believe you are the first  
18 speaker.

19 COMMENTS ON BEHALF OF AUTHORS OF NASEM CONSENSUS  
20 REPORT ON PAIN MANAGEMENT AND THE OPIOID EPIDEMIC  
21 (2017)

22 MR. BONNIE: So, my name is Richard Bonnie,

1 and I am accompanied by my colleague, Margaret Foster  
2 Riley. We've participated, both of us, in a study that  
3 was conducted by the National Academies of Sciences,  
4 Engineering, and Medicine which will issue a -- release  
5 a consensus report on end management and the opioid  
6 epidemic in 2017. The study was requested in 2016 with  
7 a -- by the FDA with a broad charge including among  
8 other things helping the Agency develop and implement a  
9 framework for taking public health considerations into  
10 account and opioid regulation.

11 I can say on behalf of the committee as a  
12 whole with whom we consulted for this presentation that  
13 we are pleased that the Agency has taken a decisive  
14 step forward to embrace the public health framework  
15 outline in the committee's report by -- and by issuing  
16 a proposed guidance document regarding the Agency's  
17 expectations, the manufacturers regarding the data that  
18 are expected during the NDA process as recommended in  
19 the report.

20 This is the first step in what we all  
21 recognize will be a challenging and iterative process.  
22 I also meant to say earlier that in drafting our

1 comments here and submitting them, we were joined also  
2 by Dr. Aaron Kesselheim, professor in the Medical  
3 School at Harvard and also Patricia --

4 MS. ZETTLER: Zettler.

5 MR. BONNIE: -- Zettler, sorry, from Ohio  
6 State Law School, all of whom -- Aaron was a member of  
7 the committee, and Dr. Zettler was -- contributed as a  
8 consultant.

9 So essential advice that is given by the  
10 committee in the 2017 report was that the FDA consider  
11 a broad range of evidence and apply a -- what we called  
12 a comprehensive systems approach in its regulation of  
13 prescription opioids. I'll just mention it is entirely  
14 appropriate to use a comprehensive public health  
15 approach to refer to what the committee recommended in  
16 the report.

17 I did want to highlight that the reason that  
18 the systems approach was used also as a way of  
19 referring to what we recommended was that the Agency  
20 actually also asked us to think about how to develop a  
21 formal model once the broad public health  
22 considerations were being taken into account that would

1 enable us to quantify the range of possible effects of  
2 different types of regulatory actions that could be  
3 taken, not only by the Agency in its work, but also by  
4 the other governmental agencies that regulate in this  
5 field.

6           We applaud the Agency for developing a draft  
7 guidance with the recommendations of the committee's  
8 report in mind. The Agency's proposal to consider  
9 broad public health effects in its overall benefit-risk  
10 assessment of opioid analgesic drugs is an important  
11 first step in implementation of the committee's  
12 recommendations and will lead to significant benefits  
13 for the public health. FDA should move to finalize the  
14 public health approach which balances the individual  
15 needs for pain control with considerations for broad  
16 public health consequences of opioid use in a disorder.

17           This approach is obviously permitted by the  
18 existing statutory authority, and we were pleased to  
19 see that the Agency recently, in responding to the  
20 Public Citizen's request for a moratorium, indicated  
21 quite clearly that they agreed with the committee's  
22 assessment also that initiating this public health



1 broad view of public health considerations in the  
2 Agency's decision-making in this area is well within  
3 the existing Agency authority. I quote from Dr.  
4 Woodcock's letter, you probably note that the draft  
5 guidance and the public discussion of the draft  
6 guidance builds on and seeks to formalize FDA's  
7 historic practice of considering the larger public  
8 impact of our regulatory decisions regarding opioids.

9           So, we applaud the Agency again for having  
10 taken this initial step. The -- they all are, however,  
11 mentioned in the report additional actions after this  
12 initial step is taken that the Agency needs to address  
13 to accomplish the public -- comprehensive public health  
14 approach. This is not the time obviously to go to them  
15 in depth but let me just mention three very important  
16 further steps that need to be taken.

17           First, it's very important to collect a wide  
18 range of data that bear on the public health  
19 consequences of opioid use and of the effects of public  
20 health interventions that go beyond obviously the data  
21 that's typically connected in connection with approvals  
22 and clinical trials. Secondly, it's important to

1 strengthen post-approval oversight, including the REMS  
2 as the Agency itself has recognized in these matters  
3 will continue to be intensified as we go forward. And  
4 then thirdly, and very importantly, the committee  
5 recommended a full review of currently marketed and  
6 approved opioids in a comprehensive study.

7           First with regard to the data, the -- in each  
8 data, not just from well-designed clinical trials, but  
9 also from other sources that can help inform an  
10 assessment of opioids public health effects. This  
11 should include traditional sources, as well as less  
12 traditional sources including non-health data to  
13 understand the real-world impact of opioids in the  
14 various domains that are important for a public health  
15 analysis. The FDA should quickly establish guidelines  
16 for the collection and analysis of such data.

17           With regard to REMS, FDA must take steps to  
18 improve post-approval monitoring of opioids. REMS is  
19 currently structured or not meeting public health needs  
20 for opioids. FDA should routinely provide public  
21 information about how well the REMS are achieving such  
22 goals. The Agency should consider convening a forum

1 that allows for public input to advise on appropriate  
2 modifications, and the Agency should immediately take  
3 steps to require any necessary modifications to the  
4 existing REMS including creative approaches such as  
5 academic detailing, educational interventions, post  
6 monitoring of messaging to healthcare providers and  
7 should use independent third parties rather than  
8 manufacturers to lead the REMS. A key advantage of  
9 initiating this process also is that it would enable  
10 the Agency to use actual real-world experiential data  
11 from drugs already in the market to help develop the  
12 framework by conducting oversight.

13           Oh, in fact I just blended my two slides here.  
14 Let me -- so this is what I actually was just referring  
15 to, the committee recommended importantly a -- an  
16 opioid -- what we call an opioid study implementation  
17 process to review currently marketed and approved  
18 prescription opioids to assess their safety and  
19 effectiveness based on the same standards that are  
20 applied to new drugs. The FDA -- the Drugs and  
21 Cosmetics Act, in our view, does not provide a legal  
22 basis for taking a different approach to assessing

1 benefits and risk for currently marketed products than  
2 it does for unapproved products. This process can be  
3 undertaken while assuring an adequate access for pain  
4 treatment options, and the cost should not increase as  
5 long as sufficient numbers of generic manufacturers  
6 continue to produce those opioid formulations that do  
7 remain on the market.

8           And again, as I have said out of order, a key  
9 advantage of initiating this process is that it would  
10 enable the Agency to use experiential data from drugs  
11 already on the market, helping develop the framework  
12 that needs to be developed for application of the  
13 comprehensive public health approach.

14           Then finally, in conclusion, the FDA's  
15 decision to consider opioids broader public health  
16 effects is a crucial step in the Agency's response to  
17 the opioid crisis. All these recommended actions,  
18 acquisition and analysis of new data, strengthening  
19 REMS and conducting a full review of all opioid drugs  
20 can be taken using FDA's existing statutory  
21 authorities. This is all part of a holistic approach  
22 to drug review that properly balances individual's need

1 for an adequate pain relief and public health  
2 requirements to combat opioid use disorder. Obviously,  
3 this is going to be a challenging process going  
4 forward, but obviously it is an urgent one, and we  
5 remain available to help the FDA in any way the basic  
6 bip [sic].

7 DR. THROCKMORTON: Down the table, to my  
8 panelists. Gerald, you'll have to raise your hand if  
9 you want to have, except (ph) based on that.

10 MR. DAL PAN: Dr. Bonnie..

11 SPEAKER: Mic.

12 MR. DAL PPAN: Dr. Bonnie, you had mentioned  
13 the use of less traditional sources of data. I can  
14 think of a lot of things that you might need. Can you  
15 give a few examples of things you might think are more  
16 important than other kinds of data sources?

17 MR. BONNIE: Well, in our comment letter, we  
18 did identify a number of these areas specifically that  
19 they thought would be indicative of the kind of data  
20 that we had in mind. And maybe rather than looking for  
21 it in the letter.

22 DR. THROCKMORTON: Okay. Great. Thank you

1 very much. Other questions? Pete -- Dr. Stein?

2 DR. STEIN: Thank you for the presentation.

3 Can you say a few more words about the -- how you  
4 conceive that the OSI process, are you thinking about  
5 this as looking in groups of agents, or you're looking  
6 at this as individual agents? Are you looking -- and  
7 any comments about how you would prioritize or how you  
8 would select this, obviously it'd be a wide range of  
9 drugs that potentially could be included. How would  
10 you foresee that being organized just at a high level?

11 MS. RILEY: So, we didn't go into the detail  
12 of an individual versus the systems piece. I would say  
13 we started with a model deci (ph), but deci wouldn't  
14 necessarily control. What we're looking for is an  
15 effective review, and if you could group different  
16 classes with each other, that would be fine. What  
17 we're looking for is to understand the public health  
18 effects of the existing drugs as well. That's going to  
19 be very much tied to the data that is being collected  
20 at the same time because with all -- in fact all three  
21 parts of this are very closely aligned because you need  
22 the data, you need parts of the REMS pieces in order to

1 conduct that OSI review. We did not go into exactly  
2 the systematic way, where you would start, where you  
3 would end in having a group.

4 SPEAKER: Thank you.

5 DR. THROCKMORTON: Thank you, Dr. Bonnie.  
6 Next speaker is Dr. Michael Carome from Public  
7 Citizen's.

8 FDA'S RESPONSE TO THE NATIONAL ACADEMIES 2017  
9 RECOMMENDATIONS FOR A NEW OPIOID REGULATORY  
10 FRAMEWORK: WOEFULLY INADEQUATE IN SUBSTANCE,  
11 DEVOID OF NECESSARY URGENCY

12 DR. CAROME: Good morning. I'm Dr. Michael  
13 Carome, Director of Public Citizen's Health Research  
14 Group. The following comments were prepared jointly  
15 with my colleague Dr. Sidney Wolfe. The only realistic  
16 interpretation of the first part of the title for this  
17 meeting, Standards for Future Opioid Analgesic  
18 Approvals, is that the FDA is very belatedly beginning  
19 the process of developing and seeking public input for  
20 such standards. That the title specifically refers for  
21 future opioid approval, not to a more expansive  
22 detailed opioid regulatory framework that already put

1 in place to evaluate currently approved and future new  
2 opioid analgesics is an admission of the dangerously  
3 preliminary progress the FDA has made thus far in  
4 developing such a framework.

5           This meeting was announced simultaneously with  
6 the now closed public comment period for the Agency's  
7 June 2019 draft guidance for industry entitled "Opioid  
8 Analgesic Drugs; Considerations for Benefit Risk  
9 Assessment Framework." Overall, we found the draft  
10 guidance to be woefully inadequate because its cursory  
11 content is far more focused on non-specific generalized  
12 factors that the FDA itself will consider when  
13 reviewing a new drug application for an opioid rather  
14 than providing industry with guidance as to what  
15 specific benefit and risk information should be sought  
16 out and included in future NDAs for approval. The non-  
17 directive nature of the draft guidance was bluntly  
18 stated by the FDA in the document's background section,  
19 "This guidance describes the various factors that FDA  
20 will consider in evaluating the benefits and the risks  
21 of an opioid analgesic drug. FDA encourages applicants  
22 to provide information relevant to these factors."



1           As an example of the lack of specific  
2 directive guidance, the draft guidance noted that the  
3 FDA will consider the following questions among others  
4 in assessing the effectiveness and safety of an opioid  
5 analgesic drug, "Do any comparative efficacy data  
6 exists for the drug relative to approved opioid or non-  
7 opioid analgesic drugs. Does this analgesic drug offer  
8 any advantages relative to available approved analgesic  
9 drugs for each indication with regard to effectiveness  
10 or duration of response? Do any comparative safety  
11 data exist for the drug relative to approved opioid or  
12 non-opioid analgesic drugs? Does this analgesic drug  
13 offer any safety advantage or disadvantages relative to  
14 available approved analgesic drugs for each  
15 indication?"

16           Merely "Encouraging applicants to provide  
17 information relevant to these factors," is an  
18 unacceptable replacement for a more specific  
19 recommendation that clinical trials, testing new  
20 opioids should include not just comparator control  
21 groups, not just placebo-control groups, to get quickly  
22 answered -- quickly the answers to these questions.

1 Among the important details lacking from the guidance  
2 are recommendations that companies seeking approval for  
3 new opioids review the previous evidence for diversion  
4 of similar earlier marketed opioids and that the  
5 companies discussed in the NDAs what intervention they  
6 plan to implement to ensure that their new opioids  
7 would be diverted less often than similar predecessor  
8 drugs as recommended by the National Academies in the  
9 2017 report which was commissioned by the FDA in 2016  
10 to review the status of FDA opioid regulation and to  
11 suggest improvements in it.

12           It is noteworthy that seven of the nine  
13 questions for today's meetings also deal with  
14 comparator assessment of the effectiveness or safety of  
15 new opioids, issues that were specifically addressed in  
16 the recommendations and discussion made in the National  
17 Academies 2017 report. Ironically, on June 20th, 2019,  
18 the day before the FDA's June 2019 draft guidance was  
19 posted for public comment, the FDA withdrew an earlier  
20 2014 draft guidance that dealt with the same comparator  
21 safety and efficacy issues, but in much more detail and  
22 a properly directive manner as reflected in the

1 following excerpt among others.

2 "As previously noted, efficacy trials for  
3 analgesics should be superiority trials. Even if a  
4 placebo-controlled design is used, sponsors are  
5 encouraged to include an active comparator in single  
6 dose, as well as multi-dose trials. An active  
7 comparator may provide useful information on the  
8 relative utility of the investigation of drug in that  
9 population, particularly when there's already an  
10 analgesic that's commonly used for the type of pain  
11 under evaluation."

12 Including such specific recommendations in the  
13 FDA guidance would be fully consistent with the type of  
14 new opioid regulatory framework envisioned by the  
15 National Academies' report. Given that National  
16 Academies' additional recommendation that the FDA  
17 develop a process for reviewing and complete a review  
18 of the safety and effectiveness of all currently  
19 approved opioids, recommendation 66, using the still to  
20 be developed opioid regulatory framework which will  
21 likely lead to some of these opioids making a move from  
22 the market, it is imperative that FDA expand its focus

1 beyond just standards for approval of future opioids.

2           In April of this year, because of the then  
3 more than 80-month FDA delay in any meaningful public  
4 response, the National Academies' 2017 recommendations,  
5 we filed a petition with the FDA to immediately impose  
6 a moratorium on approval of all NDAs for new opioids  
7 and new opioid formulations. The petition argued that  
8 the moratorium should not be lifted until the Agency  
9 has implemented the elements recommended by the  
10 National Academies for inclusion in the currently non-  
11 existing opioid regulatory framework.

12           The petition denied on September 6 would have  
13 provided the FDA and relevant advisory committees the  
14 necessary time to construct and implement the National  
15 Academies' framework. We agree with many of the  
16 comments submitted jointly by the chair, one member,  
17 and two consultants of the National Academies committee  
18 expressing their own views in response to the FDA's  
19 June 2019 draft guidance, including the following which  
20 I'd like to reiterate, "The draft guidance is an  
21 important first step in implementing the 2017 report's  
22 recommendations that will lead to benefits for public

1 health. But they remain critical actions for the  
2 Agency to take using existing authorities to help  
3 address the opioid crisis in a balanced way and fully  
4 implement the comprehensive systems approach  
5 recommended in the 2017 report."

6           Although the draft guidance begins to  
7 implement the recommendations of the National Academies  
8 committee's 2017 report, much remains unstated in the  
9 draft guidance. We encourage the Agency to integrate  
10 more recommendations from the 2017 report in its final  
11 guidance or additional guidance documents with the goal  
12 of using the full reach of the Agency's existing  
13 authority. The National Academies committee  
14 recommended that FDA conduct a full review of currently  
15 marketed and approved opioids which would treat  
16 similarly all prescription opioid analgesics, whether  
17 being considered for approval for the first time or  
18 already on the market. There is no sound medical  
19 reason for using a different approach for assessing the  
20 benefits and the risk of currently marketed opioids  
21 than the Agency uses for valid applications for future  
22 unapproved opioids. Likewise, the Agency's authority

1 under the Food, Drug and Cosmetic Act does not provide  
2 a basis for taking a different approach for assessing  
3 benefits and risks for currently marketed products and  
4 for unapproved products.

5           We encourage the Agency both to move forward  
6 to finalize the draft guidance and to work to implement  
7 the numerous other recommendations in the 2017 report  
8 to embed considerations of these broader public health  
9 effects throughout FDA's regulatory framework for  
10 opioids. In announcing today's meeting, the FDA posed  
11 various questions about requiring a new opioids  
12 analgesics demonstrate a comparative advantage over  
13 existing analgesics, and about the authorities the FDA  
14 would need to impose such a requirement. We, the  
15 committee, believe that the recommendations in the  
16 National Academies committee's 2017 report would  
17 achieve much the same goals sought by a comparative  
18 advantage approach would apply to both existing market  
19 and novel drugs and have the benefit of being grounded  
20 in the Agency's existing authority. "Working to  
21 implement these recommendations therefore would be a  
22 way for the FDA to improve its efforts to address the

1 opioid crisis now without waiting for congressional  
2 action."

3 In conclusion, had the FDA acted with the  
4 urgency demanded by the ongoing opioid crisis and begun  
5 the important public process of developing a  
6 desperately needed improved opioid regulatory  
7 framework, soon after we received the detail, carefully  
8 considered National Academies recommendations 2 years  
9 ago, it is likely that the process of creating this  
10 framework would have been completed by now rather than  
11 just beginning. The FDA now must make the development  
12 and implementation of such a framework its number one  
13 priority. Thank you very much.

14 DR. THROCKMORTON: Thank you. Questions from  
15 the panel? Thank you, sir. Our next speaker is Ms.  
16 Kristin McGarity, National Council on Independent  
17 Living.

18 FDA OPIOID DRUG LABELS: A DISABILITY RIGHTS  
19 PERSPECTIVE

20 MS. MCGARITY: Good morning. My name is  
21 Kristin McGarity. I have been volunteering with the  
22 NCIL Chronic Pain and Opioids Task Force. I should say

1 by way of disclosure I'm not paid by NCIL or anyone  
2 else to do this. I paid my way here, and I'm not  
3 aligned with any company or pharmaceutical company. In  
4 fact, my dad was one of the founders of Center for  
5 Progressive Reform and good folks at Public Citizen's  
6 know him well.

7 I'm doing this because it needs doing. So, to  
8 go through quickly, NCIL is the nation's longest  
9 running organization run by and for people with  
10 disabilities. It is our perspective that people with  
11 lived experience in this subject have largely been left  
12 out of conversation. And we're going to answer  
13 question 1 about benefit-risk assessment starting with  
14 history. Years of deceptive marketing leading to  
15 widespread harm, how do we prevent that? Someone  
16 suggests FDA should change the way it works to limit  
17 the duration of prescriptions for opioid analgesics.  
18 These kinds of limits have disproportionate impact on  
19 people with disabilities, especially the most serious  
20 and complex. Some would suggest FDA should limit the  
21 indications for opioid analgesics to cancer and end of  
22 life. Problem with this is chronic non-cancer pain is



1 a huge category. It includes catastrophic damage and  
2 genetic conditions where even the most conservative  
3 guidelines suggest long-term opioid therapy may be  
4 indicated.

5           They will change downstream effects on people  
6 in that population. Twenty-million Americans have high  
7 impact or disabling pain. The few studies we have that  
8 go long term suggest somewhere around at least 5 to 25  
9 percent of patients do benefit from long-term opioid  
10 care. And it doesn't -- may not sound like much until  
11 you remember that often these are the patients who  
12 don't benefit from anything else, and it's not that  
13 small a group. Major changes have downstream effects  
14 on the practical logistics for people's lives.

15 Starting with insurance, if you look to a lot of  
16 insurance formularies, they all say opioid medications  
17 are covered for FDA label indications only.

18           We -- on our membership, we're kind of an end-  
19 of-line treatment-wise. The only things left to try  
20 are things where the risk-benefit profile is worse.  
21 Experimental medications, medical devices, surgeries.  
22 The last thing we want to do is push people in

1 directions that are riskier. Multimodal pain therapy  
2 works really well for a lot of people if they can  
3 access it in the first place, if they can get there.  
4 Newer formulations have distinct practical advantages  
5 that shouldn't be denied to people just because their  
6 conditions are long-term.

7           And in the current environment, in this tangle  
8 of new guidelines and laws and metrics, we are in a  
9 situation where doctors can actually get better quality  
10 ratings by handing all their patients one last script  
11 saying I don't do pain meds anymore, good luck, and the  
12 quality metrics don't measure what complements to those  
13 patients. Yet another barrier in prescribing makes  
14 that problem worse. Palliative care, my state just  
15 passed a law defining palliative care as not requiring  
16 a terminal diagnosis. Any kind of palliative exemption  
17 at the federal level creates a 50-state patchwork of  
18 different definitions, but good palliative care keeps  
19 people out of institutions long-term and that's what  
20 NCIL is about.

21           Downstream effects, it's important to remember  
22 that opioid medication has other benefits besides pain

1 relief. Often this is in very rare conditions that  
2 their neurological benefits, functional benefits,  
3 immunosuppression and this is something we see a lot.  
4 Now, I want to be very clear who I'm talking about  
5 here. This is a specific subset of patients who were  
6 severely incapacitated before starting opioid  
7 medication in the first place. This is a group of  
8 patients who were offered long-term of opioid therapy  
9 as a last-ditch hope of maybe getting some function  
10 back. It worked. There are people in this group  
11 who've gone for decades on the same dose as working as  
12 teachers, lawyers, engineers, doctors, and what often  
13 happens is an attempt to do a really slow taper with  
14 all the available supports and all the available  
15 alternative therapies, the original disability comes  
16 back. It's not true to say that all deterioration  
17 would taper is attributable to hyperalgesia;  
18 attributable to dependence complications. It can also  
19 be an underlying condition, it doesn't heal. But the  
20 medication really was effectively palliating.

21           So, point being if we are including broader  
22 consequences of diversion and misuse, we also need to

1 include the broader consequences of those people  
2 potentially not being able to participate in society  
3 and the contributions they would have made. So that  
4 brings us to -- and I'm not just talking about economic  
5 consequences by the way. In fact, it's wrong to  
6 evaluate people by their economic impact, but even the  
7 best multimodal integrated pain care, it should be paid  
8 for by insurance, it should be available everywhere, it  
9 should be first line.

10           It has a partial success rate, and it has a  
11 failure rate, and those are real people with real lives  
12 who can do well on a long-term palliative program.  
13 That brings us to the question are opioids safe and  
14 effective for chronic pain? It's the long question  
15 because the answer is always going to be it depends.  
16 Often though, they're not, but the evidence we have  
17 suggests the minority of patients do benefit long term,  
18 and because some of those conditions are so importantly  
19 understood and not -- they're all clearly defined,  
20 risk-benefit analysis can't be based on condition by  
21 condition, it's got to be individual per-patient level  
22 zoomed in. Obviously, we want to see a lot more

1 research, not just on pain in general, but on each of  
2 these specific conditions.

3           It's going to be very difficult for studies to  
4 predict which patients are the ones who benefit. The  
5 people who do benefit long term don't tend to sign up  
6 for studies, and there are some real ethical concerns  
7 with a disabling condition putting people in a control  
8 group for years. So, we do know from previous FDA  
9 research that science does not support strict limits by  
10 any patient, by cancer versus non-cancer. The things  
11 that cancer does to bodies, other conditions can do  
12 too. Science does not support strict limits by  
13 duration. Information on day 89 is still information  
14 on day 91. And every clinical guideline acknowledges  
15 for some patients benefit outweighs risk. But as  
16 prescribing has dropped nationally, a lot of that was  
17 just knocking down dosage on those people. Do we  
18 really need more of that? Or, could there be a better  
19 way?

20           Have you ever been to a drug company website  
21 just to look something up, and months later their ads  
22 for opioid drugs still follow you around the Internet?

1 You change the label, they can still do that. You  
2 haven't solved the deceptive marketing problem. You  
3 still have advertising that can push people toward  
4 drugs they don't need. But, what if Congress could  
5 regulate the marketing of controlled substances  
6 directly without going through the FDA label process  
7 they can effectively tie doctor's hands?

8           Substance use disorder can be a disability.  
9 For some people with other disabilities, the exact same  
10 substance may be the best risk-benefit balance we  
11 currently have. Enabling people with disabilities to  
12 work, parent, participate in society, and achieve  
13 quality of life is itself a public health benefit. We  
14 zoom all the way back out, the goal should be everybody  
15 on medication, the goal should be everybody off the  
16 medication. That right there, that should be the goal.  
17 The chairs of our task force are available at this  
18 contact information and I will attempt to answer any  
19 questions that I can, if there are any.

20           DR. THROCKMORTON: Thank you very much.  
21 Questions from the panel? Thank you. Thanks a lot.  
22 Next speaker -- next speaker is Mr. Anthony LaGreca

1 from Fed-Up.

2 FED-UP'S OPINION ON OPIOID ANALGESIC DRUGS

3 MR. LaGRECA: Good morning, members of the  
4 committee. My name is Tony LaGreca. I am the CEO of  
5 Bissell Commercial vacuums based in Plymouth, Mass. I  
6 serve of the advocacy committee of the Fed-Up coalition  
7 of organizations on the frontline of the opioid crisis.  
8 Five years ago, my son Matthew died of an acute  
9 overdose of methadone prescribed to him by a pain  
10 specialist. Two years later his partner also died of  
11 an acute overdose of methadone.

12 Thank you for holding this hearing. Your  
13 interest in seeking public input on applying the risk-  
14 benefit analysis for new opioid approvals is  
15 appreciated. I'm also grateful that in the Federal  
16 Register announcing this meeting. You welcome input on  
17 the other relevant issues as well. The other relevant  
18 issues that I will discuss is the application of a new  
19 risk-benefit analysis for removal of existing products.

20 Recommendation that FDA should consider  
21 removing existing products utilizing a new risk benefit  
22 analysis was contained in this report from the National

1 Academy of Sciences. A report tthat was commissioned  
2 by Dr. Robert Califf when he was Commissioner of the  
3 FDA. This is a picture of my son when he was young.  
4 Here is a brief excerpt from the NAS report on removal  
5 of existing products. The framework outlined in this  
6 section was designed for new opioid products and  
7 formulations. It can be applied with equal force to  
8 opioids already on the market.

9 Plus, in recommendation 6-6 the committee  
10 recommends that the FDA conduct a full review of  
11 currently marketed approved opioids. Such a review  
12 could be carried out by an expert panel that will  
13 systematically examine the current range of approved  
14 brand name and generic opioids to determine which of  
15 these drugs remain effective and safe, which might need  
16 revised labels, formulations and post market  
17 requirements and which should be withdrawn from the  
18 market entirely.

19 I am pleased that the FDA is holding this  
20 meeting and asking good questions about approving new  
21 opioids. With more strict regulations on approval of  
22 new products, while helpful, would likely have only a



1 slight impact on the opioid crisis, whereas removal of  
2 the most dangerous opioids would have a significant  
3 impact for -- impact.

4           For example, if ultra-high dosage opioid  
5 analgesics were removed from the market, many lives  
6 could be saved. It's too late for my son who lost his  
7 life to an ultra-high dosage of methadone prescribed  
8 for pain, but it's too late to spare other families  
9 from experiencing the nightmare.

10           I'd like to show you my pictures of my son at  
11 different ages. I want you to see he is just a normal  
12 child like every other kid. Graduating from college.  
13 You can see he has broad shoulders. And you could see  
14 there with those forearms. My son addiction began  
15 after a football injury in college. He was sent to a  
16 local hospital where his first prescription was 100  
17 tablets of 10 milligram oxycodone, 3 to 4 day -- 3 to 4  
18 a day as needed. Now the race was in and out of rehab  
19 for the rest of his life. I filled that prescription.  
20 I had no idea what an opioid was at the time I filled  
21 it. Once after a 30-day rehab he left the facility and  
22 got into a bad car accident. Many broken bones

1 occurred. By the time I saw him in the hospital he was  
2 prescribed 80 milligrams a day of OxyContin, which is  
3 equal to 120 milligrams of morphine.

4           On top of this he was also prescribed a short-  
5 acting oxycodone to be taken as needed for so-called  
6 breakthrough pain. My son was prescribed extremely  
7 high doses of opioids by doctors who did not realize  
8 they were harming him. This is why high dosage opioids  
9 should come off the market, the existence of ultra-high  
10 dosage pills such as prescribers at the FDA considers  
11 the dose to be safe and effective.

12           Worst problem here is that tapering off high-  
13 dose opioids can be an excruciating experience. And  
14 there are few programs in place to wean patients off.  
15 He was on these doses for months with no plan in place  
16 to ever come off. The medical community does not want  
17 to hear about how addictive these drugs are. We all  
18 know that with these high dosages one dose they get cut  
19 off. Trying to find a place for weaning patients off  
20 is near impossible. This is one reason high doses are  
21 very dangerous. The medical establishment is not well-  
22 equipped for helping patients taper off them. A year

1 after my son died, it became a bereavement facilitator  
2 for parents who watch children with substance use  
3 disorder, starting with prescription opioids.

4           Unfortunately, I spoke to hundreds of these  
5 parents over the past 4 years. Two patterns were quite  
6 prevalent. First an accident, injury or dental work  
7 introduced opioids to the child. This drug even at low  
8 levels within the body of certain people takes control  
9 of their brain. Nothing matters anymore but feeding  
10 this evil drug to the brain. Patient doesn't abuse it;  
11 the drug abuses the patient.

12           Important thing also is opioids is just a mask  
13 for pain. There were no use in recovery of injuries or  
14 ailments. The patients who shut off abruptly to  
15 prevent being dope sick they go out and get heroine and  
16 die when they get too much, or a patch with fentanyl.  
17 Others buy counterfeit pills, and some of these are  
18 also laced with fentanyl, and death occurs. This is  
19 not the majority, and that is why I'm here.

20           Many of the parents I've been with, their  
21 adult child went to sleep after taking pills for a long  
22 time and didn't wake up. No needle, no drama, just

1 going to sleep, and their breathing stopped, and their  
2 heart also stopped. Then they were found cold in their  
3 bed. This is the silent killer.

4           Adults between ages 45 and 60 or older don't  
5 get cut off from the doctors as a rule. They keep  
6 getting opioid prescriptions from their doctors. The  
7 buildup in their system shuts down the brain and death  
8 occurs. The higher the dosage, the faster this will  
9 happen. The number of deaths recorded actually is way  
10 high. Many autopsies are not even performed.

11           As I've gone around the country, I found that  
12 many places where people dying in their sleep over 50,  
13 never anything. So, when you see these numbers like  
14 400,000 since 1999 or something, that's way low, it's  
15 way higher than that. So, my son and his girlfriend  
16 both died in their sleep with a buildup of ultra-high  
17 methadone pills in their body shutting down the brain.

18           Tens of thousands of Americans have died the  
19 same way. The number of opioid deaths is way higher  
20 than that as recorded in the government. I believe you  
21 cannot increase doses under any circumstance unless the  
22 patient is terminal. Long-term use will bring an

1 unhappy ending.

2           Our country is suffering from an opioid  
3 epidemic. The word epidemic in the dictionary means a  
4 fast-speeding disease. I believe the pharmaceutical  
5 industry has caused this epidemic, and the FDA could  
6 have stopped it. You had the information way back in  
7 1999 and knew how dangerous these pills were. A  
8 disease that comes in place in a plastic bottle from  
9 your local pharmacy.

10           Last year it was reported that there were 244  
11 million prescriptions in the U.S. for various forms of  
12 opioids. So, if you look at the graph of the CDC, it's  
13 quite obvious, the more prescriptions, the more  
14 overdose deaths. It's plain and simple. It's been  
15 going on for the last 15 years, and you don't have to  
16 be a rocket scientist to figure that out.

17           If the FDA wants to have an impact on this  
18 crisis, it needs to fix past mistakes and remove  
19 products from the market that should never have been  
20 approved.

21           My son who I love very much has been taken  
22 from me. Thousands of other parents in America are in

1 the same club without their child that they loved. My  
2 two great grandchildren, Adam and Madeline, will never  
3 know their grandparents. And even worse, their  
4 grandparents will never know them. I came here on my  
5 own expense. My goal was to explain the dangers of  
6 high dose opioids and to urge the FDA to seek removal  
7 of them. Let's stop this madness.

8           And here is where my son resides now. I get  
9 to go there 3 or 4 times a week, and that is where  
10 thousands of other young people have died. In this  
11 country right now, life expectancy has been cut by many  
12 years all because of the opioid epidemic. And the FDA  
13 can change that. You guys can fix it. You guys can  
14 change the way it is prescribed, and I don't disagree  
15 with the woman who spoke before me, yes, there are  
16 certain groups of people.

17           But we should not be giving opioids to 20-  
18 year-old for getting their wisdom teeth out or getting  
19 their broken toe and putting it in. It's like we might  
20 as well just be giving them a loaded gun. As you all  
21 know, it's the same as heroine. So, let's stop the  
22 madness.

1 DR. THROCKMORTON: Thank you...

2 MR. LaGRECA: -- good look at that picture.  
3 That's what all -- that's what over 400,000 sets of  
4 parents are looking at every year, every day. Any  
5 questions?

6 DR. THROCKMORTON: Questions for the parent?  
7 Thank you, sir, very much.

8 BENEFIT-RISK ASSESSMENT OF OPIOIDS:  
9 OXYMORPHONE AS A CASE STUDY

10 DR. THROCKMORTON: Next speaker is Dr. Janetta  
11 Iwanicki from Denver Health and Hospital Authority.

12 DR. IWANICKI: Good morning. Thank you for  
13 the opportunity to speak here today. My name is  
14 Janetta Iwanicki, and I'm a scientific director of the  
15 RADARS System at Denver Health and Hospital Authority  
16 in Denver, Colorado. I'm also a physician and practice  
17 emergency medicine and medical toxicology.

18 Just briefly a bit about the RADARS System.  
19 The RADARS System is the property of Denver Health and  
20 Hospital Authority, which is a political subdivision of  
21 the State of Colorado. RADARS System provides post-  
22 marketing surveillance and research regarding many

1 prescription opioids and other drugs, and many  
2 manufacturers are subscribers to our data.

3           Our role is to provide the information needed  
4 and often required of manufacturers to fulfill DFA  
5 requests. In order to do this, we rigorously manage  
6 our competing interests. Denver Health and Hospital  
7 Authority of the governmental subdivision of the State  
8 of Colorado is a good home for independent program  
9 precisely because of its government nature.

10           Our employees, including me, receive a salary  
11 and are not allowed to have consulting or other  
12 relationships with any subscriber or government agency.  
13 For example, if someone wants our data or my advice on  
14 a topic, they must contact Denver Health, and those  
15 funds do not come to me.

16           In general, our data is independent and  
17 provides a unique view of what happens with  
18 prescription drugs after they are on the market. And  
19 subscribers, when they receive our data, whether being  
20 government agencies or pharmaceutical companies, do not  
21 have access to the raw data itself, may only use this  
22 data for regulatory purposes.



1           So, a point of consideration in the draft  
2 opioid benefit-risk guidance that I'd like to address  
3 today. In the benefit-risk guidance there is a section  
4 on public health considerations for abuse-deterrent  
5 formulations. And the guidance notes that potential  
6 unintended consequences of drugs such as abuse-  
7 deterrent formulations may be consider.

8           And in particular, one thing that's noted here  
9 is that potential tampering methods that could result  
10 in harmful effects such as injection-related harms  
11 should be considered when the approval of the drug is  
12 under review.

13           Now this is important, because as we think  
14 about what the next steps may be in benefit-risk  
15 assessment for opioids, trying to understand where  
16 drugs such as abuse-deterrent formulations may play a  
17 role is really crucial. However, one of the biggest  
18 challenges is trying to understand what those actual  
19 risks may be and trying to predict them ahead of time  
20 is particularly challenging. And this is where,  
21 oftentimes, post-marketing surveillance can be  
22 absolutely essential to really understand what may be

1 happening with these drugs in the real world.

2           So just briefly, I'd like to talk a little bit  
3 about a case study that I think is particularly  
4 relevant at this point. So, one of the things that's  
5 mentioned in the guidance is the concept of a small  
6 versus a large volume extraction of the drug. I like  
7 to talk a little bit about what that means before we  
8 get into our case study.

9           Small-volume extraction is when a pill  
10 intended for oral use is dissolved in something small,  
11 less than 10 milliliters, to be injected by someone.  
12 Oftentimes water, saline or alcohol are used for this  
13 process. And extraction, generally speaking, is  
14 followed by testing with different sizes of the needle  
15 to assess syringeability in the setting of Phase 1  
16 studies prior to an DFA meeting.

17           Large-volume extraction is typically 30 to 100  
18 milliliters. And this, if you can think about that  
19 volume, this is the size of a small medicine cup or  
20 larger. It's really not feasible for an injection.  
21 Generally speaking, injection users are using small  
22 insulin syringes or perhaps something slightly larger

1 than that. Injecting 30 to 100 milliliters would be a  
2 huge volume.

3 This can be done with either simple or  
4 advanced solvents. And particularly this is relevant  
5 for the concepts of dose pumping in oral  
6 administration. So, by dissolving a pill into a volume  
7 and drinking it one can sometimes overcome abuse-  
8 deterrent features. However again, it's difficult to  
9 inject.

10 So, case study I'll be talking about today is  
11 that of Opana ER. Opana ER is an extended release  
12 oxymorphone that was reformulated to deter intranasal  
13 administration. It was approved in 2011 without an  
14 abuse-deterrent label claim. And the biggest issue  
15 that was observed after it -- this new formulation was  
16 on the market were unintended consequences associated  
17 with intravenous administration.

18 In particular thrombotic thrombocytopenic  
19 purpura-like illness was noted and needle-sharing  
20 behaviors along with HIV and Hepatitis C transmission  
21 was very high. A few things about Opana ER that were a  
22 little bit unique, and we'll talk a little bit more

1 about momentarily. But I think reasonably the data  
2 after this drug was on the market led to its removal at  
3 the request of the FDA in 2017.

4           So, looking a bit of RADARS data associated  
5 with Opana ER, this was presented to the FDA. What we  
6 see is that before the reformulation from 2010 through  
7 the end of 2011 a relatively large quantity, 34 percent  
8 of cases, involved inhalation or intranasal use of this  
9 drug. However, after reformulation we did see a  
10 decrease in intranasal use, down to 21 percent.

11           Unfortunately, this was accompanied by an  
12 increase in injection, up to 29 percent. This shift  
13 was not -- has not been seen with other abuse-deterrent  
14 formulations such as OxyContin. And this really  
15 highlights how crucial post-marketing data can be in  
16 trying to understand where that risk-benefit ratio may  
17 lie for a killer drug.

18           So, what you see here is data from poison  
19 centers from across the United States related to  
20 injection and inhalation and nasal use of these drugs.  
21 First on the left, what you see is that there is quite  
22 a high rate in the period before reformulation of

1 intranasal use. That orange line on the left you can  
2 see was rising quickly. After reformulation, the blue  
3 line on the right shows a decrease in that intranasal  
4 use.

5           However, when we look at injection associated  
6 with this what we see is that there is actually quite a  
7 bit of a different pattern. Injection use was also on  
8 the rise, as you see on the left of that orange line.  
9 After reformulation the blue line shows that there was  
10 a slight decrease after use. And on this left panel  
11 here what you're seeing is these are rates per  
12 population so looking at the overall public health  
13 impact.

14           So, in general, we saw that injection rates  
15 were rising per population, but they flattened out  
16 after the reformulation. More crucial though, on the  
17 right-hand side what we see is that when we look at  
18 this by the amount of the drug available, amount of  
19 prescriptions out there, there was very little impact  
20 that was happening by that reformulation. So, what  
21 this suggests is that reformulation may have decreased  
22 the total number of people who were exposed to this

1 drug, but those who were exposed, the amount of  
2 injection that we saw, was staying about the same.

3 Not only that, but we also see that now there  
4 are these high-risk behaviors associated with it  
5 despite the fact there is no decrease in that behavior.  
6 So, an in-depth study of Opana ER injecting behaviors  
7 was performed in Starke County, Indiana. There were 25  
8 intravenous Opana ER users. And there is -- the study  
9 characterized how they used this drug. We looked at  
10 extraction volume, how they prepared it, and the  
11 rationale for why they were sharing intravenous  
12 solutions.

13 So, few things about how this drug was shared  
14 that I think are also important to know. The drug was  
15 pretreated. This means that it was browned and heated  
16 in an oven for several minutes. Then typically a 40-  
17 milligram tablet was split into 4 pieces. Each of  
18 those 4 pieces was then mixed with a small amount of  
19 water, and what that meant was each of those injections  
20 then were split again into, about a quarter tablet led  
21 to about 4 injections per 1-ml insulin syringe.

22 So, what this means is that Opana ER was

1 extracted in a small volume and split into multiple  
2 injections each of less than one millimeter. So again,  
3 we're talking about very small quantities, much less  
4 than what you would have imagine with a 100 ml large  
5 volume extraction.

6           So why did people share these IV solutions of  
7 Opana ER, the volumes were so small. Well, really one  
8 of the things that's really crucial here to understand  
9 is that oxymorphone is very unique drug. It's 10 times  
10 more potent intravenous taken orally. And so, what  
11 that means is that a 40-milligram tablet has a huge  
12 volume of potential morphine equivalent when given  
13 intravenously, and this leads to solution sharing and  
14 unsafe injection practices.

15           And the gelling product that was used to make  
16 this abuse-deterrent formulation was not sufficient to  
17 deter injection of a desirable intravenous dose, which  
18 again, lead to unintended consequences associated with  
19 these behaviors.

20           So just to make this a little bit easier to  
21 understand, looking at an Opana ER 40-milligram tablet,  
22 up to 16 people could have an injection off of a single

1 tablet, which is massive. And again, it all comes back  
2 to the fact that it's a uniquely potent opioid  
3 intravenously, different from other drugs. For  
4 example, oxycodone, even if extracted under ideal  
5 conditions really only provides enough morphine  
6 equivalent for a single person to inject. And this  
7 matters when we think about how we do risk-benefit  
8 assessments.

9           So, in conclusion, some learning here. Opana  
10 ER was extracted in small volumes, not large, and dose  
11 driven was shared -- dose sharing was driven by IV  
12 potency and not volume. Intravenous deterrent should  
13 be assessed by the ability or difficulty to get an  
14 ideal dose intravenously. And the present extraction  
15 is not really a clinically meaningful measurement. It  
16 really matters how many morphine equivalence you can  
17 receive.

18           Finally, guidance should reflect IV potency as  
19 a key factor for influencing IV dose sharing. Post-  
20 marketing surveillance is crucial to detecting  
21 concerning behaviors, and early planning for  
22 surveillance allows detection early and intervention



1 when unintended consequences occur, because human  
2 behavior is unpredictable. Thank you. And I'm happy  
3 to answer questions from the panel.

4 DR. THROCKMORTON: Thank you very much. Let  
5 me just ask a question. So, the guidance does speak to  
6 -- asks sponsors to evaluate whether increased or  
7 decreased risks of a particular product based on its  
8 specific characteristics. You know, I think delivery  
9 device and type, that sort of figures, but you're  
10 suggesting we add something related to pharmacology if  
11 I'm understanding?

12 DR. IWANICKI: Yeah. I think considering  
13 bioavailability is really crucial, and it's not  
14 something I've seen addressed so far in the guidance to  
15 this day.

16 DR. THROCKMORTON: Sorry; yes, go ahead.

17 DR. STEIN: This is a related question.  
18 Certainly, I've some of these behaviors being regional.  
19 Do you have any suggestions? Obviously, yours is a  
20 network, so I presume looking at a region and  
21 characterizing this behavior in that region. Do you  
22 have any suggestions for how the challenge of finding

1 regional patterns might be addressed? You've given  
2 something like the RADARS System, which is looking at  
3 one region where you may or may not see this kind of  
4 behavior.

5 DR. IWANICKI: Yeah. So, RADARS System is  
6 somewhat unique, because we do have a broad geographic  
7 coverage across the country, but I think your point is  
8 an important one. I think finding ways to perform  
9 signal detection to identify geographic regions when  
10 there are issues really is crucial, and the best way to  
11 do that, no one network, as far as this research, is  
12 perfect. And so, finding ways to combine data from  
13 multiple different networks and utilizing that via  
14 modeling to look for signal detection I think is the  
15 next step in the future.

16 DR. THROCKMORTON: Other questions? Thank you  
17 very much. Meredith, we are at break now. What time  
18 should we have people come back?

19 UNIDENTIFIED SPEAKER: 10 -- 20 minutes..

20 DR. THROCKMORTON: So back at 10:30 please.  
21 Thank you very much.

22 BREAK

1 (Recess)

2 ROLE OF POSTMARKETING SURVEILLANCE

3 IN OPIOID APPROVALS

4 DR. THROCKMORTON: All right. Why don't we go  
5 ahead and get started again? The first speaker is Dr.  
6 Dart from RADARS for Denver Health and Hospital  
7 Authority.

8 DR. DART: Good morning everyone. My name is  
9 Rick Dart and I'm the -- thank you.

10 I'm the Director of Rocky Mountain Poison and  
11 Drug Center and a professor at the University of  
12 Colorado. And my research for the past 15 years has  
13 been on abuse of prescription drugs specifically. I  
14 want to join the others in thanking the Agency for  
15 doing this because I think opening up the topic of what  
16 standards we should apply is extremely useful, and I'm  
17 looking forward to getting that task I've started.

18 I'm also Executive Director of the RADARS  
19 System, and the RADARS System provides post-marketing  
20 surveillance data for the pharmaceutical industry, but  
21 also for government and researchers. And much of this  
22 was already covered by Dr. Iwanicki in her

1 presentation. So that saves me a good 45 seconds of my  
2 presentation.

3           So, what does a pharmaceutical product need  
4 for approval? To be approved, it has to show that it  
5 can be manufactured appropriately, and that's actually  
6 a major advance and why the FDA was initially started.  
7 It has to show that it's effective and safe when used  
8 as directed. In the past, that safety component has  
9 generally been fulfilled by the sponsor establishing a  
10 call center that accepted spontaneous adverse event  
11 reports, which was a good thing, but it's not the most  
12 rigorous approach. It works because most drugs don't  
13 really develop major new problems after their  
14 introduction.

15           The problem, as we've discovered in the United  
16 States, is that prescription opioids are different.  
17 Not all issues can be identified before marketing and  
18 not all-important adverse events are actually new  
19 adverse events or unexpected adverse events. The  
20 current system isn't really focused on trying to detect  
21 changes in expected adverse events, it's focused on  
22 unexpected events. And for example, for the opioids,

1 respiratory depression and death have always been  
2 expected adverse events for any opioid drug.

3           So, the problem we have today is not from  
4 unexpected events, but from unexpected uses of the drug  
5 producing the same adverse events. To their credit,  
6 FDA has addressed these issues. For example, this  
7 table makes it clear that they plan to consider risks  
8 related to both the broader public health and to  
9 consider these risks relative to other currently  
10 available analgesic drugs.

11           It may not seem like a big change, but it's  
12 important, and I fully support these changes. But  
13 there are a couple implications that we should  
14 consider. For example, this means there are at least 3  
15 different risk issues now involved in the draft  
16 guidance. Individual risk appears to be the same  
17 concern we have for any drug. What are the risks for  
18 that individual usually using the medication as  
19 prescribed, although for opioids there is also  
20 dependence and addiction?

21           The population risk or broader public health  
22 is new, and I think really important to add what is the

1 effect that a drug may have on the broader public  
2 health. As we discovered, this is a critical issue for  
3 opioids and likely for other drugs as well. The  
4 addition of comparative risk or risk relative to other  
5 analgesic drugs is extremely important, but also the  
6 most difficult to study.

7           For example, generic drugs are commonly  
8 abused. How do we compare a new opioid to a generic?  
9 So, I made this table for us. What if we wanted to  
10 compare across the oxycodone products for example?  
11 Well, right away we're in trouble, because only the  
12 branded extended release products have required post-  
13 marketing surveillance.

14           On the left, I provided 5 specific outcomes  
15 identified by FDA, although there are many others of  
16 course, and then described the requirements. And you  
17 can see that because they're essentially all generic,  
18 single entity oxycodone products do not have any or  
19 minimum. There're multiple reasons for this situation,  
20 but whatever the reason, we can't effectively compare  
21 it across these products currently.

22           This is a big problem because most of the

1 opioids available, diverted or abused, are immediate-  
2 release preparations. The press would have us believe  
3 that they're extended release, but the truth is they're  
4 immediate. The figure on the left shows the total  
5 grams dispensed for immediate release and extended  
6 release analgesics in United States. As you can see,  
7 90 percent of the market is immediate release. And  
8 this is reflected in actual levels of abuse. The right  
9 panel shows that abuse cases as recorded at Poison  
10 Centers are also predominantly immediate release.

11 But this raises the question, how do we gather  
12 safety information on generic drugs? I believe the law  
13 establishing generic drugs allows them to use safety  
14 data from the branded drug. For example, generic  
15 hydrocodone acetaminophen products would rely on the  
16 brand name Vicodin for safety data.

17 However, there's essentially no real Vicodin  
18 sold anymore; it's all genericized. So, in the end,  
19 these companies really don't have a responsibility to a  
20 requirement, I should say, to monitor the safety of the  
21 drugs. So, my first recommendation is that we need the  
22 same post-marketing surveillance required for every

1 opioid product.

2           And this echoes what previous speakers have  
3 said. This means both extended release and immediate  
4 release. It means both abuse-deterrent and non-abuse-  
5 deterrent. And it means both branded and generic  
6 products. This needs to be required, because the data  
7 will not be collected unless it is required. In our  
8 society pharma's mandate is to maximize shareholder  
9 value and not to do safety monitoring that is not  
10 required.

11           Now some of you may wonder what about the  
12 required FDA opioid REMS? This is a good concept, but  
13 it primarily addresses educational objectives, assuring  
14 that the prescriber and the patient understand the  
15 drug. That's great, but it does very little about  
16 requiring monitoring for population safety risk or the  
17 risk compared to other drugs. But more is needed than  
18 simply post-marketing surveillance; standardization is  
19 needed. Currently, post-marketing requirements are  
20 negotiated individually between FDA and a sponsor at  
21 the time the drug is approved. This essentially  
22 requires FDA to anticipate what will be different about



1 these drugs, and this is just impossible for anyone to  
2 do.

3           Furthermore, the draft guidance asks for  
4 comparative data, and this is impossible as well when  
5 each negotiation results in a different collection of  
6 surveillance tools and a different -- very different  
7 set of data and analytics procedures on that data. To  
8 illustrate this point, this slide addressed the lack of  
9 a common data set just for oxycodone.

10           Let's say the generic producers of single  
11 entity oxycodone, for example, Roxicodone 30-milligrams  
12 is a very popular drug abuse. Let's say they were  
13 required to perform rigorous surveillance. If  
14 standards are not developed, then a manufacture of  
15 single entity oxycodone might decide to use treatment  
16 centers for their surveillance program even if they  
17 were required to have surveillance, while the extended  
18 release sponsor might decide to say use diversion  
19 programs. How would one interpret these results if  
20 they differ? And they will differ. It's impossible as  
21 you can see. And don't forget, there are literally  
22 dozens of products depending on the category, so the

1 permutations really are endless.

2           So, my second recommendation is that the same  
3 elements of surveillance should be available for each  
4 product to improve the quality of comparisons. A  
5 common data model would simplify and speed up analysis  
6 of data in the future, especially the speed up part,  
7 and not mention -- not to mention that it would  
8 decrease the expense per sponsor. In addition, common  
9 analytical approaches should be provided preferably  
10 with the input from multiple and knowledgeable parties,  
11 and there are many at the stage in the U.S. because of  
12 the epidemic.

13           My final point is that we must include drugs  
14 other than just the opioids. I realize that FDA is  
15 already addressing this concern, but I want to  
16 emphasize the point that all drugs with CNS affects are  
17 abused. Even Diphenhydramine is commonly abused.  
18 These data are from the RADARS' analysis of the  
19 National Poison Data System from the American  
20 Association of Poison Control Centers of 2006 to 2014.  
21 Opioids are the highest. I took them off, because of  
22 space; they would be the highest on here, but you can

1 see that after that come the Benzodiazepines, very  
2 high, but even Dextromethorphan is very commonly abused  
3 in the United States.

4           And worse, the abuse of essentially all these  
5 categories is rising. So, we're currently in the  
6 process of exchanging an epidemic of prescription  
7 opioid abuse for an epidemic of abuse of other  
8 prescription drugs as people switch away from opioids,  
9 to heroin, of course, which is a huge problem, but also  
10 to multiple other drugs that are available.

11           So, my third recommendation is that the same  
12 method should be required for all drugs with CNS  
13 effects. This is a large task, I realize, but is real  
14 and emerging and needs to be addressed proactively now.  
15 I would add that we at least need to include those  
16 illicit drugs as well, illegal drugs that are similar  
17 to commercial products, for example, and may lead to  
18 abuse such as the amphetamines.

19           So, in summary, we need rigorous and  
20 meaningful post-marketing surveillance that is required  
21 of each opioid product. This postmarketing  
22 surveillance should be standardized to allow for

1 meaningful comparisons, and these principles should be  
2 applied to all medications with potentially desirable  
3 CNS effects. Thank you.

4 DR. THROCKMORTON: Thank you, Dr. Dart.

5 Questions? Gerald?

6 DR. DAL PAN: Could you talk a little more  
7 about what this common data model that you propose  
8 would be, what its scope would be, how it will be used?

9 DR. DART: That's a big task. The idea would  
10 be -- my concept is that there would be a fixed and  
11 variable portion to this. In other words, there would  
12 be certain data elements that are required of every  
13 sponsor, but obviously not every drug is identical.  
14 You might for some drugs, for example, using the Opana  
15 ER example for some drugs that you're worried you might  
16 have a variable portion that you add to that sponsor.  
17 So, all sponsors would do a common data set that would  
18 allow us to do basic surveillance of that drug. And  
19 then if there are special concerns, that could be  
20 tailored to each sponsor's individual product.

21 DR. DAL PAN: So, if I understand, the  
22 sponsors then would collect data from various sources

1 put it into a structured format that would be common  
2 across them and then those data could be pooled or  
3 analyzed?

4 DR. DART: That's right. That's right.

5 DR. DAL PAN: Could you also talk about  
6 something we've noticed here, and that's the challenge  
7 of identifying what product the patient actually really  
8 takes?

9 DR. DART: Yes.

10 DR. DAL PAN: And certainly, ingredients might  
11 be known, the active substance, then getting down to  
12 what product is, we've seen a lot of imprecision in  
13 that area.

14 DR. DART: There is imprecision in that area,  
15 and it varies by the data collection method that's used  
16 for sure. Some are more reliable than others, but I  
17 guess my point is that I think if we put our minds to  
18 it we could figure out how to do this. I can think of  
19 ways to be able to ascertain products or cross-  
20 reference products so that we could get more accurate  
21 identification. So, for example, in a drug diversion  
22 program, for example, you often have the product and

1 you can know what the product is because you can  
2 actually identify it.

3           It is true that in a system such as poison  
4 centers, you're using the subject's belief in what they  
5 took. There is some value in that, I think, because  
6 then you know what they think they took, but in those  
7 you would have to have either some sampling method or  
8 something that -- and I guess my point is really to  
9 start working on those rather than just say, we can't  
10 really do that. I think we can if we put our minds to  
11 it.

12           DR. DAL PAN: Thank you.

13           MS. SIPES: Thanks for your presentation. I'm  
14 Grail Sipes. I'm the Deputy Director of CDER for  
15 Regulatory Policy. I was wondering if you could talk a  
16 little bit more about some of the authorities that  
17 might be necessary for this activity, particularly the  
18 standardization and the surveillance area.

19           DR. DART: Well, I am not lawyer by any  
20 stretch. I'm trying to identify a need, I think, more  
21 than to say how to solve it. I don't -- every time I  
22 think I understand the -- what the FDA is empowered to

1 do then I find that I'm wrong. So, I hesitate to get  
2 in there. It's just that I think what's very clear to  
3 me that is -- and I -- this is -- I'm not trying to be  
4 critical of industry, but they're not going to do  
5 something they don't have to do, and that's just the  
6 way it is. Every company in the United States is like  
7 that, and the world is like that, right?

8           And that's the system we have set up. So, I'm  
9 happy living within that. That means in a situation  
10 like this, because I think the opioids or CNS active  
11 drugs are different, we need to actually be more  
12 stringent and require it rather than suggesting.

13           DR. THROCKMORTON: Dr. Stein?

14           DR. STEIN: Can you say a little bit more  
15 about what kind infrastructure would be needed to  
16 operationalize something like this? Obviously, we're  
17 going from fairly limited, somewhat more patchy (ph),  
18 surveillance to what you're really referring to, very  
19 systematic national surveillance and markedly expanding  
20 numbers of the agents that we need, that we believe are  
21 under surveillance of accumulated (ph) and apply in a  
22 large number of non-opioids. How you just -- in

1 general terms, what are you thinking in terms of the  
2 kind of infrastructure necessary to operationalize that  
3 kind of larger surveillance approach?

4 DR. DART: Well, the general concept that was  
5 alluded to earlier is that you can't -- you really  
6 can't get all the information you want from one system  
7 at all because there's many different facets to  
8 substance abuse, and the people are always trying to  
9 hide those activities. And so, you have to identify  
10 specific objectives. That's probably the key thing  
11 here, and then see which data sources answer that  
12 question and then require those data sources of all of  
13 the sponsors.

14 So, there would be a process there where you  
15 do that identification of what you actually are trying  
16 to measure then agree on how you're going to measure,  
17 and then companies would know how to provide that data,  
18 and there's several. I think one of the issues here  
19 is, so far, it's been so fragmented that there really  
20 isn't any -- you know, we're a government agency, there  
21 isn't really -- there hasn't been a big interest from  
22 the data analytic companies because there -- it's



1 different for every product. There is no standard  
2 product they can roll out. So, I maybe cutting my own  
3 throat here, but the reality is you need to have that.  
4 And I think if we ever want to know what happens when  
5 you pull -- when you take Opana ER off the market, what  
6 happens to all the drugs around it, including the non-  
7 opioids. We're just not going to know that in the  
8 current system. We can get some hints, but we're  
9 really not going to know the answer to that. Sorry; I  
10 can't be more specific..

11 DR. STEIN: Okay.

12 DR. THROCKMORTON: Just ask a couple more  
13 questions, so it does seem quite expansive, I agree,  
14 especially when you threw in the illicit drugs. You  
15 also wanted to have this system. Do you envision a  
16 group that would be leading this? Are you thinking  
17 this is something that the FDA would lead? Or is it a  
18 -- especially with the illicit, I am wondering if there  
19 is another mark.

20 DR. DART: That's a great question. And I  
21 have to admit I haven't thought about it. So, I guess  
22 the new system ER is sort of a benchmark to compare to

1 more than I'm actually going to get the detailed data  
2 on them for, if no other reason, that they are so  
3 variable and so non-standardized. I mean one of the  
4 beautiful things about FDA is that you have standard  
5 products that are produced, and you know how much drug  
6 is on that type of thing when they are produced  
7 appropriately. For the illicit, you never have  
8 information. And so, I think that would be much less  
9 specific, and to be honest, easier to implement in many  
10 ways. Kind of goes -- I would be happy to talk more  
11 about it because I think it's a more extended  
12 conversation.

13           But the -- for me is that the regulated drugs  
14 are going to be -- are going to remain a big problem.  
15 They're not going to go away just because of illicit  
16 products. You seem to be adding to the problem rather  
17 than -- it's not a zero-sum game. What I am seeing is  
18 expansion essentially of both markets if you want to  
19 view it as a market phenomenon.

20           In other words, prescription opioids are going  
21 down. The other CNS active prescription drugs and OTC  
22 drugs are actually expanding substantially, and heroine

1 is expanding. So I am kind of getting off the topic  
2 here but I see that if -- that we're going to need to -  
3 - we need to get our hands around the whole -- the  
4 whole picture or else we're going to constantly be  
5 playing whack-a-mole, and we wouldn't know where we  
6 stand, and no agency will be able to say to Congress,  
7 hey, we've made progress here. Right now, I don't know  
8 if we made progress or not.

9 DR. THROCKMORTON: Thank you very much.

10 OPIOID AND ALTERNATIVE PAIN MANAGEMENT

11 EFFECTIVENESS AND OBSTACLES

12 DR. THROCKMORTON: Next speaker is Ms. Tasha  
13 Olson from the Pain Community.

14 MS. OLSON: Hi everyone. I am Tasha Olson. I  
15 am a chronic pain sufferer. Okay, so I come here not  
16 representing any organization or cause, other than I  
17 represent my own experience and my friends in the pain  
18 community that suffer from chronic pain, and some of  
19 the obstacles that we still have been running across  
20 that we would have hoped had been fixed or we thought  
21 had been fixed. So, I'm go bring up a couple of those.

22 And FYI, I am going to ready my presentation

1 because I recently had a stroke. So unfortunately, my  
2 aphasia isn't doing so well. But let's go on here.  
3 Who am I? Right. So, I do still work full time, so I  
4 am considered high-functioning as a chronic pain  
5 sufferer, but I've worked extremely hard to stay  
6 working, suffering from chronic pain. I am very  
7 involved one-on-one with other chronic pain communities  
8 and other individuals that suffer from chronic pain. I  
9 am also a recovering addict and a recovering alcoholic,  
10 and that started in 2001, was my recovery birthday,  
11 which was before I was injured.

12           So, a little bit about my journey. You do --  
13 I want you to understand what I have tried, what we do  
14 in the pain community, everything that I have to bring  
15 into a discussion like this and some of the hiccups  
16 that I have seen. Like I said, I've been a recovering  
17 alcoholic addict since 2001. But I was injured in  
18 2010. I had multiple skeletal, from an accident,  
19 skeletal damage as well as soft tissue and nerve  
20 damage, peripheral and motor neuropathy, and I also  
21 have several severed nerves.

22           So currently, the conventional therapies I

1 have gone through is obviously multiple surgeries. I  
2 do frequently have injections, radio frequency, cold  
3 laser therapy, ultrasound therapy on soft tissue  
4 damage, traction. I do now have a spinal cord  
5 stimulator which was put in in 2012. I undergo  
6 physical therapy still and also some occupational  
7 therapy. Pain psychology has been a very large part of  
8 me still being part of my own working community. And  
9 of course, medications. As far as unconventional in  
10 some -- in some scopes, that is unconventional  
11 treatment, I of course have undergone limited  
12 chiropractic acupuncture massage.

13 I do still use binaural beats, which is  
14 something that helps distract from pain. Obviously, it  
15 worked with nutritionists and anti-inflammatory diets.  
16 I have tried essential oils and also meditation and CBD  
17 oil. I do want to clarify quickly what I talk about as  
18 far as being a chronic pain sufferer.

19 I think it's critical that this -- to this  
20 discussion that you understand what I am saying when I  
21 say chronic pain. I define chronic pain as long-term  
22 permanent pain, not acute pain. Most of us are -- do

1 deal with extended release opioids. So, I am not  
2 speaking to acute or surgical pain or treatable injury  
3 pain. Do know that this definition many times is  
4 beyond 12 weeks is chronic pain, and to us in the pain  
5 community we do drive that into more sections. There  
6 are some of us who have what we call forever pain until  
7 someone else comes up with it. But then there is the  
8 pain past 12 weeks where you shattered your leg on a  
9 ski slope, no offence to any skiers, but that is a pain  
10 that eventually may go away and is not necessarily  
11 treated long term as we are.

12           So, we know that we're not, as far as the  
13 chronic pain that I have, we are not necessarily a huge  
14 community. But one thing we do know is that I have  
15 friends that have pretty much given up with some of  
16 their restrictions on being able to get opioids that  
17 they need. Most of those are extended release, not  
18 immediate release, for acute pain.

19           So, pain patients, they do need the  
20 medications that are prescribed by qualified pain  
21 doctors. But there is also a need for more  
22 alternatives for pain, and we very much encourage

1 developing the drugs that we currently have on the  
2 market to understand more about how we can use them,  
3 how we can get them into a severe pain community, and  
4 the effect that they have on some of the other  
5 medications that were brought up earlier. Some of them  
6 aren't considered opioids but may still be dangerous  
7 that have -- very much have a -- may have a  
8 relationship that becomes very useful.

9           We would like to think that pain can be  
10 effectively treated without these acute. If we can do  
11 that, then it's a win-win for everybody that the U.S.  
12 would be happy. Pain doctors would feel as though they  
13 can -- they can treat their own patients, and that  
14 chronic pain community would feel like they were taken  
15 care of.

16           If pain can be effectively treated, I think  
17 there is also the question -- if addiction or recovery  
18 can also be relieved by some of these pain mechanisms  
19 and that the risk-benefit analysis really needs to  
20 reflect these kinds of goals. So, pain physicians,  
21 here is a few obstacles we've run into. We have  
22 several pain doctors that really feel as though they

1 are being restricted at this point to what they feel  
2 they need to give, and that includes the extended  
3 release opioids that are so important to the really  
4 chronically pain sufferers.

5           So, we do think that they need a little more  
6 authority back, because I do think that as far as pain  
7 specialists and pain physicians that are qualified for  
8 those kind[s] of pain that they are the ones who do  
9 know best. And I do like to see collaboration that  
10 comes between regular physicians, but also some of the  
11 more unconventional things.

12           Here is an example. When I have to get my  
13 upper back fixed what I do is the day before I go and  
14 get injections. I have a chiropractor that works on  
15 getting my ribs back in place. I go in. I have the  
16 neck injections and upper back, and 6 hours after that,  
17 I see an acupuncturist who is able to release these  
18 muscles right here. And it makes the treatment far  
19 more effective. And that's because of collaboration.

20           I know nobody wants me to go on about  
21 insurance and pharmaceuticals probably. However, I  
22 have couple of things to say, most of it is I am going



1 to give you an example of what I have recently gone  
2 through. Recently my pain team made the decision to  
3 transition me from some of my previous medications to a  
4 Butrans Patch. I don't work for that company, I am  
5 just saying the name of the patch, right, an extended  
6 release. So, my pharmacy said, oh, sure you can have  
7 that for \$475 a month, so that's great. Unfortunately,  
8 of all the people who may get the most benefit from a  
9 nonacute pain patch, how many of them are going to have  
10 that kind of money? Four-hundred fifty dollars a  
11 month, that's tough.

12           So, I called my insurance company to ask them,  
13 can you please cover this? And they said to me, I  
14 wrote it down so I wouldn't forget, we can't cover it  
15 or make an exception, but for around \$12 a month we can  
16 get you oxycodone. Could you ask your doctor if that  
17 will work instead? That's tough. And we hear that all  
18 the time, and that's tough.

19           Because I know it's tough on our physicians  
20 too when they know that all we can afford possibly is,  
21 you know, is something like that as supposed to \$450  
22 that will keep us a little more cognitive. I do pay

1 out of my pocket for that pain patch, unfortunately.  
2 We would also like to see multiple dosing alternatives  
3 in some of the patches that are currently out there in  
4 some of the opioids.

5           The research on that could be very helpful for  
6 us. We do not necessarily need the total dose that is  
7 available. So that would be nice, to see an incentive  
8 for that. As I said, we -- any testing that's done,  
9 long-term transdermal medication is great for us. I  
10 don't want to pop pills. I would much rather slap on a  
11 patch every week; you know, most of us would. And that  
12 also makes it a little bit harder for an addict or  
13 someone who isn't in our community to get a hold of  
14 those medications and abuse them if they're in a format  
15 that is much harder to abuse.

16           So, we'd also like to obviously see knowledge  
17 of alternative pain relief that gets out there for us.  
18 I think that beyond that we would also like the  
19 accessibility of it. And unfortunately, with our group  
20 of people, where people are going to have to ask us,  
21 and we would like to be a resource in order to make  
22 that happen. And I know I am out of time. Any

1 questions at all?

2 DR. THROCKMORTON: You had a couple of last  
3 thoughts. Any last-minute things that you wanted to  
4 say?

5 MS. OLSON: Oh, stroke brain, it's not good.  
6 These are just some of the incentives I already  
7 mentioned that you see on there. We have incentives.  
8 We would like to see more cross-treatment. We think  
9 it's effective to working away from opioids as far as -  
10 - as I talked about, mixing up different kinds of  
11 therapy that could be done.

12 We would love incentives for insurance  
13 companies to be able to prove out some of these  
14 alternative treatments and to be able to support us  
15 getting them. Obviously, we'd like to see the approval  
16 and promotion of these by insurers, research on safer  
17 transdermals would be great. We like to see the  
18 combination and the advantage of using some of our  
19 other medications with that, and of course more dosing  
20 options. How was that?

21 DR. THROCKMORTON: Thank you, Ms. Olson.  
22 Questions from the panel? Thank you very much.

1 MS. OLSON: Thanks.

2 STANDARDS FOR FUTURE OPIOID ANALGESIC APPROVALS AND  
3 INCENTIVES FOR NEW THERAPEUTICS TO TREAT  
4 PAIN AND ADDICTION

5 DR. THROCKMORTON: Our next speaker is Dr.  
6 Andrew Kolodny from Brandeis University.

7 DR. KOLODNY: Hi. My name is Dr. Andrew  
8 Kolodny. I am an addiction psychiatrist. I am Co-  
9 Director of the Opioid Policy Research Collaborative at  
10 Brandeis University, and I am also the Director of  
11 Physicians for Responsible Opioids Prescribing, which  
12 is called PROP.

13 My comments today are on behalf of PROP and  
14 its members. PROP members are from diverse  
15 specialties, including pain, addiction, primary care,  
16 internal medicine, emergency medicine and public  
17 health. I have no industry relationships to disclose,  
18 but will disclose that I have received income, helping  
19 states and municipalities sue opioid manufacturers for  
20 their role in the opioid crisis.

21 I am going to cover three related topics.  
22 First, I am going to just explain briefly why at a time

1 when deaths involving illicit Fentanyl was soaring why  
2 it is still important to focus on prescription opioids.  
3 In other words, why this meeting today is important. I  
4 am going to next talk about something you've heard  
5 already this morning, the need for FDA to apply a new  
6 risk-benefit framework for existing products. And  
7 lastly, I am going to talk about the benefit side of  
8 the risk-benefit equation or really the lack of  
9 evidence supporting benefit.

10 This is a slide that probably looks familiar  
11 for several years. It was the CDC's Chief speaking  
12 point about the opioid crisis. The green line  
13 represents opioid prescribing. The red line represents  
14 death. The blue line represents addiction. And the  
15 CDC's point was that the soaring increase in opioid  
16 prescribing was resulting in parallel increases in  
17 addiction and overdose deaths.

18 We know that things have changed since 2010.  
19 This is current opioid overdose death data, national  
20 data. The brown line here is fentanyl deaths, and the  
21 orange is prescription opioids. Blue is heroine, and  
22 we see that fentanyl deaths have surpassed prescription

1 opioid and heroine. There is a popular narrative to  
2 explain what's happening today that's sometimes  
3 referred to as the three waves. What you are hearing  
4 is that there was a crackdown on the pills which  
5 resulted in drug users switching from prescription  
6 opioids to heroine, and then they switched from heroine  
7 to fentanyl, and the opioid crisis has consistently got  
8 worse. And there are problems with that narrative.  
9 It's inaccurate, and it masks important differences.  
10 For example, it masks the fact that fentanyl does not  
11 hit the whole country. Illicit fentanyl deaths have  
12 really been affecting mostly the eastern half of United  
13 States.

14           The three-wave narrative also masks important  
15 racial differences. In fact, the geographic area where  
16 we have seen the largest increase of deaths involving  
17 illicit fentanyl is Washington, D.C. which has a large  
18 population of survivors with the heroine epidemic in  
19 the 1970s who have managed to beat the odds for many  
20 years but now are dying because of the dangerousness of  
21 the heroine supply.

22           To really understand the opioid crisis, you

1 have to understand the epidemiology of the opioid  
2 crisis. We have different cohorts of opioids-addicted  
3 Americans. We have a young white group that has been  
4 switching to heroine after getting addicted to  
5 prescription opioids. Their addiction began after  
6 1995. A middle-aged and older white group that hasn't  
7 really been switching to heroine. And this older non-  
8 white group which are really survivors of a much  
9 earlier heroin epidemic in the 1970s. The fentanyl is  
10 really hitting this first group and the third group  
11 very hard.

12           Before fentanyl emerged and something that we  
13 were seeing with that up until really -- up until 2012  
14 when the heroine supply became very dangerous. The  
15 group where we saw the highest rate of overdose deaths  
16 were really middle-age, white people, and it was deaths  
17 involving prescription opioids. When the heroine  
18 supply became very dangerous, mainly because of  
19 fentanyl, that's when things really became to change.

20           In states though that haven't been plagued  
21 with heroine and fentanyl, the deaths have really  
22 closely tracked changes in prescribing. As prescribing

1 began to trend more cautiously we saw deaths come down.  
2 Sort of a last point about this narrative, the three-  
3 wave narrative of a crackdown causing drug users to  
4 switch. Lastly, another reason why this narrative is  
5 incorrect is that there really hasn't been a crackdown.  
6 We are still massively over-prescribing. What you are  
7 looking at here in blue is oxycodone consumption in the  
8 United States per capita compared to oxycodone  
9 consumption in Europe. And what this means, the fact  
10 that our opioid consumption remains so high is that  
11 many Americans are still becoming opioids-addicted. It  
12 means that we still have a high incidence rate of  
13 opioid addiction, and with a high incidence rate of  
14 opioid addiction, the opioid crisis will not come to an  
15 end.

16           Fortunately, prescribing has continued to  
17 trend in a more cautious direction. You would see the  
18 waves are peaked around 2011, 2012. But even with the  
19 most optimistic forecast, by 2023, we'll still be at  
20 about double our opioid consumption; double what it was  
21 in the early 1990s.

22           Now, if you look since 2012, we've seen opioid



1 prescribing come down. Those in favor of new opioid  
2 approvals have argued that, you know, FDA approving new  
3 opioids clearly isn't resulting in more opioid  
4 prescribing because of the downward trend. But what we  
5 don't know is what this graph would look like today had  
6 FDA really changed its policies on new approvals long  
7 ago, and I think it would look very different. And  
8 something that I would hope that FDA understands is  
9 that drug makers don't invest millions of dollars to  
10 bring a product to market and then sit on their hands  
11 and just hope doctors will prescribe it.

12           They do everything they can to make sure that  
13 doctors will prescribe it. In fact, even before a  
14 product gets approved there are unbranded aspects of a  
15 campaign to prime the market. This is something we're  
16 learning about through the opioid litigation, through  
17 internal documents that have become public.

18           We've heard about the NAS report. This  
19 morning we heard from Dr. Bonnie. I'd like to point  
20 out that the report didn't just call again for new  
21 criteria for approval, but it really did call for  
22 looking at removing existing products or new criteria

1 for existing products, and the report was endorsed by  
2 Commissioner Gottlieb.

3           This is just a section from the report urging  
4 FDA to do a full review of all marketed products,  
5 looking at the need for revised labels, formulations,  
6 post-marketing requirements and to consider withdrawing  
7 some products entirely from the market. After FDA  
8 endorsed this report, almost immediately a petition was  
9 filed with FDA from organizations including public  
10 health commissioners, consumer safety advocates, my  
11 organization PROP, [and] addiction advocacy  
12 organizations, urging FDA to now apply these new  
13 criteria and really to begin with the most dangerous  
14 opioids that exist. If you're going to really think  
15 about what products should be withdrawn from the  
16 market, the ultra-high dosage opioids are the most  
17 sensible place to start where we appreciate that FDA  
18 held a meeting on this topic a few months ago. And we  
19 remain hopeful that FDA will act on the petition's  
20 request.

21           Lastly, I want to talk a bit about the safety  
22 -- the efficacy side of the equation, the effectiveness

1 side of the equation, something you've heard from Dr.  
2 Bonnie in a comment to an FDA docket and from Dr.  
3 Kesselheim is that despite clear evidence of harms  
4 related to opioids, we lack evidence of benefit. This  
5 is something you've heard from former FDA commissioner.  
6 He said this publicly on 60 Minutes, that the FDA made  
7 a mistake in allowing opioid manufacturers to promote  
8 opioids for chronic pain.

9           FDA heard this. It was really part of an AH -  
10 - an AHRQ review that looked at all of the evidence  
11 supporting opioid use, long-term use, and concluded  
12 that we don't have evidence that this helps people when  
13 used long-term, but we do have evidence of serious  
14 harms.

15           Lastly, I just want to talk quickly about the  
16 use of enriched enrollment, randomized withdrawal which  
17 is really where FDA is getting the bulk of its  
18 information on efficacy of opioids for chronic pain.  
19 And the use of this clinical trial methodology didn't  
20 come from a public hearing like this one or from FDA  
21 consulting experts. It came out of private meetings  
22 with industry, and this was a presentation by Bob

1 Rapaport crediting impact, these private meetings with  
2 enriched enrollment.

3           Let me just finish up by explaining why  
4 enriched enrollment, randomized withdrawal should not  
5 be used. It's certainly something that drug makers  
6 like, because when you try to do a clinical trial the  
7 appropriate way, when you compare opioids to placebo  
8 you see a very high dropout rate. And over 12 weeks,  
9 many of the patients who get the placebo, their back  
10 pain will improve. Enriched enrollment, randomized  
11 withdrawal, the methodology there was to give all of  
12 the patients opioids in a 4- to 6-week open label  
13 phase. And then you see the drop outs or maybe half  
14 the patients drop out because they don't tolerate  
15 opioids.

16           And then you have the remaining group that are  
17 asked, let's say, half of the patients are asked, did  
18 you find opioids helpful for your low back pain? If  
19 they say no, they are also removed. Then that's your  
20 enriched sample. Then, you randomize half to be  
21 switched to placebo. The group being switched to  
22 placebo is of course going to have an increase in pain

1 because they are going through withdrawal and increase  
2 in pain is a symptom of opioid withdrawal. You now  
3 have lost the double-blind. All of the patients, if  
4 they are switched to placebo, know it. People who  
5 performed the study know it, and you've now created a  
6 situation where the placebo group has increased  
7 sensitivity to pain; something that's not controlled  
8 for. So, I do not believe that FDA should consider  
9 enriched enrollment randomized withdrawal to meet the  
10 requirement for adequate and well-controlled studies.  
11 And, you know, when the risk side of the equation is so  
12 clear, FDA really should be requiring better evidence  
13 of efficacy for the benefit side of the equation.  
14 Thank you.

15 DR. THROCKMORTON: Thank you, Dr. Kolodny.  
16 Questions from the panel? Thank you, sir.

17 WHAT RESEARCH TELLS US THAT CAN IMPROVE FDA  
18 APPROVAL STANDARDS AND REMS FOR OPIOIDS

19 DR. THROCKMORTON: Sorry, Dr. Zuckerman. Find  
20 your name. Next person is Dr. Diana Zuckerman from the  
21 National Centre for Health Research. Thanks.

22 DR. ZUCKERMAN: Thank you very much. I just

1 want to say the National Centre for Health Research  
2 does not accept funding from pharmaceutical or device  
3 companies, and we're also not involved in any lawsuits.  
4 The Center conducts research, scrutinizes other  
5 peoples' research, and tries to explain the research  
6 results to the public, to medical professionals and to  
7 policymakers. My personal perspective, I am trained in  
8 epidemiology, I was on the faculty at Vassar and Yale  
9 and a researcher at Harvard, and then I worked at U.S.  
10 Congress for a dozen years before becoming President of  
11 the National Centre for Health Research.

12           As everyone here knows, the usual perspective  
13 for what's safe and effective means -- for prescription  
14 drugs means that the benefits outweigh the risks for  
15 most patients under certain circumstances if prescribed  
16 for approved use, if used as directed, and if -- and  
17 based on studies that are particular number of weeks or  
18 months or years. And we -- and of course for opioids  
19 now the FDA is looking at how they can reduce the  
20 likelihood of doctors prescribing inappropriately,  
21 which is not an issue that is usually raised and what  
22 can FDA do to reduce the chances of patients abusing a

1 drug.

2           And we agree with the guidance that FDA now  
3 wants to consider how opioids might be abused or used  
4 inappropriately and have that be part of the equation.  
5 And we believe that better research and more specific  
6 labeling can, in fact, reduce the chances of addiction,  
7 and FDA has an important role in that. I just want to  
8 start with a simple issue, and that is what words we  
9 used and how some of them have PR value more than  
10 public-health value. The term abuse deterrent has  
11 often been misinterpreted to mean that people are less  
12 likely to become addicted to those products.

13           And, in fact, research shows that almost half  
14 of physicians misunderstand the meaning of abuse  
15 deterrent. And I'm sure patients and family members do  
16 as well. So, if a drug is crush resistant, call it  
17 crush resistant, and don't call it abuse deterrent.  
18 And if it's tamper-resistant, it should be proven to  
19 actually reduce tampering in the real world. These are  
20 just simple terms that should be clear, and they should  
21 only be used when they mean what people think they  
22 mean.

1           In terms of new research requirements, we  
2 believe that proof of abuse deterrent or tamper-  
3 resistant or less addictive. The issue is compared to  
4 what and under what circumstances. So, types of  
5 patients should be the same as those that are in the  
6 indication. The risks and the benefits in the short  
7 term and the long term should be established before  
8 approval, not after. And I'll go into a little more  
9 detail on this. So, in terms of long-term and short-  
10 term efficacy, we know now that research shows that  
11 many patients with chronic pain that for many of them,  
12 opioids are no more effective than over-the-counter  
13 painkillers.

14           So, FDA should require studies that compare  
15 new opioids with non-opioid painkillers, not just with  
16 other opioids. And the studies should compare short-  
17 term use as well as long-term use, and short-term use  
18 can be a week or less; it can be 3 days, it can be 5  
19 days. Long-term use, you know, I'm not going to say  
20 what exactly that means, but certainly more than a  
21 month is something that is very important.

22           And the labels and all the advertising should



1 have clear black box warnings and clearly marked  
2 contra-indications and warnings. And those warnings  
3 and those -- that information should include  
4 information that what happens if this drug is taken for  
5 more than 3 days or more than 5 days or more than a  
6 week, more than 30 days. It should be very specific in  
7 terms of the times and how addiction is more likely  
8 after specifically used for a period of whatever number  
9 of days. And when we're looking at the risk to benefit  
10 ratio, we have to look at which patients we're talking  
11 about. Some types of patients might be more likely to  
12 become addicted, and that wouldn't be just sex or race  
13 or age. It could be comorbidities and other issues,  
14 and that should be studied and specified. And the FDA  
15 should not be approving opioids for types of patients  
16 that they didn't study.

17           Only the types of patients that were studied  
18 should have an indication. And if that were true, we  
19 think that more companies would have more diverse  
20 populations in their studies. I just want to use one  
21 example which was an opioid implant from 2016. This is  
22 at a time when FDA already knew about what was

1 happening with opioids, and yet, there was an  
2 application that was based on a single 6-month control  
3 trial with major design flaws. I don't have time to go  
4 through all of them.

5           But, for example, patients receiving the  
6 device who discontinued the study without providing  
7 efficacy data were excluded from the intention to treat  
8 analysis. That should not happen. My personal  
9 favorite was when patients who missed their urine, drug  
10 tests were considered negative instead of positive.  
11 Obviously if they missed their test, you know, you  
12 should think, well, maybe there is a reason. And in  
13 addition, in this particular -- for this particular  
14 product, 84 percent of the patients were white, and it  
15 was not that big a sample. And yet the decision was  
16 that FDA approved that product.

17           I want to end up by talking about the REMS  
18 program, which of course, enables FDA to approve  
19 products that would otherwise be considered too risky.  
20 And for opioid REMS, we agree with the FDA that REMS  
21 should be offered for all opioids and for all health  
22 professionals dealing with pain management. I want to

1 point out that an analysis provided to the FDA by Josh  
2 Sharfstein and Caleb Alexander of Johns Hopkins  
3 indicates that the REMS for turfs, that's the immediate  
4 of these fentanyl, were not effective. It was clear  
5 that these products were being wildly used by patients  
6 who should not have gotten them. There were all these  
7 red flags that the REMS were not working, and yet, the  
8 red flags were ignored.

9           Just briefly going to talk about the previous  
10 REMS programs that FDA had for long-acting opioid  
11 prescribers. Only 20 percent of those prescribers  
12 completed the voluntary training. Only 59 percent of  
13 prescribers were even aware that the training was  
14 available. And I am just going to quickly go through  
15 some of the results of what they -- what the doctors  
16 learned who took this training.

17           The blue is correct answers, the grey is  
18 incorrect answers. Here is a basic question, what is  
19 the recommended way to safely confer an opioid tolerant  
20 patient to extended release opioids? You can see most  
21 of the doctors got that wrong. Oops, I don't know what  
22 happened there.

1           Then, there were a bunch of other questions  
2 about is the family history of mental illness relevant?  
3 Are there specific federal limits to the quantities  
4 prescribed? You can see that vast majority are getting  
5 some of these answers wrong. Should prescribers  
6 perform a comprehensive physical exam? Got that wrong.  
7 Should they systematically perform drug screening and  
8 follow up visits? Almost everybody got that wrong.

9           So, the question is, how well are these REMS  
10 working? And how can we make them work better in the  
11 future? In the past many doctors don't know about the  
12 training. Half the doctors who started -- excuse me,  
13 started training didn't complete it. Eighty percent of  
14 the long-acting opioid prescribers weren't getting  
15 trained. And even the doctors who were trained weren't  
16 learning everything they needed to know.

17           So -- and another thing is that the sponsors  
18 are the ones that are evaluating. So, they tend to  
19 say, look, the opioid crisis is decreasing, and so, our  
20 REMS are working. But we all know that there is lot of  
21 other reasons why things are changing. And we don't  
22 think that sponsors should be evaluating the REMS.

1           So, will guidance -- your guidance improves  
2 REMS? I hope so. We think that, yes, training would  
3 be for all doctors, that's good, and all pains --  
4 health professionals, that's important. It would be  
5 specific; the REMS would be specific to the specific  
6 opioid product. We think that's good. But there is a  
7 big problem. If it's voluntary, there still would be a  
8 lot of health professionals not getting it. And if  
9 there are no clear incentives for doctors to complete  
10 the training and actually learn, in other words there  
11 should be certification to prove that they have learned  
12 what they need to learn. And of course, the big  
13 question, who is going to evaluate the impact of the  
14 REMS, and it shouldn't be the sponsor. Oops, I am  
15 sorry; I do have just a couple more things.

16           So, when you look at the guidance, and you  
17 think of what's there, which is great, and what the  
18 reality is, you need to know who is going to monitor  
19 risks of prescribed opioids in the real world and how  
20 many of these drugs will be used off label versus for  
21 the indication that FDA has approved it for. And you  
22 know the sad story about who is going to actually read

1 the labels, even the black box warnings, who is going  
2 to be influenced by the ads.

3           So, in conclusion, I just want to say that  
4 although I am focused on new opioids in my talk, I  
5 agree that the old opioids on the market also need to  
6 be studied, absolutely, need to be studied, the generic  
7 ones need to be studied. I was very impressed with Dr.  
8 Dart's remarks, thank you very much. And the --  
9 especially the enriched enrollment, which is something  
10 that just was mind boggling to me I have to say. But  
11 thank you very much for the opportunity to be here, and  
12 I'm glad to answer any questions.

13           DR. THROCKMORTON: Thank you, Dr. Zuckerman.  
14 Questions from the panel.

15           MS. SIPES: Thanks for your presentation. I  
16 wanted to go back to your point about when you were  
17 talking about the risk-benefit ratio, and you're  
18 talking about how the drug should not be approved for  
19 any types of patients that were not studied. I was  
20 wondering if you could comment a little bit more on  
21 that in terms of how that would work in a practical  
22 level, how the trial will be designed and how the

1 groups would be defined.

2 DR. ZUCKERMAN: Sure. And that's a great  
3 question and something that comes up a lot with FDA  
4 approvals where sometimes these people in the studies  
5 are mostly white or mostly man or mostly women, but  
6 then the product is approved for everybody. With  
7 opioids, we can't know every single group. Obviously,  
8 you can't study every single group. But there are  
9 certain major groups that we think should be studied.  
10 Obviously major racial groups, men and women, age is  
11 important. Sometimes drugs are approved that have only  
12 been studied on people under 65, and they should be  
13 studied on people of all ages. And comorbidities are  
14 really important as I think especially mental health  
15 and some other groups that have tend to -- have a  
16 tendency to self-medicate. So, you want to make sure  
17 that the product is going to be safe and effective for  
18 those major groups. And obviously, you can't do every  
19 single possible demographic health group.

20 MS. SIPES: So, the underrepresentation of  
21 some of these types of patients, is this something that  
22 you perceive to be unique to the opioid area? Or are

1 you seeing this in other therapeutic areas? And how  
2 would you propose that clinical trials be conducted so  
3 that you can actually bring in a more diverse  
4 population of patients?

5 DR. ZUCKERMAN: I know that sponsors usually  
6 say we're trying to have a diverse population. This is  
7 what we've got. But we also know that when sponsors  
8 design their studies, they want the best possible  
9 outcome for their studies. And so, there is a tendency  
10 to have the healthiest sick people in whatever group it  
11 is. This is an issue that is not just opioids, it's  
12 just that because of the problems with opioids it's  
13 sort of a bigger problem. But, yes.

14 So, if -- we believe that if the company has  
15 an incentive to have a more diverse patient group and  
16 do subgroup analysis, that's what's really important.  
17 You don't want five African Americans in a group of a  
18 thousand patients. You want to have enough of each of  
19 these major groups that you can separately analyze them  
20 to see to the benefits outweigh the risks for that  
21 particular group.

22 MR. STEIN: In terms of the content of the



1 REMS, you mentioned making -- including more product-  
2 specific information. Are there other recommendations  
3 you have regarding what you see as particularly  
4 important to add to what's in the current training that  
5 the REMS provides? Are there areas that you think need  
6 to emphasize more or need to be included that aren't  
7 included?

8 DR. ZUCKERMAN: I think what -- you know, that  
9 the REMS would look different if it was specific to  
10 specific products. And so that take -- you know,  
11 that's a harder question to answer and one that I think  
12 is an important one that you're looking into. But I  
13 think that the biggest problem with REMS is the  
14 voluntary nature and the lack of certification, and I  
15 know FDA doesn't like to tell doctors what to do and  
16 require certain training. But I think the opioid  
17 crisis is one that is serious enough that training  
18 should be required, and certification should be  
19 required.

20 DR. THROCKMORTON: Thank you very much.

21 INCENTIVES FOR NEW THERAPEUTICS TO TREAT PAIN AND

22 ADDICTION: AN INDUSTRY PERSPECTIVE

1 DR. THROCKMORTON: And our next speaker is Dr.  
2 Danielle Friend from a Biotechnology Innovation  
3 Organization.

4 DR. FRIEND: Good morning. I first want to  
5 thank the FDA for hosting this meeting and allowing us  
6 to share our thoughts. I'm Danielle Friend, Director  
7 of Science and Regulatory Affairs at the Biotechnology  
8 Innovation Organization or BIO. BIO is the world's  
9 largest trade association representing biotechnology  
10 companies, state biotechnology centers and other  
11 related organizations within the United States and  
12 across the globe. Thank you.

13 The focus of my comments today will be on the  
14 last question included in the docket, in mechanisms for  
15 spurring investment and development of novel and safer  
16 therapies moving forward. In February of 2018, BIO  
17 released a report on the State of Innovation for Highly  
18 Prevalent Chronic Diseases, taking a look at the  
19 current investment trends and pipeline for pain and  
20 addiction therapies. You can find this report on our  
21 website. I'm going to briefly step through some of the  
22 data that was included in that report and discuss why

1 it's important for us to provide some regulatory  
2 certainty and some incentives for companies that are  
3 developing pain and addiction therapies moving forward.

4           Perhaps one of the most striking figures that  
5 was included in that report was a chart that looks at  
6 investment, venture funding as a function of U.S.  
7 healthcare spending. What I hope you can appreciate,  
8 in the lower right-hand corner, is what you see for  
9 both pain and addiction. So, compared to many other  
10 therapeutic areas, pain and addiction impacts a wide  
11 range of people, resulting in high amounts of U.S.  
12 healthcare direct costs. However, venture capital  
13 spending for those therapeutic areas is relatively low.

14           Another way that we can look at investment in  
15 R&D in a particular therapeutic area is to take a --  
16 take a look at Phase I clinical trial starts. This  
17 chart is examining Phase I clinical trial starts in the  
18 context of pain, and each bar represents the Phase I  
19 clinical trial starts for a given year. What I hope  
20 you can see is from 2013 to 2017 there was a reduction  
21 in the number of Phase I clinical trial starts for pain  
22 therapies. We have seen a slight uptick in 2018, and

1 we're hopeful that that trend continues.

2           In, you know, in taking a look at these  
3 investment trends and what is in the current pipeline,  
4 one of the things that we also looked at was clinical  
5 trial success rates. And so, this chart takes a look  
6 at clinical trial success rates for all therapeutic  
7 areas compared to clinical trial success rates for pain  
8 therapies. The gray bars represent all therapeutic  
9 areas, and the orange bars represent that for pain.  
10 And what I hope you can appreciate is that across the  
11 board in Phase 1, Phase 2, Phase 3 pain therapeutics  
12 have a lower clinical trial success rate as compared to  
13 all other therapeutic areas.

14           Lastly, I just want to point out the last set  
15 of bars, when we take a look at therapies that advanced  
16 from Phase 1 all the way to approval, most therapeutic  
17 areas are, I guess, taking into account all therapeutic  
18 areas together. There's about a 10 percent clinical  
19 trial success rate, which is 1 in 10. However, for  
20 pain therapies, it's much lower; it's 2 percent or 1 in  
21 50. I just wanted to mention here the current pipeline  
22 for addiction therapies as well. The far right-hand

1 column is a chart looking at the currently available  
2 options for treating opioid use disorder. The left-  
3 hand column -- excuse me -- the right-hand column is  
4 the current pipeline. And you can see that there are  
5 only four therapies currently in the pipeline for  
6 treating opioid use disorder. And you'll see just  
7 below that, two therapies are now not active or  
8 discontinued.

9           So, taking all of this data, BIO pulled  
10 together a working group, which is now made up of  
11 approximately 30 of our member companies, really to  
12 identify what were the barriers for preventing  
13 investment in R&D into pain and addiction therapies  
14 moving forward. We identified three key pillar areas.  
15 I will just discuss one of those today, but I think  
16 others have talked about some of the reimbursement  
17 issues, and that certainly discourages investment and  
18 R&D for these therapies.

19           But for the purposes of my talk today, I'll  
20 focus in on really some of the policies that would be  
21 helpful in the regulatory space. So, my following  
22 slides have a couple of recommendations, and we'll just

1 step through those very quickly here. Just want to  
2 mention that BIO plans just in that formal comments and  
3 the dockets will have much more extensive information  
4 for the FDA in that public docket.

5           But one of the first recommendations we would  
6 like to just highlight is that some of our companies  
7 have indicated that there have been delays in their  
8 ability to engage with FDA, particularly for the  
9 division of anesthesia, analgesia and addiction  
10 products. I do want to emphasize that we recognize  
11 that the FDA has been inundated with meeting requests  
12 to an unprecedented number. And I also want to  
13 recognize that our member companies have indicated that  
14 this division in particular has been extremely  
15 transparent and as flexible as they can as far as  
16 requests go.

17           But we would like to request that the FDA  
18 prioritize fully staffing and resourcing this division  
19 so that they can appropriately engage with and review  
20 pain addiction products moving forward. Our second  
21 recommendation focuses in on providing guidance for  
22 sponsors that are developing pain addiction therapies.

1 I will say the FDA has announced its intention to  
2 withdraw the 2014 draft guidance on analgesic  
3 indications, and Commissioner Gottlieb indicated, you  
4 know, his concern regarding some of the barriers for  
5 innovation in that guidance. Our companies are  
6 sincerely looking forward to the release of that  
7 guidance and, you know, strongly believe that it will  
8 help them develop their pain therapies moving forward.

9 I will step through a couple of areas that we  
10 would like to hear more from the FDA on. We certainly  
11 believe that these areas will spur innovation and help  
12 companies that are currently developing products in the  
13 pipeline. So, with this request, we ask that FDA hold  
14 a series of public stakeholder meetings to discuss  
15 several topics and then develop or update guidance as  
16 relevant.

17 So, one topic in particular is opioid-sparing.  
18 We recognize the FDA held an advisory committee meeting  
19 in November of 2018, and we appreciate that. We are  
20 looking forward to further conversations around  
21 opioids-sparing, specifically in the acute and chronic  
22 pain space, as well as the evidence that might be

1 needed in order to reference opioids-sparing and  
2 labeling products and the length of clinical trials and  
3 desired design of clinical trials to demonstrate  
4 opioids-sparing.

5           Similarly, I think it's important for there to  
6 be further conversations around mechanisms for  
7 evaluating pain. I think many stakeholders understand  
8 that the current 1 through 10 scale, you know,  
9 certainly doesn't capture the entire picture of an  
10 individual's pain. So, having public stakeholder  
11 meeting around mechanisms for evaluating pain is  
12 important.

13           Similarly, innovative clinical trial designs  
14 that might be used for developing pain therapies. Also  
15 want to recognize that the FDA recently included a pain  
16 protocol in the innovative clinical trials pilots. We  
17 appreciate that, and we're looking forward to  
18 learnings.

19           In the addiction space, we would also like to  
20 have more stakeholder discussions and develop an  
21 updating of guidance on reduction of opioid use and  
22 specifically how the reduction of opioid use can be



1 used as an endpoint. Also recognizing the FDA release  
2 guidance on efficacy end points for medicated-assisted  
3 treatment. We're looking forward to seeing updates to  
4 that guidance and hopefully finalization, as well as  
5 further discussions around possible innovative clinical  
6 trial designs that can be used in the context of  
7 addiction therapies.

8           Our third recommendation that I want to  
9 mention today is asking the FDA for clarification  
10 around how companies can take advantage of existing  
11 expedited approval pathways. It's our understanding  
12 that companies developing pain and addiction therapies  
13 can actually use expedited approval pathways. However,  
14 in speaking with our companies, it remains unclear to  
15 them some of the eligibility criteria for both pain and  
16 addiction therapies, including the level of evidence,  
17 the public health benefit and ability to address unmet  
18 medical need, as well as the expected engagement with  
19 the FDA.

20           So further clarification from the FDA via  
21 guidance would be greatly appreciated. One quick thing  
22 that I do want to mention in the context of expedited

1 approval pathways is that in speaking with some of our  
2 companies that work in the acute pain space, they are  
3 very interested in breakthrough therapy designation.

4           However, because acute pain therapies advance  
5 through clinical trials so quickly, the additional  
6 engagement that one will receive through breakthrough  
7 therapy designation, they are not actually able to take  
8 advantage of that additional engagement given the speed  
9 of the trials in particular. So, I just wanted to  
10 highlight that.

11           And then our last recommendation, just for the  
12 purposes of the talk today is to mention that we know  
13 that the NIH is working very hard with our HEAL  
14 Initiative. And then in particular, they have their  
15 EPPIC-Net Program which is a clinical trial program  
16 which will allow the testing of pain therapies in  
17 particular through this EPPIC-Net Program.

18           We certainly think that the FDA has value to  
19 add in those conversations regarding potential clinical  
20 trial design for the assets, as well as selection of  
21 endpoints. And we encourage the FDA to be vocal and  
22 clear about how they're engaging with NIH on the EPPIC-

1 Net Program. Further, as FDA continues to advance  
2 their policies, we encourage them to interact with  
3 other federal agencies as relevant. As I mentioned,  
4 BIO will be submitting more extensive comments to the  
5 docket in November. But at this point I'm happy to  
6 answer any questions that the panel may have.

7 DR. THROCKMORTON: Thanks very much. I'll  
8 begin just to point out that the 2014 guidance has  
9 already officially withdrawn, so.

10 DR. FRIEND: Sorry, if I wasn't clear. Yeah,  
11 we're looking forward to seeing the update on that...

12 DR. THROCKMORTON: Yeah, that was done  
13 recently, but it is in fact accomplished. Other  
14 questions from members of the panel. Peter?

15 MR. STEIN: You went over the low rate of  
16 Phase I to approval for novel pain medications. Can  
17 you speak about some of the barriers in particular as  
18 to what leaves them really (inaudible)? And I'd also  
19 be curious, obviously there are many reasons for the --  
20 on the prior slide for the low investment relative to  
21 the U.S. direct healthcare prospective. If you could  
22 speak more about some of the background as to what you

1 think contributes in particular to that low rate of  
2 investment?

3 DR. FRIEND: Sure, sure. So, to your first  
4 question regarding the low clinical trial success  
5 rates, I think there are several factors that  
6 contribute to that, but one of the key things that we  
7 hear from our member companies is the issue with  
8 placebo effect in the context of pain. That that is a  
9 huge issue, you know, with running the pain clinical  
10 trial. So, I would say that it's probably the most  
11 significant impact that we hear in that space.

12 As far as, excuse me, the lack of investment  
13 for pain and addiction therapies. You know, certainly  
14 the -- my comments today have focused on regulatory  
15 certainty and making sure that that exists. Some of  
16 the other pillars that Bio has focused on include  
17 really looking at the payment and access space. So,  
18 for example, novel pain and addiction therapies, there  
19 are reimbursement and access barriers that prevent  
20 those therapies from being reimbursed by insurers, and  
21 so that is actually determined from investors entering  
22 that space as well as companies. And then the other,

1 the one key -- the other people pillar that I also did  
2 not mention due to the limit of amount of time I had to  
3 speak is focused on really the, you know, basic  
4 neurobiology of pain and addiction. And that's where  
5 we see that NIH can play an important role. And  
6 certainly, again, just emphasizing the importance of  
7 FDA engagement with NIH on those efforts.

8 MS. SIPES: Okay. Thanks for your  
9 presentation. Could you expand a little more about --  
10 you were talking about expedited pathways and questions  
11 arising about public health benefit and ability to  
12 address unmet medical need. Could you expand on that a  
13 little bit?

14 DR. FRIEND: Yeah. So, we will be providing  
15 some more extensive comments within the comments that  
16 we'll be submitting to the docket, but there just seems  
17 to be some confusion from companies as to whether pain  
18 and addiction therapies can qualify given the, some of  
19 the current definitions, such as unmet medical need and  
20 benefit.

21 DR. THROCKMORTON: And so, I -- Others? I'll  
22 follow up. I have a question about your heal

1 initiative slide, and this may be something that you  
2 will be submitting a comment to it. Exactly what  
3 outcomes you'd like to see from that engagement between  
4 the FDA and NIH around the HEAL Initiative would be  
5 really useful.

6 DR. FRIEND: Sure. We'll be happy to submit  
7 those to the docket as well.

8 DR. THROCKMORTON: Thank you very much.

9 And with that, we are at the end of the  
10 morning session. I will have us back at 1:00 o'clock,  
11 Meredith, for the beginning of the afternoon session.  
12 Thank you very much.

13 LUNCH

14 (Recess)

15 DR. THROCKMORTON: We have a list of speakers  
16 that have registered, and then we'll move from there to  
17 the open public hearing speakers. At present we have  
18 three people that have signed up for the open public  
19 speaking part of the afternoon. The first person  
20 that's going to be talking this afternoon is Mr.  
21 Matthew Iorio. Apologies in advance. Please, sir,  
22 you're welcome to come up. Thank you.

## 1 BARRIERS TO INNOVATION

2 MR. IORIO: Thank you. First off, thank you  
3 very much to the FDA for allowing me to come up and  
4 make this presentation. My name is Matthew Iorio. I  
5 have my Regulatory Affairs Certification and my  
6 master's in Regulatory Affairs and Health Policy. I  
7 also have 9 years of experience as an executive at a  
8 generic contract manufacturing organization of  
9 controlled drugs, and I am currently the President of  
10 Eighty Eight Pharma.

11 So as a disclosure, this discussion is a  
12 perspective of a for-profit pharmaceutical company, and  
13 we are actively developing products in this space.  
14 Eighty Eight Pharma is a startup. We were founded in  
15 2017. We operate out of the Mansfield Bio-Incubator in  
16 Mansfield, Mass. So, we're going to be one of the  
17 smaller companies that the Agency has interactions  
18 with. We don't have manufacturing facilities, so we  
19 outsource all the different manufacturing that we do,  
20 and that structure allows us to be a native part 4  
21 company, which is a term I just made up to describe  
22 that we don't go into drug devices or biologics. We

1 can go into any direction or combination depending on  
2 what suits a product development so that unique  
3 structure allows us to develop innovative products like  
4 this guy, which is a fixed point in a unit of use, a  
5 container that holds 15 tablets. Each one of those has  
6 a spring-loaded hammer with the cavity that has  
7 naltrexone, and when you push the button, it will be --  
8 we're deploying. So that's the sort of products that  
9 we're developing.

10           So, the opioid epidemic has acted like a  
11 tracer dye injected into the United States. People who  
12 were invisible are now the focus on the nation. I find  
13 it breathtaking and hopeful to watch the new  
14 developments every day as the most powerful nation in  
15 history develops unheard of -- or deploys unheard of  
16 resources to help Americans struggling with opioid use  
17 disorder. The focus extends to many vulnerable groups,  
18 including people who are incarcerated, people with OUD,  
19 who are struggling with mental illness or who have HIV  
20 and HCV. We now see people with OUD who live in rural  
21 communities, urban communities, tribal communities or  
22 people who are struggling with despair.



1           Finally, the focus extends to people who are  
2 in chronic pain and need to navigate this complicated  
3 and stigma-laden medicine. I see tangible efforts like  
4 to SUPPORT Act that's fixing longstanding problems.  
5 For instance, historically methadone treatment has not  
6 been covered by insurance. If you needed treatment for  
7 OUD, you had to show up at the methadone clinic with  
8 cash in your pocket. That was a stigma-based  
9 regulation born out of the belief that showing up to a  
10 methadone clinic is not an opportunity to get better.  
11 Now all FDA-approved medication assisted treatments are  
12 covered by Medicaid -- will soon be covered by  
13 Medicaid.

14           Switching gears to another critical  
15 legislative effort, broadband. We're talking a lot  
16 about telehealth, telemedicine and telepsychiatry to  
17 very remote areas. And for these to work, we need to  
18 make sure that the federal plan to expand the broadband  
19 infrastructure is doing what it's intended to do. To  
20 do telemedication assisted treatment, we need Internet  
21 connections sufficient to clearly see each other  
22 through video chat. So that's where we need to get to.

1           Jumping right into the guidance. My  
2 understanding is that the reasoning for the guidance is  
3 sort of a preventative action for future epidemics.  
4 So, my thought is that most improvements in that  
5 benefit-risk profile would be by reducing risk with  
6 minimal to moderate production efficacy. So, I was a  
7 little bit surprised to see in Section C, does this  
8 analgesic drug offer any advantages relative to  
9 available approved analgesic drugs for each indication  
10 with regard to effectiveness or duration of response?

11           I see that as an opening to create a higher  
12 potency or extended release drugs. And while that  
13 might satisfy making a drug safer in some aspects, I  
14 don't think that that's sort of what is the expectation  
15 that's going to come out of this guy. Just wanted to  
16 mention that.

17           Moving on. Does the Agency have the authority  
18 to require -- to address these issues? So, 21 CFR  
19 820.3, this, of course, is in the device side, design  
20 validation shall improve software validation with risk  
21 analysis where appropriate. So, if you've ever done  
22 device hazard analysis, you know that you have to

1 consider second-order hazards. So, switching back to  
2 the drug side, you've got ICH Q9 quality risk  
3 management. If you're doing quality by design, you  
4 should be doing hazard analysis. And so, you should  
5 have a lot of this baked into your development already.  
6 So, I don't think that actually any new authorities are  
7 required.

8 I think the existing authorities could be  
9 used. You've got your ICH Q9 with your hazard  
10 analysis. You've got the risk-benefit assessment  
11 described in a recently issued draft guidance, which is  
12 sort of pointing in the direction of what your hazard  
13 analysis should include. And then most importantly,  
14 the Agency has the ability to withdraw marketing  
15 approval of unsafe drugs, and that's something that  
16 we've talked about, or I've heard talking about quite a  
17 bit today. And I think in a way, that would be helpful  
18 to the industry because you could remove some of the  
19 less safe products and their generic equivalents,  
20 Don't forget about those when you have available more  
21 safe products that would eventually have generic  
22 equivalents. I think that would be helpful.

1           Alternatively, you could go to a straight  
2 standards approach, sort of new legislation modeled  
3 after something like the Federal Motor Vehicle Safety  
4 Standards. But these iterative standards apply better  
5 to devices than drugs. But if you start to look at  
6 some of the things that we're packing on to these  
7 opioid analgesics with the REMS program and  
8 prescription drug monitoring programs, we're getting  
9 well beyond just that, you know, the molecule. So,  
10 whoever put this question in, thank you. This is going  
11 to make one of my points perfectly. So please consider  
12 that existing opioid market consists largely of  
13 relatively inexpensive generic drugs. So, this is from  
14 the Surgeon General's Spotlight on Opioids. The effect  
15 of the opioid crisis are cumulative and costly towards  
16 society, an estimated \$504 billion a year in 2015,  
17 placing burdens on families, workplaces, the healthcare  
18 system, states and communities."

19           And then from the *Wall Street Journal*, "The  
20 Ohio Trial is slated to take place before the U.S.  
21 District Judge in Cleveland, who is overseeing the  
22 consolidation of some 2,000 cases brought by cities,

1 counties, Native American tribes and other entities  
2 seeking to recoup the public costs of opioid addiction  
3 and abuse. So, you've got \$504 billion, which is the  
4 opioid crisis cost to society divided by 216 million  
5 opioid prescriptions and that equals \$2,333 cost to  
6 society per opioid prescription. So, you have to ask  
7 yourself are these \$15 bottles, or are these \$2,348  
8 bottles? And then who pays this cost and who should  
9 pay this cost?

10 Now of course, this is the elephant in the  
11 room because for as long as we're going to be stuffed  
12 with these \$15 bottles of generic opioids, nothing is  
13 ever going to be able to come in that's going to be  
14 safer because it's going to be more expensive, and it's  
15 not going to get coverage.

16 If you look at it, more features mean more  
17 cost. More cost means more reimbursement. And here's  
18 what we're really looking for proof of net savings, so  
19 you get lower reimbursement, and that means lower  
20 penetration and to make the product viable companies  
21 raise their price. So, you've got high priced  
22 therapeutics chasing high risk individuals and the end

1 result is a lower overall impact on that \$504 billion.  
2 And if you want to see this in action, as some of you  
3 who came before me was talking about, how they went in  
4 for a buphen (ph) patch that costs \$400 a month, which  
5 is the safer alternative. Their insurance may not  
6 cover it. And they offered them a \$12 prescription for  
7 oxymorphone. That is exactly why it's difficult to  
8 bring in your safer innovative products because you are  
9 always undercut by this extremely cheap, and they're  
10 effective generic opioid medications. They're just not  
11 as safe as we would like them to be.

12           So, we get to justify higher prices for safety  
13 innovation. This is something that we're going to need  
14 to do or at least I will need to do if I'm going to get  
15 my products to market. How should comparative  
16 advantage be defined and can be quantified? Really it  
17 must be quantified to be persuasive to payers and the  
18 public about their merits and their advantage. You  
19 have to quantify it in order to justify the increased  
20 cost of your safer innovation. So how do you justify  
21 it or how do you get your slightly -- your products  
22 with more features, more safety improvements in market?

1 Either the Agency just root for us, hold off the other  
2 products, or you go to a process of cost benefit  
3 justification with all that economic data.

4           So, you could set up a system where at launch  
5 -- this is going to be at launch, you would have N  
6 communities. You randomly select interventional and  
7 control communities, which is problematic because  
8 you've got informed consent on second-order people so  
9 that might make this a challenging thing to justify it.  
10 Pick your endpoints that payers care about. Figure out  
11 what payers care about. Figure out what the Centers  
12 for Medicare & Medicaid Services care about, which  
13 interesting enough is a meeting on Friday, so we'll  
14 figure that one out. And then what epidemiology tools  
15 can be used, and who hosts them.

16           And actually, there's another discussion also  
17 on RADARS. This actually will define this sort of  
18 thing. Then you ask yourself through low cost phone  
19 surveys, chat-room monitoring, and community data be  
20 acceptable to support endpoints. There's never really  
21 been sufficient for the Agency, but if it's used  
22 broadly for economic data, that might be possible.

1 That is the end of my time. So, I will take questions  
2 if you have any?

3 DR. DAL PAN: Yeah. About this Phase IV  
4 prospective observational study that you're proposing -  
5 - random intervention and control book, what are the  
6 interventions you're talking about?

7 MR. IORIO: Sure. So, you've picked your  
8 communities to deploy your intervention -- you pick 10  
9 communities, you would launch in 5, and 5 you decide  
10 not to launch into. And so, you have that differential  
11 where you could make some determinations using a  
12 randomized sort of style, and hopefully, be able to get  
13 the power to make some of these determinations.

14 MR. PAN: That I get, but what is the  
15 intervention that will be randomized of particular  
16 medicine, some other treatment strategy, an educational  
17 program?

18 MR. IORIO: It could be any one of these. So,  
19 let's for instance say you had a proposal fixed  
20 quantity unit-of-use blister packs, and the Agency  
21 moved forward with that, which actually I think is a  
22 really good approach trying to limit some of the excess



1 medication on the market. You want to determine if  
2 that is effective at preventing this and subsequent  
3 harms that having excess medication in tablets to  
4 happen. You can pick your communities that you're  
5 going to launch, you randomly pick out of your -- and  
6 the ones that you're going to launch those blister  
7 packs into and the ones that you're not going to launch  
8 the blister packs into. And then maybe over time, you  
9 can sort of see some of that get that differentiation  
10 and see if you're making that happen.

11 MS. SIPES: And thanks for your presentation  
12 and on the same topic that Dr. Dal Pan was just asking  
13 about, do you view this as you sort of suggesting this  
14 as something that companies would undertake, or would  
15 this be a requirement? If so, how would that work?

16 MR. IORIO: So, there are potentially some  
17 claims that if a company might want to make they would  
18 have to go through this route. I mean this is a little  
19 bit extreme and, but you could. If we're looking at  
20 say an abuse deterrent technology, and we're trying to  
21 determine if it's actually had an effect in the  
22 community on lowering abuse, you have to set up some

1 sort of a -- some sort of a way to determine that. And  
2 this would be a way that in the post-marketing phase if  
3 you try to figure out if your abuse deterrent  
4 technology is working. You know, there's been  
5 challenges right now with figuring out if abuse  
6 deterrent technologies work with a product like the one  
7 that we're developing. We're trying to limit excess  
8 medication so at some point, we have to actually make  
9 determinations; is this effective? And we have to set  
10 up some sort of a trial. And this is sort of my best  
11 approach, of course, in taking feedback, you know. How  
12 can we set this up? How can you actually do these  
13 sorts of studies? You know, these are done to some  
14 extent in academia and the academia -- there's some  
15 approaches with say vaccines and different things that  
16 have used these sort of approaches, but just sort of  
17 how do we use this now for some of these innovations  
18 that we feel like we're going to have an impact, we  
19 want to justify their impact. How do you start to do  
20 this?

21           This is important for the second-order  
22 effects. The first-order effects you enroll your

1 subjects, you track them, you know what they are going  
2 to do. How do you then track the other people in those  
3 communities who you're assuming are having some sort of  
4 an effect, if it'll be a positive or negative? You  
5 have to figure those second-order effects out and so  
6 you have to sort of dig down to the community level for  
7 these second-order effects. But I think that's sort of  
8 squeezed dry. If you're trying to actually make, I  
9 mean, maybe a claim or at least a health economic  
10 justification about the second-order effects, how do  
11 you get to those? I think that's challenging.

12 DR. THROCKMORTON: So just to continue in the  
13 theme so in the guidance that -- the draft guidance  
14 that we have, are we to talk about the use of data of  
15 this kind mostly in terms of understanding it and under  
16 the abuse or misuse populations those kinds of things?  
17 Are you suggesting that we think about requiring these  
18 kinds of data in different settings than those or use  
19 them to support different kinds of endpoints than we  
20 talk about in the guidance?

21 MR. IORIO: So, it most likely discussion  
22 about how are we going to establish some of these

1 second-order effects? Let's say we launch a product  
2 and we anticipate it's going to have some sort of a  
3 beneficial effect on the patients and on second-order,  
4 on the community. If we just launch the product and  
5 then you look at the overall trends, that's not as  
6 persuasive as having some sort of a randomized aspect  
7 to it. So, what we're currently looking at is  
8 launching a product, tracking it and looking at the  
9 effects. Well, with a little bit of forethought if you  
10 can actually deploy strategically as you're monitoring,  
11 you might be able to pick up some of these more solid  
12 effects, potentially some of these second-order effects  
13 just trying to get down to that. It's just a question  
14 of when you launch, you know, a little more strategic  
15 about how you're launching so you might be able to pick  
16 up some of these. Of course, it does get back to some  
17 of these -- said issues, some of the challenges with  
18 it. But when you're looking at the second-order  
19 pieces, how do you get down into those? It's  
20 challenging and actually proves -- may not prove, but  
21 actually get it some of that persuasiveness that having  
22 a randomized element to it will get you that.

1 DR. THROCKMORTON: Great. Thank you very  
2 much. Our next speaker is Dr. James Campbell from  
3 Centrexion Therapeutics.

4 FDA SUPPORTING INNOVATION IN PAIN THERAPEUTICS:

5 AN INDUSTRY PERSPECTIVE

6 DR. CAMPBELL: So, hello everyone and it's a  
7 real pleasure to be here and thanks so much for the  
8 opportunity to talk to you today. So, I'm going to  
9 represent a biopharma perspective, and my remarks are  
10 going to pertain to the issue in particular of  
11 incentives.

12 Centrexion Therapeutics is a company whose  
13 sole focus is developing non-opioid, non-addictive  
14 novel therapies for the treatment of chronic pain. Our  
15 portfolio, I'll just mention in passing, includes  
16 products in Phase III going all the way to pre-  
17 clinical. We actually have six products in our  
18 pipeline. And again, all of these are focused on the  
19 issue of chronic pain. Our lead Phase III product is  
20 an injectable capsaicin, which is injected into the  
21 knee for purposes of controlling the pain associated  
22 with painful osteoarthritis.

1           It's -- with that we're here talking about  
2 novel therapies in the context of a meeting that is --  
3 has to do a lot with the use of opioids. So, I've  
4 started actually in the pain field as a medical student  
5 at Yale back in -- some decades ago. And the  
6 conversation then was about use of opioids for pain.  
7 And it's striking that the conversation still today is  
8 very similar. So, we're in a field where there has  
9 been remarkably little innovation, and we need to  
10 reflect; and when I say, "we," I mean industry,  
11 academia and at the policy level in terms of our  
12 government institutions like the FDA and NIH about why  
13 this is.

14           But I think a positive thing that we can do  
15 about the situation revolves around use of incentives.  
16 So, this slide is just a reminder slide about how  
17 biopharma company sits within a very complicated matrix  
18 that involves lots of things working. So, this wheel  
19 of intersecting components involves science, IT,  
20 regulatory issues, patient issues, payers, and then  
21 investors. All of these components have to work in  
22 order for us to innovate. So specifically, I want to

1 address my remarks to questions posed to us in the  
2 context of this meeting in particular. Do incentives -  
3 - are they needed? Which incentives would be most  
4 effective? And I want to get into the issue of what  
5 should be the criteria for designation in terms of how  
6 these incentives should be implemented.

7           So first of all, are pre-approval incentives  
8 needed? And actually, before getting into that, there  
9 are a couple of things to be said about regulatory  
10 processes that we think would be impactful in terms of  
11 bringing about innovation, bringing investors into the  
12 pain development process. So, one of those has to do  
13 with nimbleness of interactions. So, investors pay a  
14 lot of attention to the processes that occur in terms  
15 of drug development, in terms of what is the nature of  
16 the interactions. So quite often they deal with great  
17 formal interactions that involve for example, type C  
18 meetings, which lead to further type C meetings because  
19 there are certain things that are not clear. And so,  
20 one way to put this is to refer to a nimbleness of  
21 interactions as being a component of what would be an  
22 incentive ultimately to investors.

1           The second component of this revolves around  
2 resources. So, more funding, more bodies are going to  
3 be an incentive ultimately to investing because it  
4 establishes the priority. So, if we have an under  
5 resourced agency dealing with the applications for  
6 novel drugs for pain, we're going to see a prolongation  
7 of the approval process, and it's simply going to be  
8 more cumbersome, and it's going to take longer and cost  
9 more. And so, I think this is a very important  
10 component as we consider the whole issue of incentives.

11           Another question that was brought up in the  
12 context of this meeting is what new incentives would be  
13 most effective? And so, it's pretty easy to generate  
14 this. And so, one of the incentives has to do with  
15 this nimbleness, if you will, of feedback. And I'll  
16 get into the issue of breakthrough designation  
17 momentarily and this is another area for us to  
18 consider. But there are other incentives that are  
19 going to have a great impact on whether investing in  
20 new novel pain medications is going to make sense from  
21 an investor perspective. So significant tax credits  
22 for investment in non-opioid drug development would be



1 one of those incentives. A waiver of FDA filing fees  
2 would be another incentive that would be meaningful.  
3 And then, there is the incentive of market  
4 exclusivities.

5           So, in terms of incentives, one of the  
6 brilliant innovations in terms of designatory process  
7 that's been impactful for a number of diseases is the  
8 orphan product designation. So, this 7-year data  
9 exclusivity provision by the -- this orphan product  
10 designation has brought forward a number of novel  
11 therapies for diseases that just otherwise would not  
12 have been investible. So, it's to apply this to the  
13 field of chronic pain would have wonderful comments for  
14 having meaningful impact. And so, a suggestion would  
15 be that the 10-year market exclusivity provision would  
16 be a very decisive statement at the government level  
17 that, "Hey, this isn't important, and there has been a  
18 possibility of innovation, and we need to do something  
19 about this. And this is a part of our way of dealing  
20 with this opioid crisis and our way of leading to  
21 innovation where there has been very low over decades."

22           Somewhat related to this is another incentive,

1 and this relates to a voucher, a drug priority review  
2 voucher. So, this has been impactful in areas like  
3 pediatrics and for tropical diseases. And this would  
4 be of -- if this was applied to the development of  
5 novel non-opioid drugs chronic pain, this would have a  
6 -- this would make investment in the chronic pain area  
7 immediately highly desirable on the part of investors  
8 who would really stimulate innovation.

9           And finally, the third question is about how  
10 the -- these designations might be deciding. And we  
11 note that in the description of breakthrough  
12 designation that there is some level of clarification  
13 that would be very helpful. For example, in the  
14 breakthrough designation presently, there's reference  
15 to preliminary clinical evidence. Well, what is  
16 preliminary clinical evidence mean and if that  
17 preliminary clinical evidence only applies to a late  
18 stage Phase II product, what kind of impact on  
19 development is that going to have? And what does  
20 substantial improvement mean? And then thirdly what  
21 are meaningful controls in terms of deciding that a  
22 therapy is a breakthrough therapy? In a sense a

1 therapy that works over placebo is almost by definition  
2 a breakthrough therapy. So, this is another idea I  
3 think that would be helpful guidance in terms of making  
4 better use of this breakthrough designation. So those  
5 are my remarks, and I'll stop there.

6 DR. THROCKMORTON: Great. Thank you very  
7 much. Could you clarify that, the last comment that  
8 you made there about a product that beat placebo be by  
9 definition a breakthrough?

10 DR. CAMPBELL: Right now, I think there are a  
11 couple of things just for clarification, so I think  
12 getting fast track status is relatively easy in the --  
13 within the analgesia division. One further issue is  
14 that there needs to be a greater clarity with regard to  
15 what the impact of breakthrough would be over a fast  
16 track? And right now, I think there is some  
17 uncertainty about what that exactly means in terms of  
18 the processes within the intervention division. And we  
19 get a sense that there is some difference of opinion in  
20 leadership about that issue.

21 In terms of take a problem like painful  
22 osteoarthritis of the knee well, if you have a drug

1 that works, it's almost by definition a breakthrough  
2 for osteoarthritis of the knee. It's almost by  
3 definition a breakthrough because right now we are  
4 stuck with steroids, which have issues of toxicity. We  
5 have HA's which are uncertain in the terms of their  
6 efficacy. We have NSAIDs, which are a problematic  
7 class in terms of long-term of therapy and morbidities  
8 related to cardiovascular disease and GI toxicity and  
9 kidney impacts; so how well suited are these for long-  
10 term therapy? So, if you have a therapy that works in  
11 that broad pain category, isn't that a candidate to be  
12 a breakthrough therapy. So, I think it would be  
13 helpful to clarify what the standards for breakthrough  
14 should be.

15 MS. SIPES: On slide 6, you mentioned, first  
16 of all, FDA commitment to a series of meetings,  
17 feedback prior slides. Can you explain a little bit  
18 whether -- because we have a series, different  
19 categories of meetings, are you actually still talking  
20 within those categories your type A, B, C, your CPIN  
21 meetings, were you proposing something --?

22 DR. CAMPBELL: I'm sorry, I didn't quite

1 understand clearly the question?

2 MS. SIPES: You mentioned that on slide 6 --  
3 I'm sorry -- FDA commitment to a series of meetings and  
4 feedback. And I'm just asking a clarification because  
5 we have different categories of meetings the type A, B,  
6 C and your CPIN meetings that you mentioned here, are  
7 you proposing some other form of meeting?

8 DR. CAMPBELL: So, I think the intention is  
9 that there needs to be order and there needs to be some  
10 rules based for interactions. But on the other hand,  
11 if there are questions, and for example, that lead to a  
12 type C submission and then there is a response that  
13 takes a long time, and some of the issues are pretty  
14 easily clarified and could be clarified even with a  
15 phone call. But then because there's lack of  
16 clarification there, how the company goes back to the  
17 division to get this done. Right now, it almost looks  
18 like there needs to be another type C meeting, which  
19 then the clock continues on. In the meantime, how to  
20 deal with a pretty straightforward issue might be  
21 handled quite differently and much more nimbly if you  
22 will in a way that would save time and suit the needs

1 for helping the drug properly towards the ends of  
2 safety and efficacy studies.

3 DR. THROCKMORTON: Just to follow up on that.  
4 So, one way of heard that intention discussed was in  
5 terms of regulatory certainty versus speed of response.  
6 So, if you are looking for an informal response that  
7 maybe exactly that, that's something that a phone call  
8 could potentially get you. But that if you are looking  
9 for something that would be -- you could act on from a  
10 regulatory perspective, they're needed to be more  
11 formality. The question was how to find the right  
12 degree of formality recognizing that with speed comes a  
13 loss of some of that interaction -- loss of that  
14 certainty.

15 DR. CAMPBELL: Yeah. I think you're  
16 describing the situation. I think a -- we don't see  
17 informal contacts occurring, and I think if there were  
18 to be informal contacts, there could be clarification  
19 on what the issues are so that when it comes time to  
20 come up with the -- a more informal interaction then we  
21 can make sure things are outlined, so it's bit more  
22 efficient process. So, I think there is a place for

1 this recognizing that there -- ultimately there is a  
2 need for a formal process, and there is a need for  
3 formality. We see -- the feedback we get is that there  
4 is inconsistency between divisions on this -- and  
5 that's understandable. We would see the process to be  
6 more efficient if it was more interactional is maybe  
7 the word I am acting on.

8 DR. THROCKMORTON: Other questions? Thank you  
9 very much.

10 DR. CAMPBELL: Thank you.

11 DR. THROCKMORTON: Our next speaker is Dr.  
12 Judy Ashworth from Pinney Associates.

13 ASSESSING THE VALUE OF NOVEL OPIOID ANALGESICS

14 DR. ASHWORTH: Good afternoon. To begin with,  
15 I would like to thank the Agency for the opportunity to  
16 be here and speak today, and for holding this public  
17 hearing. By way of disclosures, I'm the chief medical  
18 officer at Pinney Associates, where I advise  
19 pharmaceutical companies that also that includes  
20 biotechs, and primarily with those working on CNS sided  
21 drugs and in new analgesic development. We advise on  
22 clinical and regulatory strategies. And, with an

1 emphasis particularly at Pinney Associates, with regard  
2 to abuse liability assessments and how companies can be  
3 guided through the expectations of the FDA and the DEA  
4 during the course of their development of compounds.

5 I also serve as the chief medical officer at  
6 Harm Reduction Therapeutics, which is a non-profit  
7 pharma company that's working for an affordable  
8 naloxone product on the OTC market. Although, I and my  
9 colleagues at Pinney Associates provide consulting  
10 services for many companies developing other  
11 medications, we neither solicited nor received any  
12 outside input into this presentation, nor did I receive  
13 any reimbursement for my travel or any compensation for  
14 being here.

15 My colleagues and I agree with the principle  
16 that a new opioid analgesic should be able to  
17 demonstrate some level of incremental improvement with  
18 respect how to use potential, or to some other  
19 relevancy to the outcomes, such as disparate pressure  
20 compared to existing schedule to opioid -- opioids that  
21 are currently on the market. However, today's  
22 healthcare system, even if a novel opioid product were



1 to be able to demonstrate an incremental benefit such  
2 as one of these, around policies around product  
3 labeling as well as scheduling under the CSF -- the CSA  
4 offers little basis for differentiation of these  
5 products. So as a result, third party payers have  
6 minimal motivation to accept these new opioids into  
7 their formulas and because they are more expensive than  
8 generics, of course, and also healthcare providers have  
9 little information regarding these potential benefits  
10 within the label.

11 So, from the FDAs proposed topics for today's  
12 discussion, I want to address two. And the first one I  
13 want to address is actually more to should sponsors of  
14 new opioid analgesics be required to demonstrate some  
15 comparative advantage relative to the existing opioids  
16 on the market.

17 For 17 years I worked at Grunenthal, which is  
18 a German pharmaceutical company in the development of  
19 analgesic medications including Tapentadol, as well as  
20 if you use the term formulations. As you know it's  
21 longer than the expectation of EMA, the European  
22 Medicines Agency, that sponsors do include active

1 comparators in the development of their analgesics.

2           So, given that Grunenthal was at that time  
3 collaborating with Johnson & Johnson here in the US on  
4 that development program with Grunenthal our global  
5 development program did have an active comparator in  
6 every single trial except for one, in the chronic pain  
7 and acute pain program. And I'm talking about the  
8 trials for submission and this, of course, was again it  
9 was needed because we went and -- we had to also submit  
10 in New York.

11           Thus, within the respective NDAs that was  
12 submitted to the Agency for Tapentadol, the FDA had  
13 substantial amount of data in its hands regarding the  
14 comparison of Tapentadol to other opioid antagonists  
15 with regard to efficacy, as well to safety in both the  
16 treatment and the clinical issues.

17           Unfortunately, even though these data were  
18 converged, randomized multi-pronged trials accepted by  
19 the Agency's basis for -- in these indications, the  
20 Agency didn't allow any comparative data into the  
21 labels. These all confirmed these trials not because  
22 they were elected or from -- it is just a simple matter

1 of policy, we don't allow comparative data describing  
2 these.

3           Though even if a sponsor gets it for a novel  
4 analgesic which has demonstrated benefits over schedule  
5 2 opioid currently on the market without allowing any  
6 of this relevant data into the label, and I'm not  
7 saying big plates, just to have the data, the relevant  
8 data into the label, two things happen. Companies are  
9 left to educate the healthcare providers on these  
10 benefits for verifications, posters, conference calls,  
11 all of which will increase the need to scrutinize and  
12 consider suspect even when the data originated from  
13 trials and deemed acceptable for improving the drugs  
14 from third party payers and other organizations have  
15 learned a reason to encourage uptake of these products  
16 usually on a differentiated label.

17           So, when you ask what the FDA can potentially  
18 consider changing, in order to incentivize sponsors to  
19 develop novel opioids with better safety profiles, is  
20 to provide comparative data during that development and  
21 allowing these data into the label, is one area where I  
22 would point out to consider. This would help shift the

1 driving away from more commonly prescribed in the  
2 media, immediate releases schedule 2 opioids as being  
3 retracted for abusive origin. They account for the  
4 major prescription opioid abuse (inaudible).

5 With regards to topic 9, the FDA specifically  
6 asks for ideas regarding free-marketing incentives to  
7 encourage sponsors to develop and release better  
8 opioids.

9 The company use incentive, which was also just  
10 discussed by the Agency in the free-marketing space's  
11 expert reviewed mechanisms, which was back already  
12 reviewed in breakthrough therapy. And I think most  
13 companies have developed these two formulations they've  
14 gotten faster at. And that made that movement to a  
15 traditional line a bit more quickly than have they not  
16 have that. So, don't take it away, I'm not saying  
17 that.

18 But, the biggest challenge that these  
19 companies are facing is in the post-marketing world.  
20 It's not getting to the market, it's getting market  
21 access. Market access has proven to be an absolute  
22 nightmare for ADF (ph) companies as they currently

1 constitute only minimal fraction of the opioids in the  
2 market. This has sent a loud and clear signal to other  
3 companies and to investors to think twice before  
4 investing in any novel opioid analgesics.

5           The progress in bringing the policies to third  
6 party payers who favor an immediate release schedule 2  
7 opioids over safer products such as ADFs have impacted  
8 the potential for these products and make any impact  
9 with respect to the products. This includes the VA  
10 whose policies continue to discourage the use of these  
11 products because they are more expensive than the over-  
12 the-counter -- I'm sorry, the generic IR opioids. And  
13 this is counter to the FDA's efforts to transform the  
14 market to a safer environment.

15           The VA is likely to correct its claim that  
16 abuse rates were, actually in their population, low,  
17 and, again we know that the abuse is just foundations  
18 and specifications, are being well monitored. It is  
19 the diversion of these drugs which is the material  
20 aspects of society.

21           Even for morphine schedule 3 partial agonist  
22 with a lower risk for -- more risk for, I guess, for

1 depression, is only allowed by unique payers to be  
2 prescribed after a patient has filled two schedule 2  
3 drugs. And I don't know what that means to pay along  
4 those. But you can even get a schedule 3, safer  
5 compound at the service and that was mentioned in the -  
6 - this morning.

7           Due to these challenges, with regard to the  
8 access even with expedited review, there remains a  
9 substantial disincentive for companies to develop safer  
10 opioid products. I spent the last few years of my time  
11 in Grunenthal in section evaluation. I was involved in  
12 assessing the newest analgesics, which are novel  
13 opioids, and that any associates, as I mentioned,  
14 continue to work with and advise more companies and  
15 pharma companies are involved in this space.

16           There's a lot of pharmacy signs out there for  
17 our understanding of the opioid system and how to  
18 better target these receptors and interact with them  
19 concerning most of (inaudible). The companies working  
20 in this space are struggling to find investors,  
21 development partners, and due to this -- it's all due  
22 to the constraints on market access.

1           Again, I look at countless assets and look  
2 better to have some benefits, and they were turned down  
3 usually before due diligence because it was due to  
4 market access. So, we all seen [sic] what's happened  
5 to the ADFs and differentiated opioids like Tapentadol,  
6 Buprenorphine and that's what's scaring away most of  
7 it.

8           So, to summarize what can the FDA do, number  
9 one, allow comparative data into product labels. I  
10 know this is what you think, but the FDA can't solve  
11 the opioid epidemic by itself, but it can play an  
12 important role, in regard to the abusive prescription  
13 products and making sure that safer and better products  
14 get to the market that allow that relevant comparative  
15 data gets into the labels so that prescribers and  
16 payers can recognize the differentiation from  
17 (inaudible).

18           Work with DHHS and VA and third-party payers  
19 to encourage prescribing products for, which clinical  
20 studies and increasing billboard advertisement, suggest  
21 progress for abuse and overdose.

22           And lastly, work closely with other relevant

1 federal agencies to provide white papers that elucidate  
2 the issues and prescribe which -- what federal agencies  
3 can and cannot do, so there is better understanding and  
4 continue to encourage sponsors to develop applications  
5 and so forth. Thank you very much.

6 DR. THROCKMORTON: Thank you very much. Any  
7 questions from the panel? Thank you very much. Next  
8 speaker is Dr. Chris Storgard from Heron Therapeutics.

9 OPIOID-SPARING INDICATION, A PRE-APPROVAL  
10 INCENTIVE FOR NEW THERAPEUTICS TO  
11 TREAT ACUTE PAIN

12 DR. STORGARD: Good afternoon. Thank you for  
13 the opportunity to participate in this very important  
14 meeting. My name is Chris Storgard. I am the Senior  
15 Vice President of Clinical Development with Heron  
16 Therapeutics. I will be discussing pre-approval  
17 incentives for non-opioid acute pain treatments.

18 To encourage drug development in important  
19 public health areas there are existing incentives that  
20 should also be applied to encourage the development of  
21 non-opioid acute pain treatments. These include  
22 automatic fast track and priority review designations,



1 extension of patent exclusivity, and the granting of a  
2 priority review voucher. As these require legislative  
3 action, they would likely take time to implement. To  
4 address the opioid crisis facing our nation today,  
5 immediate action is also needed.

6           The pre-approval incentive we propose could be  
7 implemented now. This is for FDA to provide a clear  
8 development pathway to obtain an opioid-sparing  
9 indication for new, non-opioid pain, acute pain  
10 treatments. This could be implemented now because it  
11 is aligned with current regulations. The indications  
12 and usage section recognize that a manifestation of a  
13 recognized disease or condition is appropriate for an  
14 indication. The requirement for opioids is a serious  
15 manifestation of ineffective pain relief in the post-  
16 operative setting.

17           This is also aligned with current guidance  
18 that states applicant should consider whether other  
19 information, in addition to the disease or condition as  
20 warranted, be included. Opioid-sparing warrants  
21 inclusion because it will alert prescribers of what the  
22 product can do. It would immediately and unequivocally

1 inform prescribers that the product reduces or  
2 eliminates the need of opioids per FDA standards. This  
3 is important. It provides assurance for prescribers  
4 that they can reduce opioids without compromising pain  
5 control. This assurance is essential to impact opioid  
6 prescribing habits.

7           It also provides a clear differentiation  
8 between products based on solid evidence of opioid-  
9 sparing benefits. This benefits the patients, because  
10 when prescribers are better informed patients get  
11 better care. This is not about promotion. This is  
12 about how to best inform prescribers to help patients.  
13 Prescribers are much more aware of a product indication  
14 when they are updated in the clinical study section.  
15 And as I will demonstrate the information in the  
16 medical study section regarding opioid-sparing, maybe  
17 at a varying quality, and the relevance to prescribers  
18 is less clear. Including opioid-sparing in the  
19 indication is more likely to affect patient access and  
20 coverage. This directly impacts patients. If it's not  
21 on the hospital formulary, it is not covered by payers,  
22 patients don't have access to the treatment.

1           Last November at the advisory committee  
2 meeting on assessment of opioid-sparing outcomes in  
3 trials of acute pain, the FDA presented four products  
4 with relevant labels. All four products include  
5 mention of opioid-sparing information in the clinical  
6 study section. None have an indication statement  
7 referring to opioid-sparing. All four products  
8 included randomized, double-blind placebo-controlled  
9 trials however none included an active control. And  
10 with regards to opioid-sparing, results were not  
11 replicated for studies for non-statistically rigorous.

12           Here are the opioid-sparing statements from  
13 the clinical study section from three of the four  
14 products. The first two indicate clinical benefit has  
15 not been established or not demonstrated, and in the  
16 last the statement is actually included twice with the  
17 percent reduction in opioids. But there is no  
18 information on whether this reduction conferred any  
19 benefit. It's unclear how a prescriber should use this  
20 type of information in the clinical study section when  
21 treating patients.

22           But there are some potential challenges with

1 providing opioid-sparing indication, and they include:  
2 are there unintended consequences; what degree of  
3 opioid-sparing is needed; and can we generate the  
4 appropriate evidence in the confines of the clinical  
5 trial? We can address these challenges. But without a  
6 clear development path, it is uncertain if overcoming  
7 these challenges will result in the granting of an  
8 opioid-sparing indication.

9           At the November advisory meeting the FDA  
10 identified potential unintended consequences of opioid-  
11 sparing, such as what if a prescriber habits do change  
12 and there is decreased analgesic benefit, increased  
13 poly-pharmacy , or now a new analgesic with abuse  
14 liability? What if prescribing of opioids does not  
15 change and there are more leftover pills? And, what if  
16 the labeled opioid-sparing effect does not confer  
17 benefits in clinical practice? We believe these  
18 concerns can be mitigated. First, opioid-sparing must  
19 not compromise pain control.

20           In the acute, post-operative pain setting, the  
21 use of multi-modal analgesic regimens is already  
22 recommended and well-established, abuse liability

1 assessments are already required and in place.  
2 Leftover pills, this is where we believe an opioid-  
3 sparing indication could have the greatest impact,  
4 because an indication statement most effectively  
5 informs prescribers, and this can help change  
6 prescribing habits.

7           Lastly, we believe that the evidentiary rigor  
8 required to obtain an opioid-sparing indication means  
9 it should be as likely to confer benefits in practice  
10 as any other indication.

11           To what degree of opioid-sparing warrants an  
12 indication? This is important to define because it  
13 forms the basis of evidence generation and study  
14 design. There is agreement that the more opioids a  
15 patient consumes the more opioid-related adverse events  
16 they are likely to experience. However, there is no  
17 consensus on what degree of opioid reduction, in and of  
18 itself, is clinically meaningful.

19           The approach often proposed is to link opioid  
20 reduction to a reduction in the incidence of opioid-  
21 related adverse events. However, the impact of these  
22 events can be difficult to demonstrate for many

1 reasons. First measurement of these events is not  
2 standardized, nor validated. Most of the common  
3 adverse events from opioids can also result from  
4 surgery or anesthesia. And, most of the significant  
5 events are too infrequent to power a study of it all.

6           So, to overcome these challenges, we proposed  
7 post-operative opioid-free status as a clinically  
8 relevant endpoint for obtaining opioid-sparing  
9 indication. Opioid-free is an unequivocal, easily  
10 quantifiable, objective measure of opioid-sparing  
11 benefit. Opioid-free means no adverse events to  
12 opioid. Opioid-free means no risk of transitioning  
13 from acute to chronic opioid abuse. And importantly,  
14 opioid-free means no opioid discharge prescriptions, so  
15 there's no leftover pills to fuel the opioid epidemic.

16           The opioid-free endpoint is feasible to assess  
17 in clinical trials. As with all the efficacy  
18 endpoints, the definition must be pre-specified, but it  
19 may be different depending on the situation. The  
20 durability of the effect should be confirmed. And it  
21 should be compared to an active control, in order to be  
22 clinically relevant. And as I mentioned before, it

1 must demonstrate that opioid-free does not come, as a  
2 result of increased pain.

3           We believe that a pathway for inclusion of  
4 opioid-sparing in the indication statement will  
5 incentivize development of innovative non-opioid pain  
6 treatments. We believe this can be implemented now,  
7 because no modifications to the current FDA standards  
8 and requirements for granting an indication statement  
9 are needed. To warrant an opioid-sparing indication,  
10 the existing evidentiary standard statistical rigor  
11 should apply. We have proposed that opioid-free is a  
12 clinically meaningful endpoint, it's clinically  
13 feasible in clinical studies, and supports an opioid-  
14 sparing indication.

15           Providing a development path to obtain an  
16 opioid-sparing indication, will incentivize  
17 development. But more importantly, it will benefit  
18 prescribers. They will be more informed, and this will  
19 benefit patients and they can facilitate the needed  
20 change in opioid prescribing practice.

21           DR. THROCKMORTON: Gerald?

22           DR. PAN: So, if I understand your proposal

1 correctly, you would perform a clinical trial  
2 development program in a post-operative setting. In  
3 the point of your outcomes here, is they discharge  
4 opioid-free. How does this address the widespread  
5 outpatients of opioids for conditions where opioids  
6 might be needed for a longer period of time, or at  
7 different doses?

8 DR. STORGARD: So, this proposal is  
9 specifically for an acute pain treatment. So, it may  
10 not be applicable to the chronic pain situation, but  
11 even managing the acute situation is critical, because  
12 we do know that six percent of patients who get opioids  
13 in the acute setting become chronic users. When you  
14 take a look -- the number surges in the current year --  
15 that's about 2.5 million patients, and of that, nearly  
16 a hundred -- sorry, half a million become actually  
17 addicted. So, although six percent may seem small,  
18 given the number of surgeries, it's a very important  
19 sizable population, where this approach would actually  
20 have application.

21 DR. STEIN: Thank you for these thoughts.  
22 But, a question about criteria for opioid-sparing. So,



1 you've gone through a detailed presentation on sort of  
2 the opioid-free as criteria. Are there other criteria  
3 that you considered -- obviously there's been  
4 discussion of different approaches to decide, you know,  
5 opioid-sparing, and you didn't comment on some of the  
6 other types of approaches. So, for example as patients  
7 are discharged earlier from a trial, plus procedure,  
8 and might need -- still might need opioids at  
9 discharge. Are there other kinds of criteria that you  
10 would consider as relevant to reduction in the  
11 requirement for opioids even patients who were  
12 discharged on opioids?

13 DR. STORGARD: There are certainly other  
14 criteria to look at. The reason we're proposing  
15 opioid-free is that it's clear-cut. The challenge for  
16 some of these other criteria, as I mentioned, there are  
17 challenges in measuring them. The adverse events are  
18 often confounded just from the event itself. And when  
19 you look at simply percent reduction, well, what  
20 percent is meaningful? So, this is a very clear-cut  
21 endpoint. If you are not taking an opioid and there  
22 are settings, such as bunionectomy and herniorrhaphy,

1 or others where that should occur right after the  
2 surgery.

3 So, you could be measuring this inpatient, you  
4 can follow the outpatient. So, it's a very clear-cut  
5 endpoint that we believe has real applicability. There  
6 are other endpoints to consider, maybe challenging, and  
7 I think that may be contributing to why we haven't had  
8 that opioid-sparing indication today.

9 MS. SIPES: Thanks for your remarks. One  
10 quick question, getting back to sort of where that  
11 would be the degree to which an opioid-sparing  
12 indication would incentivize development, you also  
13 mentioned that inclusion of an opioid-sparing claim in  
14 the indication is very important for access and  
15 coverage on your presentation. How do you think -- can  
16 you walk through a little bit more on how you think --  
17 peers would react to inclusion of that opioid-sparing  
18 claim in the indication given the continued  
19 availability of other types of opioids?

20 DR. STORGARD: So, I can't speak for them, but  
21 I can only assume. And, I think that if we can offer  
22 payers the fact that this new medication has [been]

1 proven to allow patients to be mobile and free, either  
2 immediately, and long-term after the surgery, then  
3 we've seen the cost effects of opioids, 504 billion a  
4 year. So, I believe to be able to show definitely --  
5 this with the medication you can avoid opioids, six  
6 percent of those patients who get exposed in the  
7 operative setting become chronic users, there is an  
8 economic benefit. More importantly there is, actually,  
9 you know, the benefit to [the] individual patient and  
10 the benefit to society as well.

11 DR. THROCKMORTON: Thank you very much. Next  
12 speaker is Dr. David Hewitt from Karuna Therapeutics.

13 CONSIDERATIONS FOR ACCELERATING THE DEVELOPMENT  
14 OF NONOPIOID ANALGESICS

15 DR. HEWITT: Thank you very much for allowing  
16 me to speak today. I am just thinking -- get this  
17 stuff over there. So, I'm going to be talking a little  
18 bit about some considerations for accelerating the  
19 development of non-opioid analgesics. Let me know if  
20 you can't hear me -- this may not be working always  
21 that well.

22 So, we talked earlier about what some barriers

1 are to the development of novel analgesics. Now, I  
2 just thought I'd go over some of my favorites. One is  
3 it's a very highly genericized market, pain is. And I  
4 say this from being both inside big pharma, and also  
5 have been in a -- you know, being at a CRO, I've gone  
6 to see some of these statements. Opioids are  
7 inexpensive and, as we saw, there are a lot of opioids  
8 that are generic. The benefit-risk of novel analgesic  
9 therapies is something that really hasn't been  
10 discussed that much. I think there is guidance when we  
11 talk about the benefit-risk of opioids, but non-opioids  
12 are more problematic.

13           It's not clear where that standard would be  
14 relevant to the opioids, or it really had more of a  
15 discussion of the benefit-risk posed to individuals and  
16 the society overall. Or one could ask oneself is  
17 whether we could have a side-effect profile, a benefit-  
18 risk profile of a non-opioid analgesic that would be  
19 similar to an anti-psychotic or an anti-convulsive.  
20 And, I think that's a debate that we can have. I'm not  
21 sure how much baggage for the benefit-risk would look,  
22 compared to those.

1           Another barrier was the current non-opioids  
2 and antacids work really well for a large number of  
3 people. And, a lot of companies actually don't always  
4 perceive, and on that need, I didn't recently look at  
5 the top 50 companies, just now, that are looking at  
6 drugs for analgesia, not a lot out there so. And,  
7 obviously that is one of the perceptions.

8           Interestingly, pain is a target obviously for  
9 both proven and unproven alternative medicine  
10 approaches, there's also a large number of medications  
11 that are OTC, as you're aware, and that cannabinoids  
12 are now becoming more used commonly. They have the  
13 benefit of -- working on both the sensory  
14 discriminative point of pain, which is what most of our  
15 drug approvals are based on, but it probably also works  
16 on the sensory effect component of pain which we really  
17 don't have great measures, which we could talk about  
18 later.

19           There is a -- there are a large number of pain  
20 indications which is a good thing because it helps you  
21 differentiate your drug. But also, if you want to get  
22 a joint pain indication, it's a lot of work. It's a

1 lot of work and it may be a bit of disincentive. So,  
2 I'm not saying we shouldn't have them the way they are  
3 right now, but I do think we should think about why we  
4 need such a large number.

5           And, of course, every time you have a negative  
6 study in pain, it's the same as a negative study in CNS  
7 or depression. Negative studies are uncommon because  
8 of the high placebo effect. And so, we're always sort  
9 of dealing with that big issue. And, then there is the  
10 question of predictive value of pre-clinical models. I  
11 like preclinical models, but a lot of people are  
12 calling to question their value. And I can tell you  
13 that for large -- a number of pharmaceutical companies  
14 -- it's become a big issue.

15           There's also the value of translation on  
16 medicine approaches, which I think are also very  
17 valuable. They could be very useful, but they're  
18 really not available to -- they may not be good for  
19 making 'go,' 'no-go' decisions in terms of further  
20 development. They may be good at making 'go,' 'go  
21 slow' or 'go gung-ho', but they're not very good at  
22 making, you know, the decision to actually drop a

1 study, or not.

2           So, I wanted to just talk about a few things  
3 we might be able to consider to speed up development of  
4 novel, non-opioid analgesics. One is we should  
5 consider enhancing use of existing accelerated  
6 development programs, frugal pathways, including  
7 breakthrough status, which have been discussed already,  
8 and streamline the development requirements for novel,  
9 non-opioid analgesics. Sometimes, it feels like, you  
10 know, that it's got a bit of a high bar. We should  
11 designate priority review. I think this also have been  
12 discussed for NDAs of non- novel, non-opioid  
13 analgesics. We should focus more FDA resources to work  
14 with industry to develop additional accelerated  
15 developmental approval pathways. Being part of this  
16 would be coming up with better endpoints scales. We  
17 don't have great scales for pain. They are still  
18 basically 0 to 10 scales, with the assumption that pain  
19 is luminal (ph) we know it's probably logarithmic, like  
20 taste is and hearing, and our other sensory inputs.  
21 So, I don't think our instruments really are completely  
22 valid to represent the pain experience.

1           We should develop new pre-approval incentives  
2 to provide accelerated development with more limited  
3 pre-approval study packages, and a great dependence on  
4 host proven studies, including real world evidence. I  
5 think this is a very hot area. We should be thinking  
6 about double-blind placebo control studies that give  
7 you certain amount of information, but they don't  
8 really paint the whole picture. There should be a  
9 consideration for additional incentives to target  
10 indications, specific indications, as well as the at-  
11 risk populations or susceptible populations. Ideally,  
12 it would be great if we had a biomarker and we could  
13 say that this biomarker they're going to -- this person  
14 is going to have addiction problems, or they are not  
15 going to have addiction problems. But, we don't have  
16 that right now, but we may in the future.

17           But there are target populations we should be  
18 considered about. When a soldier comes back from war,  
19 and they've got significant traumatic pain, and there's  
20 a little bit of PTSD associated with that as well, we  
21 should be targeting our therapies to that important  
22 population, because they're going to be living with



1 that pain for a very long time, and putting them on an  
2 opioid for significant amount of time could be  
3 problematic, as well for reasons, we could discuss that  
4 many people know. Again, I think we need to ensure the  
5 appropriate benefit-risk assessment relative to  
6 opioids. This is at the top debate we have, and as I  
7 mentioned before, limiting the number of trials  
8 required for a lot of pain indication.

9           We talked previously about wanting to look in  
10 a number of different populations, and certainly, we  
11 should, but I also think that sometimes it seems like  
12 maybe too many populations. I mean, for example, we  
13 could argue a low back pain is not different from  
14 osteoarthritis, since a lot of low back pain is  
15 osteoarthritis, for example. So, one, I mentioned one  
16 potential -- I'm going to be mentioning a couple of  
17 indications I think are really more for debate and  
18 discussion than something to be just stressed too  
19 strongly, but I think they're valuable to think about.  
20 One is the indication for sub-acute pain.

21           We kind of touched on that previously, but  
22 this will be potential treatment of pain lasting three

1 months or less, but we could talk about this and more,  
2 maybe it'll be plus or minus. And, it should recognize  
3 that many pain syndromes are limited in duration. Now  
4 as many of -- some of you may know, I actually did a  
5 pain fellowship, and one of the things I was talking in  
6 my pain fellowship is that chronic pain is a disease,  
7 and it is a disease. But, it's not always a disease,  
8 and that's an important thing to figure out. You don't  
9 always know when it is chronic disease and when it's  
10 not a chronic disease. So maybe, having a sub-acute  
11 pain indication will help us start to think more  
12 intelligently about that.

13           Also, if an opioid or a drug doesn't work  
14 forever -- you know chemotherapy doesn't work forever.  
15 Lots of drugs may not work forever. You've got to stop  
16 antidepressants. It's good you re-examine whether your  
17 drug is working or not. And so, a sub-acute indication  
18 will help you do that. So, we would encourage a re-  
19 assessment of the pain syndrome, the condition the  
20 disease causing the pain, and some of the underlying  
21 psycho-social factors that might be driving the pain,  
22 and really reconsider the development of the plan.

1 And, of course, one of the biggest questions is, is  
2 this pain medication helping you or is it not helping  
3 you. And one of the things -- I used to be a pain  
4 doctor at Emory, so I saw quite a few pain patients.

5           And sometimes, the only way to know whether  
6 the pain medication is working or not, is to actually  
7 ask the spouse or ask a friend because you don't always  
8 get the whole story. You know, you got to treat a  
9 whole family, and its part of the bond cycle of social  
10 model, which I'm not sure where that stands these days  
11 in medical education, but it's very valuable. And we  
12 would encourage development of therapies that would  
13 block the chrornification of pain.

14           You know this is a big issue is why in that  
15 post-operative, some people think 15 percent of pain  
16 becomes chronic. Post-operatively for herniorrhaphy,  
17 we don't understand why, we just need to understand  
18 this better and one could imagine developing new  
19 analgesics that break and prevent the chronification of  
20 pain, you know. Pain may be chronic, may be a disease  
21 but that -- but like all diseases that doesn't stop us  
22 from thinking about how we might cure it. Stop?

1           I also want to talk a little bit about  
2 increasing the duration of accessibility. This has  
3 been hit on before, so I'm going to give you my angle  
4 on it. I think we should provide an additional period  
5 of market exclusivity, that is patent extension for the  
6 development of these novel, non-addicting therapies.  
7 And this includes compounds that analgesics is a  
8 potential, but of lost composition of matter patent  
9 protection that would provide sufficient period of  
10 marketing exclusivity to incentive development.

11           One of the things many people from this may  
12 know is that with all the mergers of all these big  
13 pharmaceutical companies, there are a lot of drugs in  
14 the walls sitting on the shelves that could be  
15 developed but haven't been developed. And, they could  
16 be pulled and utilized, if there was an incentive. And  
17 that incentive would be, you know, some exclusivity  
18 associated with it.

19           We could facilitate the development of  
20 compound currently, as I said, sitting on these shelves  
21 and some of those were stopped not for any of the --  
22 any safety reasons, but because of priority. In big

1 pharma you got this thing called PTRS, which I could  
2 explain later. But it helps you decide incremental  
3 fractions between what drugs you decide to develop and  
4 what drug you do not decide to develop. So, there are  
5 some drugs that just didn't make the cut.

6           There are compounds that were initially being  
7 developed for the treatment of pain, but they were not  
8 being used for the treatment for -- developed for pain  
9 -- but those mechanisms are now seen as potential  
10 analgesics. And we can talk about that as well. And,  
11 in there are compounds that are known to be analgesic,  
12 but they have never been approved for the treatment of  
13 pain. And, those include some of my favorite drugs  
14 like Ativan Nortriptyline, the tricyclic  
15 antidepressants, as well as some of the anti-epileptic  
16 drugs anticonvulsives, which you know, obviously, some  
17 had been approved for certain pain issues, but there  
18 are others that could be interrogated.

19           Another indication I want to mention is --  
20 actually was just discussed, was the opioid-sparing for  
21 acute and chronic pain. I think this is a fascinating  
22 issue. I will add my two cents into it and you could

1 imagine the development of a lot of comments to really  
2 limit the risk of opioid therapy. Now, we're talking  
3 chronically, I guess he was talking acute, there is so  
4 much chronically that, if we could limit the amount of  
5 opioid therapy, it would be great. We could recognize  
6 that limiting the dose of an opioid, either acutely or  
7 chronically, it could have value. I think that was  
8 discussed. And, we could just advance the development  
9 of targets. And, they're maintaining analgesic effect  
10 of opioid for a long period of time.

11           As many of you know, or some of you know, that  
12 when you give an opioid, about six months later, people  
13 have, in general, increased their opioid dose by about  
14 30 percent. This was a study actually brought to the  
15 economy many, many years ago. But, the other thing  
16 that this could do is enable the tapering or  
17 discontinuation of opioids chronically. And, of  
18 course, the cynic here would say, well, any analgesic,  
19 that's a good analgesic, has the potential to decrease  
20 the analgesic that's not working. And, that's true.  
21 But, I do think there is the opportunity to start  
22 thinking in these novel ways that could help us.

1           So, in conclusion, you know, opioids have been  
2 around since the Neolithic age, it's over 7,000 years.  
3 And, it's worth thinking about that. They've been  
4 around a very, very long time. The ancient Sumerians  
5 basically recognized both the euphoric as well as the  
6 analgesic capacity of these drugs. And clearly, we  
7 need better analgesics right now that are non-  
8 addicting, and do not have death as a side effect.

9           I've discussed some of the challenges to the  
10 development of non-opioid analgesics, and I've touched  
11 on, and I think we have further discussions on the  
12 incentives and some of the creative thinking that we  
13 need to develop novel non-addicting therapies moving  
14 forward. So that concludes my talk. And thank you for  
15 your time. And I'll take any questions.

16           DR. THROCKMORTON: Thank you very much.  
17 Questions?

18           MS. SIPES: Thanks for your comments. Going  
19 back to your, I think your first slide, or second, I  
20 was wondering if you could talk a little more -- you  
21 did talk about this a little bit, but I was wondering  
22 if you could address a little bit further, your comment

1 about benefit-risk profile for novel analgesics as a  
2 potential barrier, and how you would see that working  
3 differently or what you think would need to occur in  
4 that space?

5 DR. HEWITT: Yeah. Well let me give you a  
6 couple of examples. I should tell you that a part of  
7 what Karuna Therapeutics does, we're creating a new  
8 anti-novel anti-psychotic. So even though I'm just a  
9 neurologist and have been spending most of my time with  
10 pain, I've learned a little bit about anti-psychotics,  
11 and they have a lot of adverse effects associated with  
12 them, including diabetes.

13 So, I mean, I think the questions -- and I  
14 don't know the answer to this -- I'm not presuming to  
15 say that we should have a side effect profile similar  
16 to diabetes. But, there is certainly, one could say,  
17 that that might be something that we -- that should be  
18 in the debate. And, I think one of the things I'm  
19 always worried about, particularly in drug development,  
20 when you're in the big pharma suite, is they're all but  
21 asking for the impossible. They're asking for a drug  
22 that's really effective, as effective as an opioid, but



1 with the side effect profile of a placebo. You know,  
2 that's a huge problem. Of course, placebos have very  
3 high side-effect profiles. They usually don't cite  
4 this too, but that's another story. But that's sort of  
5 what I'm thinking.

6           And, then the other thing I'm thinking about,  
7 frankly is, is that there are drugs, I won't mention  
8 any, that have been approved for analgesia for OA in  
9 Europe that weren't approved in the United States,  
10 because the side effect profile was considered  
11 unacceptable. I don't think it'd be appropriate for me  
12 to now mention a name of a drug or something you might  
13 know what I'm talking about all that. So, that would  
14 be an example of that, is that maybe we should look  
15 back and see whether the bar was too high. You know,  
16 at the same time, people might argue that the bar was  
17 low for proving opioids and there are congressional  
18 legal reasons why the FDA approves opioids, I totally  
19 understand that. I don't disagree. There is also a  
20 feeling that there may be a too high bar for  
21 nonopioids. And, we need to go back for this profile.

22           DR. HAI: So, the question on Slide 3, where

1 you mentioned limiting number of trials required for  
2 broader pain indications and limiting pre-approval  
3 study package for novel non-opioid therapies, I'd like  
4 to hear your thoughts in terms of the context of what  
5 we require for substantiating its effectiveness. Are  
6 you looking to other sources of data than typically two  
7 studies? What are you suggesting there?

8 DR. HEWITT: Well, you know, obviously, I'm  
9 referring basically to the pain guidelines that we've  
10 just withdrawn. And the idea, I won't go through all  
11 of it. But you know, need two indications and painful  
12 diabetic neuropathy plus or minus PHN, and you can see  
13 that it becomes a whole list. Meaning for a general  
14 pain indication, it's something like 12 studies or 13  
15 studies. Is that seven? I'm lost there. I mean it's  
16 a lot. So, I think, there's -- so there are two ways  
17 to solve that problem. One is you could do a study of  
18 syndromes that are very similar.

19 For instance, I did a study of -- a proof of  
20 concept study using individual and randomized  
21 withdrawal design, using Craig Avalon (ph) as a proof  
22 to -- to use that model for proof of concept studies.

1 And I use a basket of different proof of neuropathic  
2 pain syndrome. So, the question was, you know, is  
3 diabetic neuropathy small fiber, idiopathic and PHN?

4           And so, one could imagine, you could look at  
5 them all in one particular and large study, you could  
6 create it as just a mesh (ph) or you could actually  
7 create it as a basket study as well and develop studies  
8 that way. And then you wouldn't necessarily have to do  
9 so many studies, but you could cover your bases. I  
10 think somebody actually mentioned this in terms of we  
11 should study more. So that would be one thing. I'm  
12 not sure the pathophysiology of some of these pains are  
13 that different. One argued in the past that the  
14 underlying pathophysiology of the pain syndrome may not  
15 be related to conditions associated with that pain  
16 syndrome.

17           So, the hyper allergies and the allodynia, for  
18 example associated with certain neuropathic pain is  
19 certainly part of other -- it's not just related to  
20 diabetic neuropathy or postherpetic neuralgia, it's  
21 like there are other neuropathic pain conditions, as  
22 well, including phantom limb pain. And I should have

1 thrown that in there as well. That's a pain that I  
2 think it's completely under-treated. I kind of alluded  
3 to it when I was talking about traumatic injury in  
4 soldiers. But that's what I was thinking about in  
5 part. You still need to have large studies and you  
6 need to have substantial evidence in placebo-controlled  
7 studies. But, I do think, you know, these real-world  
8 evidence studies can be very useful to supplement those  
9 at the end as well. And you know, the risk of being  
10 wrong that would get it is lower. It is less  
11 problematic if you're putting drugs that don't kill  
12 you, and don't make you addicted. And so, I think  
13 there's a reason to think that it's -- you can be wrong  
14 and approve drugs, and maybe they won't, over time, be  
15 an effective cross over all conditions. But you can do  
16 those studies post-hoc and then see them. I think a  
17 lot of this also has to do with sort of the education  
18 of physicians, as well and their ability to really  
19 interpret the data that they're seeing.

20           And I think one of those problematic things we  
21 had out there we don't talk about is really physicians'  
22 ability to look at the data and not just the label, the

1 data for all my decisions.

2 DR. THROCKMORTON: Thank you very much. And  
3 next speaker is Dr. Beatrice Setnik from Altasciences.

4 ABUSE DETERRENCE AND OTHER NOVEL APPROACHES TO  
5 ADDRESS THE PRESCRIPTION OPIOID EPIDEMIC

6 DR. SETNIK: I'd like to thank the Agency for  
7 giving me the opportunity to speak today. I wanted to  
8 address some of the abuse deterrence and other  
9 approaches to address the prescription opioid epidemic.

10 As a disclosure, I am a full-time employee at  
11 Altasciences and I do consult with various  
12 pharmaceutical and biotech companies. And the opinions  
13 that I express today are solely my own.

14 So, the status quo we've been talking about  
15 the opioid epidemic in 2017, the NSD wage report and,  
16 again, 11.4 million people misused opioids. And pain  
17 reliever misuse primarily was for the reasons of really  
18 being in physical pain, followed by the feelings, of  
19 course, of feeling good and high. And about half of  
20 the respondents in the survey did report that they  
21 obtained the last pain reliever they misused from a  
22 friend or relative. And this has been fairly

1 consistent over the years with NSDUH, with diversion  
2 from friends and family as being one of the primary  
3 sources of opioids.

4           The approach to the prescription of opioids,  
5 and I applaud the FDA for coming up with the benefit-  
6 risk assessment. However, not addressing currently  
7 approved and marketed opioids is not going to change  
8 the needle from the statistics we see today and will  
9 continue in that fashion until we decide to do  
10 something with the currently marketed opioids. So, in  
11 as much as a risk-benefit analysis as the dire need for  
12 approvals of opioids and analgesics, it also needs to  
13 be implemented in the assessment of the currently  
14 approved and marketed opioids.

15           And the status quo, as we've been hearing from  
16 all the speakers today, we have a market that is  
17 flooded with inexpensive, generic opioids. And, those  
18 are the go-to because they are economically priced and  
19 accessible for patients and make an economical choice  
20 for the treatment of pain in a cost-effective manner.  
21 As long as we have this conundrum, we're not going to  
22 be able to shift the needle in terms of where

1 prescription opioids are concerned.

2           The many marketed opioids don't have any types  
3 of features that will prevent problematic use or use by  
4 unintended relative administration that causes more  
5 societal consequences. And we do have now, since the  
6 onset of abusive trends and other types of approaches,  
7 some studies that have been showing evidence that these  
8 formulations can impact certain aspects of safety,  
9 including abuse and fatalities.

10           And of course, the ongoing studies are  
11 required to continue determining the effectiveness of  
12 different types of approaches of abuse deterrents,  
13 where the risk ratio, benefit ratio may be improved, in  
14 terms of reducing some of the risks associated with  
15 opioid abuse. I think one of the problems and we've  
16 spoken, and it's been alluded to today, is also the  
17 market penetration and signal of these types of  
18 studies. In order to prove abuse deterrence, one needs  
19 to collect data. Without a sufficient market  
20 penetration, it becomes very difficult to identify and  
21 follow and track signals in the real world to determine  
22 whether these types of approaches are effective in the

1 real world.

2           And as much as we have a clear path for  
3 approving abuse deterrent or other types of innovative  
4 technologies that allow for a more, a better risk-  
5 benefit ratio, the data that's collected for approval  
6 is not the same data to compel insurers and payers to  
7 bring these types of drugs on to formularies. And,  
8 until we change the fact that the funneling and the  
9 representation of the opioids that are currently  
10 marketed are very much in the hands of the payers,  
11 because they ultimately will decide what the patients  
12 will receive. And that will always be based on an  
13 economical choice, rather than for the benefit of  
14 society.

15           And, until we can force the hand to allow  
16 safer opioids or analgesics or non-opioid analgesics  
17 onto the market that have an improved risk-benefit, we  
18 are always going to be stuck with the fact that the  
19 economical choice will over power the societal benefit  
20 and what should be the right choice for society and for  
21 the pain patients.

22           Now we know that opioids are the most potent



1 class of pain relievers. So, until we have the onset  
2 of non-opioids that are as effective and as potent, we  
3 will always have this problem. A moratorium on  
4 removing all opioid approvals will simply block  
5 innovation and will prevent other analgesics that have  
6 a more favorable risk-benefit profile to coming on the  
7 market.

8           So, it simply doesn't address today's issue.  
9 And it blocks potential solutions to improving the  
10 problem with prescription opioid abuse. So, this is a  
11 problematic solution I think we need to be more  
12 creative than that.

13           The idea of opioid-sparing has been brought up  
14 today. And, I think we do need a very good definition  
15 of opioid-sparing. I think the ideal would be to be  
16 opioid free. However, that's not always a reality.  
17 The other approaches to opioid-sparing can be the  
18 switch from a more potent opioid to a lesser potent  
19 opioid, a reduction in dose, a shorter duration of  
20 opioid use, or a movement from a higher schedule to a  
21 lower schedule, or to an unscheduled non-opioid  
22 analgesic. I think all of those can be representative

1 of opioid-sparing and could have benefits to the  
2 patient.

3           And, there have been very good incentives and  
4 programs to implement supplement medical education,  
5 reducing the amounts of refills and durations for acute  
6 pain. The provision of non-opioid interventions, I  
7 think, are also very important. And, our earlier  
8 speakers had alluded to other things like acupuncture  
9 or other modalities that could also enhance opioid-  
10 sparing.

11           The risk reduction, mandating, I think in the  
12 end, if you want to solve the problem, there does need  
13 to be the risk-benefit applied to approve new approved  
14 opioids as well as marketed approved opioids. And  
15 there needs to be some mechanism of taking out the  
16 opioids that have a high-risk profile off the market  
17 and allows you to collect data and to make those  
18 decisions, faster response times, and continuous data  
19 to collect to determine which opioid should be removed.  
20 For example, like the OPANA example, where that was  
21 taken off the market because of identified signals of  
22 safety. Those types of actions need to be taken. But

1 the flood of generics that don't have any safety  
2 features, those need to be seriously considered with  
3 replacement of opioids that may have an improved safety  
4 benefit, safety risk profile.

5           The other issue is also the data collection,  
6 or the metrics. And these do have to be collected by  
7 the brand, if you're simply collecting information,  
8 and, I realized there are difficulties in sometimes  
9 understanding what type of drug was given in certain  
10 situations and poisonings, and this type of thing. But  
11 if you want to determine if a safety feature of an  
12 analgesic is effective, you need to be able to follow  
13 the data by brand.

14           And, I think, Dr. Dart alluded to the  
15 solution, there can be a solution perhaps. And maybe  
16 we make pills a little bit more recognizable, some  
17 features, so that when we have surveys or reports of  
18 overdose, or other incidents, that there may be a more  
19 reliable recall of what that patient had taken at the  
20 time, so that you can identify the brand and the type  
21 of opioid taken.

22           So, the economics play a big part of it.

1 Novel formulations are more expensive. With the  
2 replacement of safer types of analgesics, there does  
3 have to be that consideration of the cost to the  
4 patient. And, I think, if there is ultimately a  
5 replacement of safer opioids, that part of that  
6 incentive will be a larger market share. However,  
7 there does need to be consideration, careful  
8 consideration, of cost, particularly because generics  
9 would have offered cheaper alternatives.

10           The managed care formularies as I mentioned,  
11 they do pose barriers. I think they pose barriers, not  
12 only to the accessibility of safer analgesics, because  
13 of the economic choices that are made for the payers,  
14 but also, a lot of the time, there's an impediment to  
15 get going? other opioid-sparing therapies, acupuncture,  
16 all types of other things that may be effective for an  
17 individual patient level. But, increasing coverage for  
18 other opportunities to treat pain are just as important  
19 as having analgesics that are safer.

20           And lastly, I think there are a lot of  
21 opportunities for research grants and funds. However,  
22 given the extent of this crisis, having more available

1 funding for research in innovation, and ongoing  
2 research for both pharmaceutical and non-pharmaceutical  
3 interventions of pain, I think, would be very helpful  
4 as well. And that is all I had. Thank you.

5 DR. THROCKMORTON: Thank you very much.  
6 Questions for the panelists? Thank you. That brings  
7 us to our break. I believe Meredith is spot on time.  
8 So, we'll reconvene in 15 minutes at 2:45 for the open  
9 public hearing. Thank you.

10 BREAK

11 (Recess)

12 OPEN PUBLIC HEARING

13 DR. THROCKMORTON: Speakers. And I'm going to  
14 call them just to come up in order and give their  
15 remarks. The first individual is Dr. Lih Young.

16 MS. YOUNG: Good afternoon. My name is Lih  
17 Young. I think I repeat everywhere to comment on the  
18 social issues. This is one of them. And my name is  
19 Lih Young, and I'm a Ph.D. in economics by training.  
20 I'm a genuine reformer advocate, activist. I've been  
21 in a TV program, speakers, producers, including series  
22 shifted times (ph), freedom times (ph) and it's about

1 100 episodes. Each in one hour per episode.

2           And I have run for public offices since '94  
3 from local to federal, including the U.S. Senate, U.S.  
4 Congress, both several times, and Maryland state  
5 Comptroller. And, I run as Senate Rockville city  
6 mayor. And as I said, I'm concerned about social  
7 issues very much, including in government function.

8           I have been so far, for several decades, I  
9 think our civil rights are practically, are totally  
10 ignored, or you should say, violated from local to  
11 global. I think you can see how USA intel the global-  
12 wide issues our system is rigged, the election is  
13 rigged.

14           So, I think the most urgent issue we have  
15 problem here and overseas is what I call robber-ism  
16 [sic] though you can put several words linked together  
17 with a hyphen: Official-misconduct, government-gain,  
18 abuse-murder, fraud, crime, injustice in world  
19 operation. This means, including three branches, from  
20 local to federal, and again to global, and whether at  
21 judicial level or in the administrative level is  
22 basically is "big-guy" propoganda to benefit and

1 promote them self and victimize others.

2           It's not just black or brown, it's elderly,  
3 it's young and means, and old, and you can see whether  
4 it's a grandma or just baby, granddaughters, it's all  
5 the same treated, they are victims.

6           So, what we always heard is that capitalism is  
7 justice and freedom and fairness democracy, as we were  
8 told, and I don't think so. So, this system is  
9 continuing, ongoing, and spending penetrating every  
10 segment of our life, including civic, nonprofit, women  
11 or minority or churches, nonsense studies proposals,  
12 World Bank think tank, education institutions, and  
13 including the public-private partnership. This has  
14 been propagandized like a new fashion without  
15 addressing the important issues, whether they should be  
16 medically necessary or serious cost-benefit analysis.

17           PPP have been related to extreme serious war  
18 and crime, abuse of power and resources. Again, just  
19 like that, robber-ism and are causing social issues,  
20 including in the Rockville Town Center, which is  
21 basically 100 percent by the taxpayers and output is  
22 100 percent private owned. So, you called that as a

1 public-private partnership. That is total misleading.  
2 It's just the opposite, and its relation not owner  
3 victimized individual, it's not just one project only.

4           Basically, they use abuse of power, victims  
5 are everywhere, and every people, every victim is every  
6 possible way you can think of. And it's just the same  
7 with -- if you have been to the Rockville city project.  
8 And you can see and this morning we just heard in the  
9 National Academy of Science engineering medicine, they  
10 conspire with police, with 11 attorneys, conspires  
11 together with all kind of fraudulent criminal  
12 operation. So, you just keep them out of our society  
13 and serious problem. And so, we must turn this around.  
14 Otherwise every one of you will be victimized.

15           For I think the most important issue is that  
16 they will victimize it -- if you've heard the data  
17 itself is really underestimated because all the  
18 institution, their data are force, including they see  
19 your personal medical record, they don't even give you  
20 the medication, or they give you awkward medication.  
21 So, in a way --

22           DR. THROCKMORTON: Dr. Young, could you finish



1 your comments, please?

2 MS. YOUNG: Huh.

3 DR. THROCKMORTON: Could you finish your  
4 comments please?

5 MS. YOUNG: Sorry. Okay. I think my time is  
6 almost up. I'm sorry. I've submitted a written  
7 statement. And it's a lot of files and attachments,  
8 and they've all been together. And I have put them  
9 everywhere and I hope it works this time. And so, I  
10 ask to read every word, because every word is very  
11 condensed with behind these serious stories. So, I  
12 will submit the written statements. Thank you very  
13 much.

14 DR. THROCKMORTON: Thank you very much. Our  
15 next speaker is Mrs. Carrie Wentworth. Mrs. Wentworth?  
16 The next speaker is Ms. Carrie Barnhart.

17 MS. BARNHARDT: My name is Carrie Barnhardt.  
18 Thank you for allowing the stakeholder meeting and  
19 allowing me to speak. I hold a master's degree in  
20 leadership renewal and change and I'm the founder of  
21 Pain Advocate Warriors in the state of Virginia, co-  
22 leader for Don't Punish Pain Rally, and a member of the

1 American Pain and Disability Foundation. And I'm an  
2 ally with the US Pain Foundation.

3 I've been a science teacher and I've worked  
4 for three pharma companies in quality assurance before  
5 I became fully incapable of working. I'm a chronic  
6 pain patient, volunteer lobbyist, a pain advocate, and  
7 listen to suicidal pain patients. I am a great mom of  
8 a team that also has the same conditions I do,  
9 including the pain. None of my diseases have cures,  
10 most don't have any treatment. I'll spare you the  
11 details and diagnosis and only speak about one here.  
12 I'm dependent on pain medication.

13 And the pain level, pain index is much better  
14 than the 0 to 10, and I live between 36 to 40 daily ,  
15 which is about 7 or 8 on the old scale. When patients  
16 living in this agony hear the words opioid epidemic or  
17 opioid crisis, we're triggered. Yes, a medical PTSD  
18 triggered. Medical abandonment, medical harassment,  
19 profiling by pharmacies, laws, with doctors, extremely  
20 questioned about why we need these meds. Harassed by  
21 the general public, family, friends, as you know, the  
22 stigma of opioids follows everywhere.

1           Have you tried this? Have you done yoga? I  
2 shall pray for you. Have you changed your diet? It's  
3 in your head. Here's an antidepressant. So, Six  
4 percent become chronic users, like myself [sic]. Why  
5 are 94 percent denied pain relief, denied the rest,  
6 denied quality of life when they need pain meds  
7 stronger than NSAIDs and ibuprofen? Sixty percent of  
8 veteran suicides, about 22 a day, are due to un-  
9 treatment, or under-treated physical pain. Only 0.6  
10 percent of anyone that has been over-prescribed an  
11 opioid become addicts. There's a difference between  
12 being dependent and an addict. So why is it an  
13 epidemic?

14           Too many chronic pain patients are denied pain  
15 medication, at the discretion of insurance companies  
16 and state legislation, based on the 2016 CDC  
17 guidelines. State governments and every single  
18 insurance entity took the guidelines as gold and in-  
19 doored [sic] cancer patients and chronic pain patients,  
20 like myself.

21           Every month, there are patients fighting for  
22 their meds, they're fighting the MMEs. And, we're

1 fighting to also keep our vendors, too. We shouldn't  
2 have to choose between anxiety and mental health or our  
3 physical pain.

4 I was lucky to have a great pain management  
5 doctor. We had a great relationship. We worked  
6 together. And he even involved my family, which was  
7 really important. When I wasn't benefiting as much as  
8 I needed to anymore, he would increase or change my  
9 meds. Then I moved states. Now, I'm starting all  
10 over. And I've already been in the hospital seven  
11 nights out of the last two months because of pain.

12 Patients are dismissed from pain clinics  
13 because the DEA has intimidated the pain management  
14 doctors into no longer prescribing opioids. Too many  
15 pain docs are quickly closing doors or have been shut  
16 down by the DEA. We, pain patients, have too many  
17 agencies in our doctors' offices. We are deprived the  
18 very medication that keeps us out of bed, that keeps us  
19 functioning, and that keeps us constant -- from  
20 constantly thinking about ending our pain by ending our  
21 lives.

22 We instead are forced into other treatments

1 that have been proven to fail us. For example, steroid  
2 injections, these actually degrade many patient's  
3 connective tissues further with those that have rare  
4 diseases, like Ehlers-Danlos syndromes, like I have.  
5 EDS requires aggressive high dose pain therapy because,  
6 given the progressive centralized breakdown of  
7 connective tissue, patients developed intractable pain  
8 that leaves them unable to function.

9           So there needs to be this idea cemented in  
10 everyone's minds that pain management is not a one size  
11 fits all. I've had 28 surgeries so far, and not  
12 because my docs want to keep cutting me open or  
13 prescribing me more meds. My surgeries are simply to  
14 attempt to preserve what little ambulatory steps I have  
15 left. EDS requires me to have my meds, and I can't  
16 even get numbed at the dental office because I don't  
17 respond to Lidocaine.

18           So, it's not even just opioids. It's all  
19 medications. We pain patients acknowledge addiction  
20 and that battle that addicts go through. We, too,  
21 would like acknowledgement from the FDA and the CDC to  
22 get an understanding of our fight to live. We want the

1 World Health Organization to recognize an inherent  
2 right to live pain-free. We acknowledge that our pain  
3 meds do not eliminate our pain 100 percent. We deserve  
4 adequate access to appropriate pain management.

5           The WHO is fully committed to ensuring that  
6 children, as well as adults with severe pain, have  
7 access to effective pain control medication, including  
8 opioids, when needed. We hope to work with the FDA and  
9 CDC and develop a way to ensure that chronic pain  
10 patients get care that the addicts receive in their  
11 independent proper care.

12           Thank you for your time and I'll answer any  
13 questions you may have.

14   CONCLUDING REMARKS

15           DR. THROCKMORTON: Thank you very much. That  
16 ends the open public hearing session of this hearing.  
17 And, on behalf of the FDA panel, I'd like to thank all  
18 of the presenters and everyone in the audience, whether  
19 you've attended in person or by webcast, for  
20 participating in today's hearing.

21           On responding to the opioid crisis, while  
22 addressing the need for appropriate access to pain

1 management, remains a central focus of the FDA and the  
2 highest priority for us. We greatly appreciate your  
3 attention and your interest to this important topic and  
4 to today's presentations.

5 In addition, I'd like to recognize the FDA  
6 staff that participated in organizing the work, the  
7 meeting today, including the staff in the great room,  
8 the panel participants, and the many individuals within  
9 the Center who collaborated on this important hearing.

10 As a reminder, we strongly encourage you to  
11 submit docket comments by November 18, 2019. If you'd  
12 like details on how to do this, we have placed copies  
13 of the doc, the Federal Register notice in -- for this  
14 hearing -- at the registration table.

15 A transcript from the hearing shall be posted  
16 to the meeting website in approximately 30 days and we  
17 will provide copies of today's presentations on  
18 request. Please see the registration desk for that  
19 information.

20 And on that note, I am closing this public  
21 hearing. Thank you, very much, and safe travels.

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