



U.S. Food and Drug Administration

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1                   FOOD AND DRUG ADMINISTRATION  
2           CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)  
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6                   Joint Meeting of the Anesthetic and  
7   Life Support Drugs Advisory Committee (ALSDAC) &  
8                   Drug Safety and Risk Management  
9                   Advisory Committee (DSaRM)  
10  
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12                   FRIDAY, JULY 23, 2010  
13                   8:00 a.m. to 3:30 p.m.  
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18                   UMUC Conference Center at the Marriott  
19                   Adelphi, Maryland  
20  
21  
22

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3 Chief Executive and Secretary

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7 **Peter Vlasses, Pharm.D., D.Sc. (Hon.)**

8 Executive Director

9 Accreditation Council for Pharmacy Education

10 Chicago, Illinois

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12 **FDA MEETING PARTICIPANTS AT THE TABLE (NON-VOTING)**

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18 Director, Office of Surveillance and Epidemiology

19 CDER, FDA



1    **John Jenkins, M.D.**

2    Director, Office of New Drugs

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6    Director, Division of Anesthesia and

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11   Deputy Director for Regulatory Programs

12   CDER, FDA

## I N D E X

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P R O C E E D I N G S

(8:00 a.m.)

DR. KIRSCH: Good morning, everybody. Today is day 2 of the FDA and CDER Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee to discuss the issue of REMS. This meeting is now called to order.

For toxic topics as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take

1 place in the open forum of the meeting.

2 We are aware that members of the media are  
3 anxious to speak with the FDA about these proceedings.  
4 However, FDA will refrain from discussing the details  
5 of this meeting with the media until its conclusion.  
6 Also, the committee is reminded to please refrain from  
7 discussing the meeting topic during breaks or lunches.

8 Before we begin, I would like to remind the  
9 committee members that we are seeking your individual  
10 perspective on the issues that are under discussion,  
11 not the organizational perspective of any particular  
12 group or special interest. I'd also like to remind  
13 all individuals in the audience and members of the  
14 committee to silence their pagers and cell phones.  
15 Thank you.

16 DR. KHUC: The Food and Drug Administration  
17 is convening today's meeting of the Anesthetic and  
18 Life Support Drugs and Drug Safety and Risk Management  
19 Advisory Committees under the authority of the Federal  
20 Advisory Committee Act of 1972. With the exception of  
21 the industry representative, all members and temporary  
22 voting members of the committees are special

1 government employees or regular federal employees from  
2 other agencies, and are subject to the federal  
3 conflict of interest laws and regulations.

4           The following information on the status of  
5 the committee's compliance with federal ethics and  
6 conflict of interest laws, covered by but not limited  
7 to those found in 18 U.S.C. Section 208 and Section  
8 712 of the Federal Food, Drug and Cosmetic Act, is  
9 being provided to participants in today's meeting and  
10 to the public.

11           FDA has determined that members and  
12 temporary voting members of these committees are in  
13 compliance with federal ethics and conflict of  
14 interest laws. Under 18 U.S.C. Section 208, Congress  
15 has authorized FDA to grant waivers to special  
16 government employees and regular federal employees who  
17 have potential financial conflicts when it is  
18 determined that the agency's need for a particular  
19 individual's services outweighs his or her potential  
20 financial conflict of interest.

21           Under Section 712 of the Federal Food, Drug  
22 and Cosmetic Act, Congress has authorized FDA to grant

1   waivers to special government employees and regular  
2   federal employees with potential financial conflicts  
3   when necessary to afford the committee essential  
4   expertise.

5               Related to the discussions of today's  
6   meeting, members and temporary voting members of these  
7   committees have been screened for potential financial  
8   conflicts of interest of their own, as well as those  
9   imputed to them, including those of their spouses or  
10   minor children, and for purposes of 18 U.S.C. Section  
11   208, their employers. These interests may include  
12   investments, consulting, expert witness testimony,  
13   contracts, grants, CRADAs, teaching, speaking,  
14   writing, patents and royalties, and primary  
15   employment.

16              Today's agenda involves discussions of risk  
17   evaluation and mitigation strategies, REMS, for  
18   extended release and long-acting opioid analgesics.  
19   As a part of the materials for the meeting, FDA  
20   anticipates presenting a proposal for a class-wide  
21   opioid REMS and will solicit feedback from the  
22   advisory committee and public on the components of

1     that proposal.

2             The need for adequate pain control is an  
3     element of good medical practice. In this context,  
4     some persons suffering from pain need access to potent  
5     opioid drug products. However, inappropriate  
6     prescribing, addiction, and death due to prescription  
7     opioid abuse and misuse have been increasing over the  
8     last decade. This is a particular matters meeting,  
9     during which general issues related to risk  
10    evaluation/mitigation strategies for extended release  
11    and long-acting opioid analgesics will be discussed.

12            Based on the agenda for today's meeting, and  
13    all financial interests reported by the committee  
14    members and temporary voting members, a conflict of  
15    interest waiver has been issued in accordance with  
16    18 U.S.C. Section 208(b)(3) and Section 712 (c)(2)(b)  
17    to Dr. Knox Todd for serving on an advisory board for  
18    an affected firm. His participation in this advisory  
19    board may involve targets for analgesic development,  
20    including products such as extended release, and long-  
21    acting opioids and competing products, and the impact  
22    of REMS on these products.

1           The magnitude of the interest is 5,001 to  
2 10,000 per year. The waiver allows Dr. Todd to  
3 participate fully in today's deliberations. FDA's  
4 reasons for issuing the waiver are described in the  
5 waiver document, which are posted on FDA's website at  
6 [www.fda.gov/advisorycommittees/committeesmeetingmateri](http://www.fda.gov/advisorycommittees/committeesmeetingmateri)  
7 [als/drugs](http://www.fda.gov/advisorycommittees/committeesmeetingmateri). Copies of the waiver may also be obtained  
8 by submitting a written request to the agency's  
9 Freedom of Information office, Room 6-30 of the  
10 Parklawn Building. A copy of the statement will also  
11 be available for review at the registration table  
12 during this meeting, and will be included as part of  
13 the official transcript.

14           To ensure transparency, we encourage all  
15 standing committee members and temporary voting  
16 members to disclose any public statements that they  
17 have made concerning the issues before the committees.

18           With respect to FDA's invited industry  
19 representative, we would like to disclose that  
20 Dr. Bartholomew Tortella is participating in this  
21 meeting as a non-voting industry representative,  
22 acting on behalf of regulated industry. Dr. Tortella's



1 role at this meeting is to represent industry in  
2 general, and not any particular company. Dr. Tortella  
3 is employed by Novo Nordisk.

4 We would like to remind members and  
5 temporary voting members that if the discussions  
6 involve any other products, firms, or issues not  
7 already on the agenda for which an FDA participant has  
8 a personal or imputed financial interest, the  
9 participants need to exclude themselves from such  
10 involvement, and their exclusion will be noted for the  
11 record.

12 FDA encourages all participants to advise  
13 the committees of any financial relationships they may  
14 have with any firms at issue. Thank you.

15 DR. KIRSCH: We'll now begin the open public  
16 hearing.

17 The FDA and this committee place great  
18 importance in the open public hearing process. The  
19 insights and comments provided can help the agency and  
20 this committee in their consideration of the issues  
21 before them. That said, in many instances, and for  
22 many topics, there are a variety of opinions. One of

1 our goals today is for this open public hearing to be  
2 conducted in a fair and open way, where every  
3 participant is listened to carefully and treated with  
4 dignity and courtesy and respect. Therefore, please  
5 speak only when recognized by the chair. Thank you  
6 for your cooperation.

7 Both the Food and Drug Administration and  
8 the public believe in a transparent process for  
9 information gathering and decision making. To ensure  
10 such transparency at the open public hearing session,  
11 at the advisory committee meeting, the FDA believes  
12 that it is important to understand the context of the  
13 individual's presentation. For this reason, FDA  
14 encourages you, the open public hearing speaker, at  
15 the beginning of your written or oral statement, to  
16 advise the committee of any financial relationship  
17 that you may have with any company or group that may  
18 be affected by the topic of this meeting.

19 For example, the financial information may  
20 include a company's or group's payment of your travel,  
21 lodging, or other expenses in connection with your  
22 attendance at this meeting. Likewise, FDA encourages

1 you, at the beginning of your statement, to advise the  
2 committee if you do not have any such financial  
3 relationship. If you choose not to address this issue  
4 of financial relationships at the beginning of your  
5 statement, it will not preclude you from speaking.

6 For the speakers, I'll apologize ahead of  
7 time. I usually butcher up the names pretty well. So  
8 when I call your name, you can tell me how it's  
9 pronounced correctly.

10 The first speaker is Nathaniel Katz.

11 For the speakers, the microphone will turn  
12 off at three minutes. When the microphone turns off,  
13 I will expect that you'll stop speaking. Thank you.

14 You may begin.

15 DR. KATZ: Good morning. My name's  
16 Nathaniel Katz. I'm a pain management physician and  
17 I'm a former chairman of this committee. I've been  
18 working intensively on the problem of pain and  
19 prescription opioid abuse for going on 20 years.  
20 Since I chaired the first opioid risk management  
21 meeting, now eight and a half years ago, somewhere  
22 approaching 100,000 people have died of prescription

1   opioid overdoses and related events.

2                   What have we been doing all this time?

3   Innumerable forms of voluntary education, monitoring,  
4   and surveillance, the essence of the current FDA and  
5   IWG proposals. You just sat through a day of  
6   presentations describing the results of these  
7   approaches.

8                   Do you really need any more data to tell you  
9   that voluntary education does not work?

10                  I will remind you of the definition of  
11   insanity, attributed to Albert Einstein, doing the  
12   same thing over and over again, and expecting the  
13   results to be different.

14                  The days of prescribers not being trained  
15   how to safely prescribe the number one medication in  
16   the United States have to be brought to an end by you  
17   today. In my view, you need to finally recommend  
18   mandatory prescriber training.

19                  The days of millions of patients walking out  
20   of the pharmacy with potentially lethal medication and  
21   no training on how to keep themselves and their  
22   community safe have to be brought to an end by you

1     today. In my view, you need to finally recommend  
2     mandatory patient training.

3             If you require training and need a  
4     verification system in the pharmacy, it has been  
5     stated that this would excessively burden the  
6     healthcare system. That's incorrect. Over the past  
7     year, our group, with some collaborators, has  
8     designed, built, tested, and reported on the technical  
9     performance and real-world usability of such a system,  
10    and provided all this information to the FDA. Time  
11    prevents me from describing the details. Suffice it  
12    to say that the system works. It's not burdensome.  
13    And it's not expensive. And if we can do it, anybody  
14    else can do it.

15            You will hear a number of objections to such  
16    approaches. People will complain that these are  
17    registries, which are somehow inherently evil. They  
18    are not registries. They are databases, just like the  
19    databases we are all already in anyway.

20            People will claim that prescribers will flee  
21    from prescribing if they're required to participate in  
22    such programs; however, there are ample survey data

1     that indicate just the opposite.

2             People will complain that we should not  
3     implement anything without evidence.  Guess what?  
4     There is no evidence.  Nobody's been willing to fund  
5     this type of research.  This leaves you with two  
6     choices.  You can do nothing and continue to count  
7     bodies or you can recommend interventions that make  
8     sense and gather the evidence prospectively.  That  
9     seems to be an easy choice.

10            You should also know that many other  
11     interventions could have been presented, such as  
12     tamper-resistant prescription pads, automated  
13     prescription monitoring data checks, et cetera.

14            So my recommendations to you are as follows.  
15     First, mandatory training of all prescribers and  
16     patients receiving long-acting opioids as part of the  
17     elements to assure safe use of the class-wide REMS.  
18     We've shown this can be done.  After a specified  
19     evaluation period, decide whether to expand to the  
20     rest of the opioids, and whether to require some  
21     additional risk mitigation approaches I listed  
22     earlier.  When I bump into you all again eight and a

1 half years, I'd like you to have a clean conscience  
2 that you did the right thing.

3 DR. KIRSCH: Thank you.

4 The next speaker is Penney Cowan.

5 MS. COWAN: Hi. My name is Penney Cowan,  
6 executive director of American Chronic Pain  
7 Association. I want to thank the FDA for their  
8 efforts to ensure opioids will be used safely and  
9 appropriately by those who must live with pain.

10 Given the scope of the REMS outline in the  
11 report provided by Dr. Rappaport, the American Chronic  
12 Pain Association feels that the educational component  
13 should focus both on those who use the medications and  
14 the general public. Accidental overdose can be  
15 reduced by educating people who have realistic  
16 expectations about pain-relieving limits of opioids,  
17 understand how to use them, and know the importance of  
18 keeping them safe.

19 Opioid agreements would provide a wonderful  
20 opportunity for education and communication with their  
21 healthcare providers. The general public also needs  
22 to know about the risk of opioids. Pharmaceutical

1   opioids are the second highest reason for death in  
2   this country, and the majority of those were from  
3   diversion, not from legitimate users.

4           But people with pain, who are prescribed  
5   these medications, use, store, and dispose of them  
6   properly, should not be held responsible for the  
7   misuse by the general public. If the REMS is to work,  
8   we need to focus our educational efforts on broader  
9   populations. Messages need to be defined for  
10  different populations, from the very young to the very  
11  old. They need to convey the importance of taking and  
12  storing medications appropriately and also clearly  
13  defining the dangers of misuse.

14           These messages need to be more visible on  
15  the public airwaves and the mass media. This campaign  
16  will not make the problem go away, but it can save a  
17  significant number of people who might otherwise not  
18  be aware of the dangers. Unfortunately, there will  
19  always be a group who will continue to misuse these  
20  and many other types of substances.

21           While our focus remains on those who use  
22  opioids as part of their pain management regiment,



1 along with other interventions, to allow them to  
2 improve the quality of their life and increase  
3 function, we must also look beyond this group. If the  
4 general public is provided simple, clear messages  
5 about the dangers of medications, misuse and abuse can  
6 be reduced. Isn't one life worth it?

7           The American Chronic Pain Association has  
8 already begun through patient education, but public  
9 education is even more important. We urge the FDA to  
10 take the lead in this important work with the help of  
11 organizations like the American Chronic Pain  
12 Association, who have been the voice of people with  
13 pain for 30 years. Thank you.

14           DR. KIRSCH: Thank you. The next speaker is  
15 Mr. Porada.

16           MR. PORADA: Thank you. By the time this  
17 process is over, it'll be about two years. And where  
18 have we come? Basically, in a full circle. We  
19 started out with a risk map. We changed the colors  
20 and we're back to a risk map. Can we really look at  
21 ourselves and say that the things that have been  
22 proposed are going to change anything? Will some

1 class labeling or class wording in the Med guide --  
2 will a patient education piece, involuntary training,  
3 change outcomes? I don't think so. So I have a  
4 couple of recommendations that, hopefully, will be  
5 considered so we don't end up here again in two years  
6 discussing this.

7 FDA and industry, which I am happy to have  
8 seen, are starting to think about training, not  
9 education. My recommendation was going to be focused  
10 on training that are linked to specific behaviors.

11 Second, we need to understand that  
12 practitioners will want training. Our group has  
13 presented data. Others from California have presented  
14 data that show 80 to 90 percent of practitioners will  
15 comply with FDA-mandated training.

16 Third, a lot of organizations say things  
17 can't be done. They say practitioners won't  
18 participate. They say training can't be validated. A  
19 lot of this is opinion. It's not supported by data.  
20 And I would think and encourage that data be used to  
21 guide any of the decisions that are made here today.

22 Finally, voluntary training. We talk a lot

1 about unintended consequences. What are the  
2 unintended4 consequences of voluntary training?  
3 Perhaps nobody volunteers to be trained. Would FDA be  
4 happy with that? Would FDA punish industry because  
5 nobody decided to voluntarily be trained?

6 So in summary, I would say focus on  
7 training, not education. There are data available to  
8 support many of the arguments that we have been  
9 debating over the past two years, and revisit this  
10 voluntary training thing, and perhaps, consider a  
11 phased-in approach of initially being voluntary,  
12 perhaps over six months, migrating to mandatory.  
13 Thank you.

14 DR. KIRSCH: Thank you.

15 Our next speaker is Ronna Hauser.

16 DR. HAUSER: Good morning. And thank you  
17 for allowing me this opportunity to share the  
18 community pharmacy perspective, regarding the FDA's  
19 proposal for a class-wide opioid REMS. I am Ronna  
20 Hauser, vice president of Policy and Regulatory  
21 Affairs at the National Community Pharmacist's  
22 Association, and I have no financial interests to

1     disclose.

2                 NCPA represents America's community  
3     pharmacists, including the owners of more than 23,000  
4     community pharmacies. First and foremost, NCPA  
5     applauds the FDA for making the process that led to  
6     this joint advisory committee meeting a transparent  
7     one.

8                 As patient care and safety are a top  
9     priority for community pharmacists, we continue to  
10    stress the importance of patient access to therapy  
11    while safeguarding against potential for abuse and  
12    misuse. We do not believe that REMS should interfere  
13    with the practice of medicine and pharmacy and also  
14    have concerns regarding the potential proliferation of  
15    REMS programs.

16                With that in mind, NCPA does support the  
17    FDA's proposed REMS, as it promotes patient safety  
18    without restricting distribution or requiring a  
19    physician or patient registry. We also agree that the  
20    burdensome logistics of registering the nearly  
21    4 million patients currently using long-acting opioids  
22    would create a large number of prescribers and

1 pharmacies who would potentially opt out of the  
2 program.

3 In addition, we applaud the FDA for their  
4 decision to not include immediate release products as  
5 part of the REMS, as the burden to the system would be  
6 too great. The proposed approach represents the most  
7 feasible way to more easily implement a class-wide  
8 REMS into practice settings, and at this time, we feel  
9 that a more robust plan is not warranted.

10 NCPA supports the FDA's recognition of the  
11 prescriber's role to educate patients regarding  
12 medication use, storage, and disposal, and the use of  
13 a patient information sheet. Though not required by  
14 FDA, we also want to encourage that the community  
15 pharmacist's role in patient education be considered,  
16 and strongly recommend that whatever components of  
17 REMS are provided to the patient, via the prescriber,  
18 be made known to the pharmacist as well. This  
19 continuity of care will attribute to the best outcomes  
20 in overall patient education.

21 We agree with the proposal that patient  
22 education should initially occur at the physician

1 level. At the time of the office visit, the physician  
2 can examine patients to determine whether opioid  
3 therapy is appropriate and monitor for any signs of  
4 abuse.

5 When the patient visits their community  
6 pharmacy, the pharmacist provides valuable  
7 reinforcement of the physician's education through  
8 appropriate counseling.

9 Lastly, NCPA would like to reiterate our  
10 support for the creation and use of the single FDA-  
11 approved document that would be distributed with these  
12 products to replace existing written information  
13 currently distributed by pharmacies, which will help  
14 to decrease the burden caused by the abundance of  
15 product-specific medication guides. We appreciate the  
16 agency's movement in this direction.

17 Once again, NCPA applauds the FDA for moving  
18 forward with a sensible REMS approach and would like  
19 to encourage the FDA to continue to involve community  
20 pharmacists in the creation of these programs. Thank  
21 you for your time.

22 DR. KIRSCH: Thank you.

1           Next speaker is Carlton Brown.

2           DR. BROWN: Good morning. I'm Carl Brown,  
3   president of the Oncology Nursing Society. And on  
4   behalf of our 37,000 nurses and other healthcare  
5   professionals, thank you for this opportunity to  
6   present our views on this important public health  
7   issue.

8           We commend the FDA for seeking to address  
9   this issue. We do, however, have serious concerns  
10   regarding the proposal. Any opioid REMS should be  
11   reasonable and evidence based, ensuring that patients  
12   with legitimate need have access to the opioid pain  
13   therapies that they and their healthcare providers  
14   deem most appropriate.

15          We believe that any opioid REMS should not  
16   result in unintended adverse consequences, such as  
17   creating a shift in prescribing behavior that in turn,  
18   could diminish quality of life for patients and/or  
19   merely transfer the problem to a different group of  
20   Schedule II drugs.

21          Of serious concern is the FDA workgroups'  
22   reports and other documents posted on the FDA website,

1 related to the proposal, repeatedly acknowledged the  
2 lack of baseline data and evidence of the  
3 effectiveness of many of the proposed interventions.

4           Specifically, the FDA needs strong baseline  
5 data, including more insight into the sources and  
6 diversionary paths for these drugs, so that positive  
7 and negative changes can be measured over time.

8           We believe that an additional research  
9 should be conducted and urge the FDA to consider a  
10 pilot, as it would allow the agency to determine the  
11 validity and appropriateness of various interventions  
12 and allow for modification and improvements to the  
13 REMS before it is instituted on a large scale.

14           A pilot would also allow the agency to test  
15 two versions of the REMS, one focused on long-acting  
16 and extended relief opioids and one that also includes  
17 immediate-release opioids. This will help insure that  
18 the final national REMS employs evidence-based  
19 interventions that have been found to decrease abuse,  
20 while not adversely impacting those patients who  
21 require the regular use of opioids to improve their  
22 quality of life.



1           We also urge the FDA to develop systems for  
2   the safe disposal or return of unused opioids for  
3   patients and caregivers. Such a program, combined  
4   with patient education, should decrease the number of  
5   unused opioids remaining in people's homes, where they  
6   can be accessed by non-legitimate users. We support  
7   the FDA's decision not to require individual  
8   prescribers and patients to enroll in the REMS and not  
9   to require real-time verification of prescriber  
10   training at the pharmacy level.

11           Patients with cancer-related pain cannot  
12   afford the federal government's misstep in this arena.  
13   Acting in a deliberate manner, including piloting a  
14   new system, and collecting more data will help the FDA  
15   to achieve its goal of ensuring that the benefits of  
16   these drugs continues to outweigh the risks. Thank  
17   you.

18           DR. KIRSCH: Thank you.

19           The next speaker is Dr. Gorman and/or Dr.  
20   Parks.

21           DR. GORMAN: Hello. I'm Jack Gorman, the  
22   chief scientific officer for Care Management

1 Technologies, and I have no financial things to  
2 disclose. And I thank you for letting me speak today.

3 As this slide shows, physicians today are  
4 caught between the competing goals of ensuring that  
5 patients with chronic pain receive access to narcotic  
6 analgesics that they need and preventing the misuse of  
7 opioids that they prescribe. Current technology  
8 provides reliable methods to differentiate between  
9 these issues and to guide clinicians to the medically  
10 appropriate prescription of opioids.

11 There is no longer any reason to use  
12 outdated global solutions, solutions that in the past  
13 have either been Draconian and resulted in decreased  
14 access to opioids for those who need them or lacks  
15 that resulted in unnecessary prescription misused and  
16 accidental overdose.

17 As shown in this slide, this current  
18 technology uses a method called audit and feedback,  
19 which has been shown in the literature to effectively  
20 influence prescribing behavior. The technology-based  
21 implementation of audit and feedback at Care  
22 Management Technologies has had significant impact on

1 improving psychotropic medication prescriptions.  
2 Audit and feedback can help both to insure adequate  
3 access, and reduce inappropriate prescribing of opioid  
4 analgesics.

5 Missouri Medicaid has implemented the Care  
6 Management Technologies opioid prescribing initiative,  
7 and found it to be a cost effective method of  
8 identifying numerous situations in which opioid  
9 prescribing appears to be inconsistent with best  
10 medical practice

11 This slide shows us just a handful of those  
12 categories. This information is then fed back to the  
13 prescriber on a case by case basis, and will result in  
14 fewer bottles of unnecessary opioids landing on  
15 medicine shelves in Missouri. With just a small  
16 handful of algorithms presented where, you can see two  
17 driving principles that should underlie a data-driven  
18 solution for REMS.

19 First, a significant number of patients and  
20 prescribers have been targeted for an intervention to  
21 address potentially inappropriate prescribing; and,  
22 two, this group still represents only a small

1 percentage of the opioid prescribing ongoing in  
2 Missouri.

3           Consequently, we can target the problem  
4 areas without interfering with the appropriate ongoing  
5 delivery of care. This is a 21st century digital  
6 solution. We use data and algorithms to find and  
7 target the problems. We do not expend our finite  
8 resources on delivery areas that are not currently of  
9 concern. Thank you.

10           DR. KIRSCH: Thank you.

11           The next speaker is Will Rowe.

12           MR. ROWE: Thank you. My name is Will Rowe.  
13 I'm the CEO of the American Pain Foundation, which is  
14 a patient support organization. I also have no  
15 financial interests to disclose. Thank you for this  
16 opportunity to comment on the subject of these  
17 meetings.

18           I also want to thank the FDA and staff and  
19 leadership for what I saw, and many whom I spoke to, a  
20 very thorough and considerate review of the comments  
21 that were submitted, and analysis of these comments.  
22 And it struck me and many others that the comments and

1 input that was delivered was taken seriously, and  
2 showed up in what was the eventual recommendation.

3 The proposed REMS recommendation, from our  
4 point of view, was excellent in terms of providing and  
5 reflecting the balance, that is the goal of the REMS  
6 project, which is to do what can be done to curb  
7 abuse/misuse/overdose of the use of these medicines,  
8 while protecting access for people who need them.

9 The proposed REMS clearly recognizes the  
10 burden and potential negative consequences of  
11 mandatory education certification and patient  
12 registries. The focus of the REMS is patient and  
13 provider education. One of the features that stands  
14 out, from our perspective, it's not just provider  
15 education and patient education. It's a very focused  
16 and simplified version of provider and patient  
17 education that focuses very directly on safety.

18 With provider education, it's patient  
19 selection. It's dosing and patient monitoring. There  
20 is a plethora of provider education going on out  
21 there, but the focus that is contained in this, and  
22 reflected in this REMS, focusing on those three

1 features, I think is an essential and new ingredient  
2 in understanding education.

3 For patients, it is safe use, safe storage,  
4 and safe disposal. Again, there is patient education  
5 going on out there, but not that which focuses so  
6 deliberately on the safety aspects of these medicines.

7 So I would like to thank the group for  
8 putting this proposal together, and the American Pain  
9 Foundation stands ready to assist in the  
10 implementation. Thank you.

11 DR. KIRSCH: Thank you.

12 The next speaker is Betty [sic] Tully.

13 MS. TULLY: Good morning. Thank you for the  
14 opportunity to address this community. I want the  
15 record to show that I have traveled here with Chicago  
16 with my own funds. And I am not an employee or member  
17 of any pain organization. My name is Betts Tully.

18 I am a formerly diagnosed chronic pain  
19 patient who was misprescribed large amounts of  
20 opiates. I am not a medical professional, so excuse me  
21 if my layman's terms fall short. I am, however, more  
22 importantly, part of the unprecedented and tragic

1 statistics that brings this discussion to your table.

2 I am represented in those horrifying numbers of  
3 medically prescribed death and addiction that has  
4 occurred over the last decade.

5 I have been told by medical professionals  
6 that I am lucky to be alive. The discussion of  
7 overprescribing, as well as inappropriate prescribing  
8 by inadequate trained medical community, is not a new  
9 discovery for this agency. It was forewarned. An  
10 inevitable outcome was predicted and discussed by the  
11 FDA committees as far back as 2001. But the only  
12 thing that seemed to be of concern was the idea of  
13 access. Access to opiates should not be compromised.  
14 We heard a lot about access yesterday, and I predict  
15 we will today.

16 Access. When I went to the pain specialist,  
17 I was not aware that my number one right was to have  
18 access to narcotics. I went to that doctor for help  
19 with my back pain. I got little else than narcotics,  
20 along with a devastating addiction. I was also not  
21 aware that many doctors have as little as 12 hours'  
22 education in narcotic pharmacology, yet receive

1 licenses to prescribe every scheduled drug  
2 manufactured and virtually no restrictions on  
3 practices. I was not aware that there were very few  
4 requirements for a doctor to set up a business as a  
5 pain specialist, and that the system to become board  
6 certified in the specialty is voluntary. Most of all,  
7 I did not know that the majority of doctors get their  
8 information of how and when to prescribe opiates from  
9 the pharmaceutical companies that manufacture the  
10 drugs.

11 Had I known these facts, I would have  
12 declined the so-called access to pain drugs, because I  
13 didn't go to a doctor for narcotics. I went to a  
14 doctor because I thought a specialist would find a way  
15 to relieve my pain and correct my problem.

16 Some pain patients believe they have a so-  
17 called right to narcotics. They are wrong. They have  
18 a right to good medical care by a trained and properly  
19 informed physician. And they certainly don't have  
20 rights that put my health at risk. We have a decade  
21 of misinformation and manipulation that needs to be  
22 undone.



1 DR. KIRSCH: Thank you.

2 The next speakers are Drs. Budman and

3 Zacharoff.

4 DR. BUDMAN: Thank you very much. I'm Simon

5 Budman from Inflection and NaviPro. The discussion

6 yesterday talked about metrics, and I'm going to be

7 talking about metrics from substance abuse treatment

8 centers. I'll be talking specifically about the

9 NaviPro datastream.

10 NaviPro was developed with support of \$10

11 million from the National Institution on Drug Abuse,

12 also additional support from founding sponsors Endo

13 Pharmaceuticals and King Pharmaceuticals.

14 We need to go beyond the issue of measuring

15 knowledge. We need to go look at changes in

16 behaviors. We have a way to measure behaviors, and

17 measure behaviors very quickly, in terms of the

18 outcomes of the REMS. Looking at what goes on for

19 people at substance abuse treatment is very important

20 in terms of measuring how effective the REMS are.

21 I'm going to show you some data in just a

22 minute. This data comes from the NaviPro datastream

1 and substance abuse treatment centers. There's about  
2 200,000 cases in that datastream from 600 treatment  
3 centers around the country. It's growing by about  
4 1,500 cases a week. The data right now indicates that  
5 about 15 percent of patients coming into that system  
6 are abusing one or more prescription opioid. About  
7 60 percent of those patients are abusing extended-  
8 release prescription opioids.

9           This is where they get their drugs. They  
10 get their drugs from their own prescription. They get  
11 their drugs from family and friends, which was given  
12 to them or stolen. And they get their drugs from  
13 dealers. We believe that an effective REMS will affect  
14 the first two areas quite rapidly. Better patient  
15 selection will reduce the number of people coming into  
16 substance abuse treatment with their own  
17 prescriptions, and better storage and disposal will  
18 reduce the people who are getting the drugs from  
19 family and friends, that are given or stolen. It's  
20 unclear what's going to happen with drugs coming from  
21 dealers.

22           We believe that it's crucial to measure

1 knowledge, but it's incredibly important to be able to  
2 measure changes in behavior. And it's incredibly  
3 important to be able to do that in a timely way, not  
4 wait three years to get TEDS data to see if the  
5 program's working. Thank you very much.

6 DR. KIRSCH: Thank you.

7 Next speaker is Dr. Dy.

8 DR. DY: Good morning. I'm Dr. Sydney Dy.  
9 I'm an associate professor at the Duffey Pain and  
10 Palliative Care Program, Johns Hopkins Kimmel Cancer  
11 Center. I'm here to speak for the American Society of  
12 Clinical Oncology or ASCO, the world's leading  
13 professional organization representing physicians who  
14 treat patients with cancer.

15 Approximately 1.5 million Americans will be  
16 diagnosed with cancer this year. One American dies of  
17 the disease every minute. ASCO is dedicated to  
18 promoting the best interests of cancer patients. We  
19 thank FDA for the opportunity to speak.

20 The management of pain, especially chronic  
21 pain in cancer patients, is a critical issue. Many of  
22 our patients suffer from pain that would be

1     debilitating if not for the use of extended-release  
2     opioids. Oncologists are experienced with careful  
3     prescribing of these drugs. While ASCO understands  
4     the public health issue addressed through REMS and  
5     supports FDA's efforts, ASCO expressed concerns that  
6     appropriate access to these drugs not be denied to  
7     cancer patients, and that the process for obtaining  
8     these drugs should not be burdensome for physicians or  
9     patients.

10           Representing over 27,000 oncology  
11     professionals, ASCO is a unique resource for guidance  
12     for policymakers. In its proposal, FDA encourages  
13     sponsors to develop prescriber training in partnership  
14     with an appropriate independent third party. ASCO has  
15     previously commented that high quality educational  
16     materials have already been developed, both by our  
17     organization and other societies representing health  
18     professionals in pain management, in hospice and  
19     palliative care, to name a few. We encourage FDA and  
20     sponsors to use existing materials and offer our  
21     assistance in developing and reviewing new educational  
22     modules.

1           The proposed REMS includes patient education  
2 sheets to be developed by the sponsor and approved by  
3 FDA. ASCO offers its support in developing these  
4 educational materials. Our patient website,  
5 cancer.net, offers free of charge, a series of modules  
6 and articles written specifically for patients and  
7 reviewed by the cancer.net editorial board, composed  
8 of more than 150 oncologists, nurses, social workers,  
9 and patient advocates.

10           FDA has commented that it may be more  
11 efficient to link physician education to existing DEA  
12 registration. This would require new legislation, but  
13 would ensure appropriate physician education. ASCO  
14 supports this model and suggests that DEA registration  
15 be contingent upon successful completion of this  
16 educational program with CME credit.

17           Because sponsor-developed educational  
18 programs may not be developed eligible for CME, ASCO  
19 strongly encourages FDA, sponsors, and independent  
20 third parties such as ASCO, to explore with a CME,  
21 possible strategies for meeting both REMS educational  
22 goals and CME requirements.

1           FDA is required to evaluate the  
2 effectiveness of new REMS. ASCO is pleased to see  
3 inclusion of measures that will address access.  
4 Undertreatment is a continuing issue in cancer care  
5 and should not be worsened by unintended consequences  
6 of new REMS. It's very important to monitor patients'  
7 access to appropriate pain management.

8           A single education product and one  
9 assessment plan would be most efficient. This should  
10 be a collaborative effort among sponsors, FDA, and  
11 appropriate third parties such as ASCO. Thank you.

12           DR. KIRSCH: Thank you.

13           The next speaker is Theresa Grimes.

14           MS. GRIMES: Good morning. My name is Terri  
15 Grimes. I'm a nurse practitioner in pain management,  
16 associate vice president for nursing in a community  
17 hospital, and president for the American Society for  
18 Pain Management Nursing. The views I share with you  
19 are my own.

20           Thank you for a thorough and thoughtful  
21 review of REMS and for the final report of the  
22 workgroups. I support the recommendation to include

1 all opioids in the REMS process. Everyone should have  
2 access to effective pain management that includes a  
3 balanced approach toward reducing pain, improve  
4 quality of life, and improve physical functioning  
5 while promoting safety through education to take  
6 medication only as directed to secure and dispose of  
7 medication properly, and if side effects, to seek  
8 immediate attention.

9           The National Quality Forums Safe Practices  
10 for Better Healthcare 2009 update endorses 34 safe  
11 practices. Number 5, informed consent, asks patients  
12 or legal surrogates to teach back, in his own words,  
13 key information about the proposed treatments or  
14 procedures for which he or she is being asked to  
15 provide informed consent.

16           Teach-back is promoted by health literacy  
17 experts Dr. Barry Weiss and Joanne Schwartzberg.  
18 Dr. Weiss, in Removing Barriers to Better, Safer Care  
19 Manual for Clinicians, states, "There's often a  
20 mismatch between the clinician's level of  
21 communication and a patient's level of comprehension  
22 that can lead to medication errors and adverse medical

1 outcomes."

2           In 2009, the Deseret News printed that the  
3 number of prescription drug-related deaths in Utah  
4 decreased by 12.6 percent between 2007 and '08,  
5 coinciding with the health department's use only as  
6 directed campaign. Information was presented in  
7 brief, plain language with bulleted points given for  
8 the patient and caregiver to remember.

9           Teach-back should be adopted as recommended  
10 by the NQF and others. Information must be brief and  
11 to the point, no more than three to five bullets at a  
12 visit. If we want our patients to be safe, we must  
13 provide them with information that will be easily  
14 recalled. Points should be repeated by the pharmacist  
15 during callbacks and built upon at future visits.

16           More detailed instructions may obscure  
17 critical points to remember. Dr. Leonard Paulozzi is  
18 cited in a recent interview on unintentional drug  
19 poisoning deaths, that 40 percent of opioid  
20 prescriptions are written in our emergency  
21 departments. Patients are often discharged from  
22 hospitals with opioid analgesic prescriptions. These



1 patients are in need of the same process of informed  
2 consent. Please do not exclude hospitals from patient  
3 education.

4 Thank you for supporting appropriate  
5 education and training for pain management issues.  
6 Thank you.

7 DR. KIRSCH: Thank you.

8 The next speaker is Dr. Sidney Schnoll.

9 DR. SCHNOLL: Good morning. My name is  
10 Sidney Schnoll, and I'm presenting on behalf of Pinney  
11 Associates who have paid for me to attend this  
12 meeting. I'm not appearing on behalf of any of our  
13 clients, and the views that I'm expressing today are  
14 mine and those of Pinney Associates.

15 Pinney Associates develops, implements, and  
16 evaluates REMS for pharmaceutical developers and  
17 manufacturers. We consult for many of the companies  
18 in the IWG and worked with the IWG to develop the  
19 REMS, and, specifically, worked on the metrics  
20 prescriber and patient education subteams.

21 I'd like to talk, however, about the issue  
22 of prescription drug abuse, which is a very old

1 problem and has been a problem in this country for  
2 over 100 years. While it is important for FDA to work  
3 to reduce abuse, the results of the agency's efforts  
4 alone to curb prescription drug abuse will be limited  
5 because the abuse occurs mainly in those who are not  
6 prescribed the medications. Because of this, it will  
7 be a particular challenge to assess the effectiveness  
8 of the REMS, which primarily covers patients who are  
9 prescribed the drugs, a completely different  
10 population.

11           The FDA has appropriately taken a position  
12 with its REMS that there should be minimal burden on  
13 patient access and safety. However, to reduce abuse,  
14 the agency should take the lead, as Dr. Jenkins and  
15 others suggested yesterday, to develop a consortium of  
16 all interested stakeholders. One way to do this would  
17 be to resurrect the Interagency Narcotic Treatment  
18 Policy Review Board.

19           The board has not met for many years, even  
20 as concerned about prescription opioid abuse has  
21 increased. We urge the government to expand the  
22 board's remit, to address the issue of prescription

1   opioid abuse, and invite industry, prescribers,  
2   dispensers, law enforcement, prevention/treatment  
3   specialists, educators, and most critically patients  
4   to collaboratively develop a comprehensive approach to  
5   address the appropriate use of prescription opioids.

6           Industry and FDA cannot do this alone. This  
7   is not a problem that will be addressed with simple  
8   solutions. Unless an integrated approach involving  
9   all stakeholders is implemented, there is no chance in  
10   adequately addressing this problem. Thank you.

11           DR. KIRSCH: Thank you. The next speaker is  
12   Dr. Zee.

13           DR. VAN ZEE: My name is Dr. Art Van Zee. I  
14   have no financial disclosures. My comments and  
15   references are supplied on a yellow handout sheet out  
16   here. In spite of much industry promotion to the  
17   contrary, and widespread acceptance in much of the  
18   pain management community, evidence-based medicine  
19   would show that long-acting opioids are not any more  
20   effective than immediate-release opioids but do carry  
21   increased risk. These increased risks include  
22   inadvertent overdose and deaths, and a much-increased

1 risk of addiction when abused. This has been one of  
2 the loud messages of the Oxycontin story.

3           There are many concerns that I have with  
4 REMS as proposed. The proposal would not affect two  
5 significant contributors to the prescription opioid  
6 problem. First, industry marketing and promotion.  
7 Secondly, REMS as proposed would not impact commercial  
8 prescribing; now, for example, highlighted by the  
9 south Florida situation where 43 of the top 50  
10 oxycodone prescribing docs in the country are located;  
11 wherein Broward County, Florida the 115 pain clinics  
12 exceed the number of McDonald's in Wal-Marts combined.

13           I also have great concerns about the current  
14 proposal for the industry to provide REMS education to  
15 physicians regarding opioid use. It was the  
16 industry's blurring of promotion, marketing, and  
17 education that played a major role over the last  
18 decade in the prescription opioid problem, and it  
19 seems most likely that the public health would not be  
20 well served by them providing the REMS education.

21           I'd suggest the following measures could  
22 most effectively impact the prescription opioid

1 problem. Number one, the requirement for all  
2 physicians prescribing controlled drugs to have passed  
3 a demonstrated competency requirement on first  
4 obtaining a DA license and subsequent renewal of the  
5 same.

6 Two, the requirement for all physicians  
7 prescribing methadone to have a unique and separate  
8 DEA demonstrated competency. Methadone is a  
9 pharmacologically tricky and complicated drug. It's  
10 been associated with a greatly disproportionate number  
11 of overdose deaths.

12 Number three, a change in the indications  
13 for long-acting opioids, since they are no more  
14 effective, but do have significant increased risk in  
15 relation to immediate-release opioids.

16 Long-acting opioids should be freely  
17 available to all with cancer or terminal illness pain.  
18 Long-acting opioids could be restricted from use in  
19 chronic, non-cancer pain, but availability could be  
20 preserved for chronic, non-cancer pain patients who  
21 have demonstrated that they did not do well on other  
22 regimens, and this could be achieved through a

1     compassionate use program.

2                 So in summary, I strongly feel that leaving  
3     REMS as currently proposed with simply physician  
4     education and patient education by the industry would  
5     fall far short of what is needed. And I must say, in  
6     10 years, I've finished on time for the first time.

7                 [Laughter.]

8                 DR. KIRSCH: Thank you.

9                 The next speaker is Cynthia Kear.

10                MS. KEAR: Good morning. My name is Cynthia  
11     Kear, senior vice president with the California  
12     Academy of Family Physicians. And on behalf of the  
13     CAFP, we would very much like to thank the FDA, the  
14     committee, and the industry workgroup for all of the  
15     incredible and thoughtful effort that's been brought  
16     to bear on this extraordinarily complex issue.

17                In addressing this significant health issue,  
18     the CAFP believes that continuing education, within  
19     the context of continuing professional development,  
20     can and should be part of the solution. The  
21     education, to be truly effective, and to truly effect  
22     changes in clinician performance, should be carefully

1 planned, comprehensive, cohesive, use multiple  
2 educational modalities and delivery systems, embody  
3 the best principles in adult learning, be evidence  
4 based, and both respect and be tailored to the  
5 diversity of settings in which clinicians practice.

6 But effective education, whether funded by  
7 government and/or industry, must include accredited  
8 educational providers operating within today's widely  
9 accepted industry standards. Beyond effectiveness,  
10 this is the case if that education is to be perceived  
11 as credible, both by prescribers as well as by the  
12 larger community.

13 Current medical education industry standards  
14 provide clear guidelines about the need to establish  
15 firewalls between pharmaceutical companies and the  
16 prescribers who use their therapeutic agents. As Dr.  
17 Kapelow indicated yesterday, given the intricate and  
18 unique nature of this situation, flexibility is  
19 appropriate. Still, knowing how impassioned the  
20 larger debate is about conflict of interest, vis a vis  
21 content development and pharmaceutical companies, we  
22 would caution all participants to be mindful of

1 perceptions. Optics are not necessarily correct, but  
2 they are nonetheless powerful.

3           The CAFP is the largest specialty society in  
4 the State of California and the largest chapter of the  
5 AAFP. Because the majority of patients are treated in  
6 primary care by family physicians and other primary  
7 care clinicians, CAFP worked with eight other state  
8 AAFP chapters to design, develop and deploy a survey,  
9 in order to invite, in a systematic way, the voice of  
10 primary care into this discussion. And I believe that  
11 all of you have seen the results of our survey.

12           With the American Pain Society, the CAFP co-  
13 convened a summit of other stakeholders. Those  
14 attending stakeholders included clinician leaders and  
15 staff of 10 membership organizations that represent  
16 virtually all prescribers of opioids. Together, we  
17 identified and agreed to a comprehensive library of  
18 core competencies.

19           Understanding that the path forward is not  
20 easy, simple, or has sure --

21           [Microphone timed out.]

22           DR. KIRSCH: Thank you.



1           The next speaker is Dr. White-Shim.

2           DR. WHITE-SHIM: Good morning. My name is  
3 Dr. Lynn White-Shim, an assistant director in the  
4 scientific activities division of the American  
5 Veterinary Medical Association. Our mission is to  
6 improve animal and human health and advance the  
7 veterinary medical profession.

8           I'm here to underscore the need for all DEA-  
9 registered, licensed veterinarians to continue having  
10 access to sustain released opioids to relieve animal  
11 pain and suffering. Veterinary use of human-labeled  
12 drugs is codified within FDA's extra-label drug use  
13 rules.

14           As the access working group discussed in  
15 FDA's REMS proposal, DEA has found that veterinarians  
16 represent a very low number of cases of abuse. We  
17 also believe misprescribing occurs at a very low  
18 level, as veterinarians are used to tailoring specific  
19 dosing regimens for individual animals across various  
20 breeds and species.

21           The AVMA appreciates what the FDA's proposed  
22 REMS is meant to accomplish. However, the access

1 working group recommended that any proposed opioid  
2 REMS not include requirements or exemptions  
3 specifically for veterinarians, and we are unclear  
4 what this means for veterinarians.

5 We still assert that veterinary exemption  
6 would be most expeditious, and we ask that FDA to  
7 closely consider our request. If exemption is not  
8 feasible, it would be best to have REMS specifically  
9 tailored for the veterinary profession after current  
10 assessments are finalized.

11 Extended-release opioids that are currently  
12 used in animals include fentanyl transdermal patches,  
13 oral methadone, and oral morphine. These are used for  
14 severely painful conditions in animals. Methadone and  
15 extended-release morphine are also especially helpful  
16 in zoo animals and wildlife.

17 We appreciate that FDA also intends to  
18 address avoidance of improper sharing and appropriate  
19 storing and disposal. Regarding improper sharing, a  
20 number of states have already put into place  
21 prescription monitoring programs, which allows  
22 individual states to detect doc hopping. The AVMA is

1 not aware of doc hopping in veterinary medicine, as it  
2 is less likely, since veterinarians determine how  
3 painful an animal is, independent of the client's  
4 assessment.

5           However, it's important to note that the  
6 state of Kansas is currently conducting a study to  
7 determine whether veterinarians are at risk of doc  
8 hopping. The study will conclude in 2013. In the  
9 meantime, a number of states require veterinarians to  
10 report controlled substance prescriptions.

11           Regarding appropriate disposal, the AVMA  
12 believes law enforcement agencies are the appropriate  
13 entities to undertake the safe, environmentally sound  
14 disposal of opioids from clients.

15           The AVMA appreciates the opportunity to  
16 provide comments this morning. We welcome the  
17 opportunity to serve as a source of information to the  
18 FDA, and look forward to continued work with you.  
19 Thank you.

20           DR. KIRSCH: Thank you.

21           The next speaker is Dr. Burns-Lambert.

22           DR. BURNS-LAMBERT: Good morning and thank

1    you for this opportunity. My name is Robin Burns-  
2    Lambert, a board-certified anesthesiologist and pain  
3    specialist, practicing in Berkshire County, a largely  
4    rural county in Massachusetts. I have no conflicts of  
5    interest except that my travel expenses today are  
6    being reimbursed by Analgesic Solutions.

7           I am here today because I want to urge you,  
8    as passionately as I can, to promote better education  
9    of both physicians and patients about appropriate  
10   management of pain medication and the risks of their  
11   misuse. Opioid therapy has potent analgesic effects,  
12   but also carries inherent adverse risks that are not  
13   apparent to many patients, or even many practitioners.  
14   The safety and efficacy of opioid therapy would be  
15   greatly enhanced by an easily accessible, but not  
16   easily avoidable education program focused on proper  
17   management of pain medication, including a medication  
18   safety plan and exit strategy, if drug therapy becomes  
19   no longer effective.

20           Massachusetts PMP data showed us that,  
21   similar to other communities around the country,  
22   millions of doses of opioid medications are dispensed

1 to our 130,000 community residents every year.

2 Motivated by the personal and public health risks in  
3 those numbers, a group of local physicians,  
4 pharmacists, and stakeholders embarked five years ago  
5 to strengthen and improve local management of chronic  
6 pain and pain medication.

7 We discovered the most immediate barriers  
8 were the great gaps in provider and patient knowledge.  
9 The many CME programs that we offered on these topics  
10 have consistently been crowded and have created what  
11 one community doctor describes as a new community  
12 ethic in managing pain and pain medication.

13 We have heard no suggestion that providers  
14 found education on these topics intrusive or  
15 unwelcomed. Instead, they were eager for information  
16 that instills greater confidence in addressing this  
17 often challenging population of medical problems.  
18 With that increased comfort, many of our doctors who  
19 had stopped caring for chronic pain patients have now  
20 resumed that practice, thereby increasing patient  
21 access to care.

22 A REMS feasibility study recently done in

1 our community tested a short educational program  
2 designed to inform patients and refresh physicians'  
3 fund of knowledge about opioid therapy. Providers  
4 found it enlightening, and patients reported that they  
5 appreciated the educational opportunity. It's focused  
6 on medication safety.

7 Our own experience in Berkshire County makes  
8 clear that provider and patient education, in an  
9 easily accessible format, is an essential patient  
10 health and safety tool. Pain management and opioid  
11 safety knowledge cannot simply be presumed. The  
12 benefits and risks of pain medication are too great to  
13 allow essential education about them to be optional or  
14 left to pharmaceutical companies alone.

15 An easily accomplished but mandated  
16 educational exercise will reduce barriers to care and  
17 lead to a greater fund of knowledge for both  
18 physicians and patients, thereby encouraging  
19 appropriate physician prescribing practice, and  
20 decreased patient-adverse outcomes, as patient safety  
21 is our ultimate goal. Thank you.

22 DR. KIRSCH: Thank you.

1           The next speaker is Philip Saigh.

2           MR. SAIGH: Thank you. Good morning. My  
3 name is Phil Saigh. I'm representing the American  
4 Academy of Pain Medicine. The Academy was founded in  
5 1983. It's a medical society representing over 2,000  
6 physicians who specialize in pain medicine.

7           In speaking about the use of opioids, the  
8 Academy believes that we must balance efforts to curb  
9 abuse and misuse with efforts to maintain appropriate  
10 access for legitimate patients.

11          We have four points. First, we believe we  
12 must implement and fund a national prescription  
13 monitoring program, or a coordinated multi-state  
14 effort, with real-time data available to physicians  
15 and pharmacists.

16          Second, we believe the REMS must be  
17 established across all classes of opioid medications.  
18 Regulating only a specific class will not prove  
19 effective and may result in denial of access.

20          Third, we recommend that the registries be  
21 avoided, as these tend to stigmatize the patients that  
22 are involved in them. And there's no evidence to

1 suggest their appropriateness or their success.

2           Finally, we want to engage experts in the  
3 development of education programs, which include  
4 comprehensive core curriculum, which span the  
5 continuum of all medical education, and which ensure  
6 the broadest reach and accessibility.

7           With respect to this point, I'd like to cite  
8 a reference from the findings of a recent study  
9 conducted by the Alliance for State Pain Initiatives.  
10 The study examined a CME activity that was co-  
11 sponsored by the Federation of State Medical Boards,  
12 entitled Responsible Opioid Prescribing: A  
13 Physician's Guide.

14           Over 98 percent of the physicians who  
15 participated in this study indicated that the guide  
16 would be effective in helping them prescribe,  
17 communicate with their patients, and be more effective  
18 in running their practices. We strongly recommend the  
19 adoption of responsible opioid prescribing CME  
20 activity as a central prescriber initiative,  
21 educational initiative.

22           In summary, the Academy believes that



1 balance is essential in successfully addressing the  
2 prescription drug abuse problem and the problem of  
3 undertreated pain. Thank you.

4 DR. KIRSCH: Thank you.

5 The next speaker is Justine Coffey.

6 MS. COFFEY: Good morning. My name is  
7 Justine Coffey, and I'm the director of Federal  
8 Regulatory Affairs at the American Society of Health  
9 System Pharmacists. ASHP is the 35,000-member  
10 national professional association representing  
11 pharmacists who practice in hospitals and organized  
12 health systems, including ambulatory care clinics,  
13 hospital outpatient pharmacies, home care, and long-  
14 term care.

15 I appreciate the opportunity to present the  
16 views of ASHP regarding REMS for extended-release and  
17 long-acting opioid analgesics, and I have no financial  
18 interests to disclose.

19 ASHP strongly encourages FDA to explicitly  
20 exempt inpatient hospital settings from a REMS  
21 requirement for opioid drugs. Multiple healthcare  
22 providers are involved in the care of the patients in

1 a hospital.

2           Through this interdisciplinary care model,  
3 there are built-in checks on each of the healthcare  
4 providers involved in the patient's care, including  
5 nurses, pharmacists, and physicians. Patients do not  
6 self-administer drugs, and there is always a  
7 healthcare professional in the general vicinity of the  
8 patients when the medication is administered.

9           Furthermore, many hospitals and health  
10 systems have decision support systems in place to  
11 prevent inadvertent overdoses of medications. Opiates  
12 are commonly prescribed in hospitals., and patients  
13 respond in varied ways to opiates, and need  
14 appropriate monitoring and safeguards, even with  
15 standard doses. However, since these medications are  
16 so commonly prescribed, physicians understand the  
17 associated risks and side effects, as do health system  
18 pharmacists.

19           In the hospital setting, education for  
20 prescribers about appropriate patient selection,  
21 dosing and patient monitoring will not have a  
22 significant impact, since these individuals already

1 have a deep knowledge and understanding of the risks  
2 and side effects associated with opioid use.

3           Additionally, patient education, including  
4 the provision of medication guides and patient  
5 education sheets, should not be required in the  
6 inpatient setting. Federal regulations require that  
7 medication guides be provided to patients at the time  
8 of dispensing. Dispensing is the act of delivering a  
9 prescription drug product to a patient for self-  
10 administration by the patient or outside the licensed  
11 practitioner's direct supervision. Dispensing can  
12 also be the act of delivering a prescription drug  
13 product to a patient by a pharmacist under a lawful  
14 prescription. Neither of these occurs in an inpatient  
15 setting since the drug is administered rather than  
16 dispensed to the patient.

17           In closing, ASHP strongly encourages FDA to  
18 explicitly exempt inpatient hospital settings from a  
19 REMS requirement for opioid drugs. Thank you.

20           DR. KIRSCH: Thank you.

21           The next speaker is Kevin Nicholson.

22           MR. NICHOLSON: Good morning, and thank you

1 for the opportunity to speak with you today. I am  
2 Kevin Nicholson, vice president and pharmacy advisor  
3 for the National Association of Chain Drug Stores.  
4 NACDS represents traditional drug stores,  
5 supermarkets, and mass merchants with pharmacies. Our  
6 more than 150 chain member companies include regional  
7 chains with a minimum of four stores to national  
8 companies. Our members fill more than 2.5 billion  
9 prescriptions yearly, which is more than 72 percent of  
10 annual prescriptions in the United States.

11 We are pleased to have this opportunity to  
12 address FDA's expert advisory committees, that you  
13 consider FDA's proposal for a class-wide opioid REMS.  
14 As FDA recognizes in the Federal Register notice for  
15 this meeting, patients suffering from pain need access  
16 to potent opioid products. But also, we must address  
17 the growing problem of inappropriate prescribing,  
18 addiction, and death due to prescription opioid abuse  
19 and misuse.

20 With this in mind, NACDS supports the  
21 measured approach to REMS that FDA appears to be  
22 embracing, as evidenced by the FDA's proposal for the

1 class-wide opioid REMS. FDA must carefully navigate  
2 between mitigating the risks of these medications  
3 while also not negatively impacting patient care.

4 We are pleased that the proposed REMS for  
5 the long-acting and extended-release opioids follows  
6 the advice of stakeholders that emphasizes caution and  
7 deliberation over speed. Take time to develop the  
8 REMS and allow for stakeholder input to prevent  
9 negative consequences.

10 We have met with FDA officials and provided  
11 written commentary on numerous occasions concerning  
12 this proposed REMS, as well as the development of REMS  
13 policy in general. In the past, as we do today, we  
14 strongly encourage FDA to establish REMS in a step-  
15 wise fashion. In other words, first establish  
16 baseline elements that are expected to address the  
17 main concerns that FDA feels necessitates the REMS.  
18 If FDA determines that they are not effective, then  
19 consider moving on to additional elements.

20 As a scope working group has noted,  
21 prescribers are privy to the most personal information  
22 about patients. They can use this information to risk

1 stratify and make a decision whether opioid treatment  
2 is appropriate for a patient. Prescribers can decide  
3 to discontinue opioid therapy or refer patients for  
4 treatment if addiction develops. As such, we agree  
5 with FDA that prescriber involvement is critical to  
6 the success of this REMS.

7 In closing, we thank FDA for moving  
8 cautiously. We believe that FDA is taking the correct  
9 approach, which should lead to FDA achieving its goal  
10 for this REMS. Thank you.

11 DR. KIRSCH: Thank you.

12 The next speaker is Dr. Marcie Bough.

13 DR. BOUGH: Good morning. My name is Marcie  
14 Bough. I'm a pharmacist and director of Federal  
15 Regulatory Affairs for the American Pharmacists  
16 Association, APhA. APhA is the first established and  
17 largest professional pharmacist organization,  
18 representing over 62,000 members who provide care in  
19 all practice settings.

20 APhA has been actively involved in REMS  
21 discussions with FDA and other stakeholders over the  
22 last few years. As outlined in APhA's 2009 REMS white

1 paper, included in the committee member's background  
2 materials, we continue to advocate for a standardized  
3 system-based approach that is feasible and scalable to  
4 accommodate the growing number of REMS programs.

5           Specific to FDA's proposed opioid REMS, APhA  
6 appreciates FDA dedicating time and resources  
7 necessary to evaluate and implement the program.  
8 Additionally, we support provisions, balancing patient  
9 safety, access, and risk management, limiting burden  
10 on the healthcare system, and limiting unintended  
11 consequences, utilizing FDA's Safe Use Initiative to  
12 complement the REMS program, and utilizing accredited  
13 continuing education materials that include specific  
14 information on safety risk the REMS is designed to  
15 mitigate and outcome measures that capture practice  
16 changes.

17           Yesterday, the committees discussed the  
18 impact of education on practice and the benefits of  
19 public health. While not specific to pain, I want to  
20 highlight that pharmacy continues to build on the  
21 successes of immunization education. By 2010, nearly  
22 115,000 pharmacists have been trained to immunized and

1 have administered over 14 million vaccinations this  
2 past flu season.

3           Turning to recommendations, while the  
4 proposed REMS does not include specific requirements  
5 for pharmacists, APhA recommends the following  
6 improvements to strengthen the program. One, first  
7 ensure that pharmacists receive outreach and  
8 educational materials about the REMS program.  
9 Pharmacists often discuss REMS information with  
10 prescribers and patients, and need to be aware of the  
11 program elements.

12           For example, pharmacists may have patients  
13 arrive to the pharmacy with a patient information  
14 sheet they receive from the prescriber. Also,  
15 pharmacists may wish to utilize the tool and review  
16 the educational materials for their own benefit, as  
17 well as with their patients.

18           Second, we recommend recognizing the role  
19 that pharmacists play, as the medication expert and  
20 safe medication use and patient care as an important  
21 part of the healthcare team.

22           Finally, you heard yesterday, nearly



1 76 percent of extended-release opioids are dispensed  
2 through community pharmacies, all of which include a  
3 pharmacist, an important part of patient safety. With  
4 appropriate time and resources, pharmacists can  
5 further improve public health and education. We  
6 challenge FDA and sponsors to continue to evaluate the  
7 potential impact, need for an ability to compensate  
8 for counseling services at the point of dispensing as  
9 part of a REMS program.

10 In closing, we look forward to continuing to  
11 work with all stakeholders as we --

12 [Microphone times out.]

13 DR. KIRSCH: Thank you.

14 The next speaker is Dr. Rosemary Orr.

15 DR. ORR: I have a slide presentation. I'm  
16 a doctor from Seattle and from the University of  
17 Washington. I'm also the mother of Robin, who died of  
18 an Oxycontin overdose in 2006. These are the names of  
19 others of his friends who have died, friends or  
20 children of parents I know in Seattle, in the  
21 subsequent three years.

22 Because, as an anesthesiologist, I don't

1    prescribe long-acting opiates, I had to find out what  
2    I could about Oxycontin. I was astonished to find out  
3    how widespread the abuse of Vicodin and Oxycontin are  
4    in our area. Two friends of my son died in the two  
5    years after he did. The stepdaughter of a colleague  
6    died in 2008. And another colleague has a son who's  
7    been in and out of rehab for his addiction. I also  
8    know of two of my son's friends who continue to have  
9    problems with Oxycontin addiction.

10            This is the latest data from the Washington  
11    State Department of Health. And as you see, up until  
12    2008, and as you know from yesterday, deaths continue  
13    to increase; hospitalizations also.

14            I think that education of the medical  
15    community and the public is key to safe use of  
16    prescription opiates. The pharmaceutical companies  
17    have a very different mission from ours, to make money  
18    for their shareholders. We as physicians must read  
19    about evidence-based efficacy in the medications we  
20    prescribe, and we must use them safely.

21            We were told in 1995 that pain was being  
22    undertreated, and we responded as we could. I believe

1   that this resulted in widespread overuse of opiate  
2   drugs. I use every opportunity to discourage  
3   colleagues and dentists from giving out large amounts  
4   of post-operative opiates, which may remain in  
5   medicine cupboards.

6           I've been a doctor for over 40 years. For  
7   most of my career, I've worked to relieve the pain of  
8   surgery and to provide comfort to children and their  
9   families. I'm not against the treatment of pain;  
10   however, there is more we can do as a medical  
11   community and society to encourage healthy lifestyles  
12   and to use complimentary options for treatment of pain  
13   and other conditions, in addition to drugs.

14           I encourage this committee to work to  
15   control inappropriate prescribing, and inappropriate  
16   marketing of these drugs. I finish with a quote from  
17   my son. "Mom, Doctors are the biggest drug pushers in  
18   this country." And I wish I had listened to him.  
19   Thank you.

20           DR. KIRSCH: Thank you.

21           The next speaker is Rebecca Kirch.

22           MS. KIRCH: Good morning. I'm Rebecca

1 Kirch, associate director of policy for the American  
2 Cancer Society Cancer Action Network. While many  
3 effective medicines are available to relieve cancer-  
4 related pain, significant pain assessment and  
5 management deficiencies are consistently reported in  
6 the clinical settings where patients and survivors get  
7 their care.

8           The medicines that are the subject of this  
9 particular REMS are very important to people living  
10 with cancer-related pain to ease their suffering and  
11 help maintain their quality of life. As such, we are  
12 immensely grateful for the time and care that FDA  
13 devoted to this REMS process, particularly staff's  
14 consistent efforts to hear and use stakeholder input  
15 along the way. We're pleased that much of the input  
16 is reflected in the balanced background materials that  
17 are in front of the joint committee for this meeting.

18           I'd like to focus my brief comments this  
19 morning on the importance of continuing our work  
20 together to articulate specific and meaningful access  
21 measures as part of this REMS, to ensure this  
22 initiative does not inadvertently impede patient care

1 and that we also have an appropriate and timely  
2 agreed-upon exit strategy at the ready, if we  
3 determine that it does cause harm.

4 I know and am reassured that this topic of  
5 determining appropriate access measures to help  
6 evaluate the impact of REMS has been an area of  
7 intense discussion within FDA. Research findings from  
8 a prescriber's survey, that ACS CAN helped coordinate  
9 across the palliative care professional community last  
10 year, made clear how regulatory activity, in the  
11 absence of meaningful stakeholder involvement, in that  
12 case, FDA's unapproved opioids initiative, can cause  
13 real harm to patients very quickly.

14 Most significantly in that study, it  
15 included more than 2,600 responses from all 50 states,  
16 while more than half of the responding doctors and  
17 nurses confirmed that they experienced shortages and  
18 availability of important pain medicines, and more  
19 than one-third indicated that they were forced to  
20 change medications for stable patients as a result.

21 Given that learning experience, we know that  
22 evaluating the impact of this particular REMS, on

1   prescribing and patient care, and doing so at regular  
2   intervals, will be critical to the success or failure  
3   of this initiative.

4             Our hope moving forward is that FDA will  
5   continue to work closely with stakeholders to  
6   determine and agree on clear access measures, and the  
7   timeline for implementing them, to gauge how the REMS  
8   is doing, and how patients are faring.

9             ACS CAN stands ready to work with FDA, its  
10  advisory committees, and our many partners in the  
11  health professional community to help determine and  
12  agree on the most useful and appropriate measures and  
13  timelines to use regarding REMS and patient access, as  
14  well as the research process we use to implement those  
15  measures, to ensure continued access to essential pain  
16  medicines that promote better pain management and  
17  improved quality of life. Thank you very much.

18            DR. KIRSCH: Thank you.

19            The next speaker is Dr. Jacqueline Watson.

20            DR. WATSON: Good morning. My name is Dr.  
21  Jacqueline Watson, and I'm the executive director for  
22  the District of Columbia Board of Medicine. I have no

1 financial interests to disclose.

2           On behalf of the Federation of the State  
3 Medical Boards, I am pleased to speak in support of  
4 the FDA's proposal for a class-wide REMS for long-  
5 acting, extended-release opioids.

6           The Federation represents the 70 state  
7 medical and osteopathic boards in the U.S.  
8 territories. These boards are responsible for  
9 regulating the practice of more than 750,000  
10 physicians in this country. The vast majority of the  
11 boards also license physician assistants and a variety  
12 of other licensed health professionals.

13           Since 1998, the Federation has worked with  
14 major stakeholders, including leading pain and  
15 addiction specialists, medical professional  
16 organizations, state medical boards, and state and  
17 federal law enforcement to develop and promulgate  
18 guidelines for the safe and effective prescribing of  
19 opioid analgesics.

20           The resulting model policy for the use of  
21 controlled substances for the treatment of pain has  
22 been adopted, in whole or in part, by 41 state medical

boards, including the District of Columbia. In 2007, the Federation Research and Education Foundation published the handbook Responsible Opioid Prescribing: A Physician's Guide. This publication translates the model pain policy into pragmatic and effective strategies for physicians to apply in the clinical setting.

The practical guide, authored by Dr. Scott Fishman, chief of pain medicine at UC-Davis, provides physicians effective strategies for reducing the risk of addiction, abuse, and diversion of opioids that they prescribe to their patients in pain.

It has been distributed by 21 state medical and osteopathic boards to more than 150,000 physicians, other prescribers, and physicians in training. State medical boards have enthusiastically endorsed the book and continue to seek resources to support their distribution of the book. Boards have communicated to their licensed physicians that use of the book will help them safely and more effectively manage their patients' pain. This book is accredited for 7.25 Category I hours of CME education and can be



1    used to fulfill state medical boards' CME requirements  
2    for license renewal.

3               The American Academy of Pain Medicine and  
4    the Alliance of State Pain Initiatives submitted  
5    written comments on July 8th, urging the FDA to  
6    designate the responsible opioid prescribing CME  
7    activity as a mandatory element of all prescriber  
8    education curricula in REMS for long-acting opioids  
9    prescribing.

10              The FSMB supports the AAPM and ESPI  
11    proposal, and working with the ACCME, the University  
12    of Wisconsin, and/or the University of Texas,  
13    Southwestern Medical Center, the Federation has the  
14    capacity to revise and expand the CME activity to  
15    ensure the content reflects the FDA's expectations.

16              In conclusion, the Federation supports --

17              [Microphone times out.]

18              DR. KIRSCH: Thank you.

19              The next speaker is either Dean Hart or  
20    Mr. Mohler.

21              MR. MOHLER: Good morning. My name is David  
22    Mohler, and I'm speaking on behalf of NanoGuardian,

1    which is an on-dose pharmaceutical security technology  
2    company.  I am a lawyer for NanoGuardian, and that's  
3    my interest.

4               NanoGuardian appreciates FDA's including  
5    multiple stakeholders in the discussion of opioid-  
6    specific REMS, which was brought to the forefront,  
7    given the need to curb rising misuse and abuse of  
8    these medications.  However, the epidemic of  
9    controlled substance abuse has evolved well beyond the  
10   educational problems that may exist between  
11   physicians, pharmacists, and patients.  And at least  
12   in the early days of the REMS discussions, the illegal  
13   diversion of opioid analgesics was not only referred  
14   to by the agency itself as a surrogate for abuse but  
15   also referred to as a serious issue that would be  
16   included in the REMS.

17              While it's understandable that the agency  
18   has decided to focus its efforts on improving the  
19   education of the people who belong in the legitimate  
20   patient pharmacy and doctor system, there remains a  
21   looming issue, which will continue to drive the  
22   escalation of misuse/abuse of these products, the

1 criminal diversion of these medicines.

2           So while we at NanoGuardian are extremely  
3 grateful for being included in the process and support  
4 greater education, we're disappointed that the agency  
5 has not recommended using all resources available to  
6 tighten the supply chain to avoid diversion.

7           These resources include new on-dose  
8 technologies which can help law enforcement and the  
9 agency determine the source of illegally diverted  
10 opioids, such as the 100,000 Oxycontin found in a  
11 hidden compartment of a car stopped in North Carolina  
12 in April of 2009.

13           Even without packaging, on-dose technologies  
14 can help to determine the source of these products.  
15 On-dose and other technologies can aid law enforcement  
16 in determining the true source of these illegally  
17 diverted medications, and thereby reduce diversion of  
18 products throughout the nation.

19           Finally, we wanted to make a small comment  
20 aimed at correcting the record from the process. In  
21 the agency's comments about on-dose anti-  
22 counterfeiting technologies and diversion

1 technologies, the agency noted that wholesalers argued  
2 that requiring manufacturers to use on-dose  
3 technologies to aid and track and trace would put a  
4 burden on wholesalers. While some technologies do  
5 require significant downstream supply chain  
6 participation, technologies such as NanoGuardian's  
7 nanoencryption technology can work very effectively  
8 without any downstream supply chain partner  
9 participation. These technologies can provide very  
10 meaningful data to law enforcement and regulators to  
11 fight in their fight against diversion, primarily  
12 through the activities of manufacturers of these  
13 agents.

14 Thank you again for allowing NanoGuardian to  
15 participate. We look forward to seeing you again as  
16 the agency tackles the issue --

17 [Microphone times out.]

18 DR. KIRSCH: Thank you.

19 The next speaker is Fred Wells Brason.

20 MR. BRASON: Good morning, and thank you for  
21 the opportunity. I am here through the Chronic Pain  
22 Initiative in Wilkes County, North Carolina, where we

1 all know that the average of overdose deaths for the  
2 United States is 10 per 100,000. In Wilkes County  
3 last year, we had 46 per 100,0000.

4 We address this issue through the Chronic  
5 Pain Initiative, through the Medicaid authority in  
6 North Carolina, to work with the physicians in our  
7 community to determine the best way to address the  
8 overdose issue. Because of what we did with the  
9 Chronic Pain Initiative, which that study has been  
10 submitted to the FDA through the evaluation of Wake  
11 Forest University, it shows that when prescribers were  
12 working with their patients through the prescription  
13 monitoring program, they were able to find out that  
14 those patients that were doctor shopping.

15 When they had in their hands the physician  
16 contract pain agreement, they found that they were  
17 empowered to work with their patient, and the patient  
18 was empowered to discuss with their doctor the  
19 prescription and the need for possibly more pain  
20 medication. So they found the number one thing that  
21 they could use was that pain agreement that they had  
22 with their patient. In that study, that was found.

1           Working with them and working with the  
2 physicians in that, we found that 70 percent of the  
3 physicians in Wilkes County were utilizing the  
4 prescription monitoring program. The statewide  
5 average is only 20 percent. So that showed that our  
6 physicians were using what they could to work with  
7 their patients. And what we found between 2008 and  
8 2009, the scripts that were appropriated to those that  
9 died from an accidental overdose -- which was 75  
10 percent of those overdoses, meaning 25 percent did not  
11 have any script at all. The 75 percent that did have  
12 a script within two weeks of their death, that was  
13 attributable through the toxicology screen for that  
14 death that had occurred.

15           Those 75 percent, 75 percent of those, in  
16 2009 got their scripts from outside of Wilkes County.  
17 The previous year was only 15 percent. So what it  
18 showed was that the access to the illegal use of the  
19 prescription drugs had been met, because the  
20 physicians were doing what they needed to do. They  
21 were using the pain contract agreements, the emergency  
22 department was limiting the doses of what was being

1   prescribed, and they were looking at the prescription  
2   monitoring program to determine whether the patient  
3   was doctor shopping, and illegally using the  
4   prescriptions that they were trying to write.

5           So in that, we found that the community  
6   could come together. The community could provide  
7   education to the community. The individuals were  
8   instructed to lock up their medications, find a  
9   lockbox if they can. And that's another issue, that  
10  lockboxes aren't readily available. They had to go to  
11  Wal-Mart to get a cash box. But we've done that in  
12  the community to limit the access, because in North  
13  Carolina, 350 million doses of narcotic scripts were  
14  prescribed in 2009 for 9 million people.

15           So that's a lot of pills that are on the  
16  street. So the community education, the physician  
17  education, the patient education has made a difference  
18  in Wilkes County, as is shown through the Wake Forest  
19  evaluation of our project. Because we're still having  
20  the deaths, then we encourage FDA and others, as the  
21  North Carolina Medical Board did, was to prescribe --

22           [Microphone times out.]

1 DR. KIRSCH: Thank you.

2 Our last speaker in this session is Seddon  
3 Savage.

4 DR. SAVAGE: Good morning. My name is  
5 Seddon Savage. I'm a physician in pain medicine and  
6 addiction medicine. I currently serve as president of  
7 the American Pain Society, and I am speaking on behalf  
8 of APS.

9 APS is a national community of basic science  
10 and clinical researchers, and of clinicians across a  
11 broad spectrum of practice, physicians, nurses,  
12 psychologists, pharmacists, and others. APS thanks  
13 the FDA on its careful consideration of the comments  
14 of diverse stakeholders over the past two years and in  
15 work towards achieving a balanced approach to REMS.

16 We believe that REMS should ideally support  
17 improved opioid prescribing by clinicians, safe and  
18 effective use of prescribed opioids by patients, deter  
19 misuse by patients and the public, and avoid  
20 significant interference with appropriate prescribing  
21 for pain.

22 We believe that FDA has listened and in



1 large part achieved this through a combination of  
2 requirements for patient education and physician  
3 education, and very importantly, for assessment of the  
4 outcomes, the impact on both misuse, diversion, abuse,  
5 and on access to treatment.

6           Moving forward, APS stands with multiple  
7 partners ready to actively assist in design and  
8 implementation of REMS as helpful. With the  
9 California Academy of Family Physicians, we convened  
10 earlier this summer, a consortium of professional  
11 organizations in primary care, pain medicine, and  
12 importantly, addiction medicine, that included  
13 physicians, nurse practitioners, physician's  
14 assistants, pharmacists, prescribers, and dispensers,  
15 national organizations to reach consensus on core  
16 competencies for safe and effective prescribing of  
17 pain. Those competencies have been submitted to the  
18 docket, and a list of the organizations involved.

19           Collectively, these organizations have vast  
20 experience in education, training, and most  
21 importantly, implementation of practice change. We  
22 need to move beyond education to effective change in

1 practice. This will involve diverse and multi-modal  
2 approaches. Academic detailing may be a very valuable  
3 one of them, using technology as outreach to  
4 accomplish this.

5 Over the long run, clearly REMS alone is not  
6 a solution. We need public education, but probably  
7 most importantly, we need better training in the  
8 spectrum of approaches to effective treatment of pain;  
9 not just opioids, but pain treatment and understanding  
10 of pain in the core curriculum of physicians, nurses,  
11 pharmacists, physician's assistants, and others who  
12 treat patients with pain, in the core training. We  
13 will only solve this problem with that and with  
14 training in addiction medicine, which is the other  
15 side of the challenge that we're --

16 [Microphone times out.]

17 DR. KIRSCH: Thank you.

18 The open public hearing portion of this  
19 meeting has now concluded and we will no longer take  
20 comments from the audience. The committee will now  
21 turn its attention to address the task at hand, the  
22 careful consideration of the data before the

1 committee, as well as the public comments.

2 It's now time to take a 15-minute break.

3 Our clock says that it's approximately 9:30, and we  
4 will reconvene at 9:45. Thank you.

5 (Whereupon, a recess was taken.)

6 DR. KIRSCH: The meeting will reconvene now.  
7 The plan for the next section of the agenda will be,  
8 first, two clarifying presentations. We will then go  
9 back to the list that we had for members of the  
10 committee to get clarification of issues from  
11 yesterday and from today. It's important to note  
12 that, although this portion is open to the public  
13 observers, public attendees may not participate,  
14 except at the specific request of the panel.

15 So the first presentation we're going to  
16 have is by Laura Governale. And she had a number of  
17 questions given to her yesterday, and my understanding  
18 is that her presentation today will hope to try to  
19 clarify some of the issues that the committee had  
20 yesterday. Copies of Dr. Governale's presentation  
21 have been given to members the committee, and we will  
22 post them on the website after the meeting.

1 DR. GOVERNALE: Good morning. I'm here  
2 today to address a few of the questions that were  
3 raised yesterday. And one of them was about the cost  
4 of promotional spending for extended-release and  
5 immediate-release opioids. Now, these databases are  
6 used primarily by the Division of Drug Marketing,  
7 Advertising, and Communications, so they're the real  
8 experts with these data. So perhaps, if any of them  
9 are in the audience, they might want to come up and  
10 add to this.

11 So what we're looking at here is the cost of  
12 professional promotional activities for extended-  
13 release opioids from the years 2005 to 2009. And it's  
14 been kind of sporadic in the recent years. But for  
15 year 2008, there was about \$28 million spent, but in  
16 year 2009, it's gone down to about \$15 million.

17 The cost of promotional spending, it shows a  
18 cost of advertising, journal promotion, and also the  
19 cost of contacts, which is basically going to  
20 physicians' offices by the sales reps.

21 The next slide shows the total cost of  
22 promotional activities for immediate-release opioids.

1 And it was at its highest point with \$34 million in  
2 year 2005, but in year 2009, it's gone down to about  
3 \$12 million. And in this case, the professional  
4 promotional spending included cost of contacts,  
5 journal promotion, and retail value of samples, which  
6 was not included in the extended-release promotional  
7 activities.

8           So moving on, I also wanted to address the  
9 questions about the number of unique patients  
10 receiving these individual extended-release opioid  
11 products. And the trends were pretty similar to what  
12 was shown for the dispensed prescription slide. So  
13 the pink bar represents the extended-release oxycodone  
14 products, and the lighter blue bar represents the  
15 transdermal fentanyl products. And the darker blue  
16 bar represents extended-release morphine products.  
17 And the purple bar represents patients on morphine in  
18 the last couple years. The brownish bar represents  
19 the extended-release oxymorphone products.

20           If there are no further questions, I'll end  
21 here.

22           DR. KIRSCH: Thank you.

1           The next item is one of the members of the  
2 committee had questions yesterday and was able to  
3 gather some data, which we are going to allow him to  
4 present. Dr. Wolfe has got two slides.

5           DR. WOLFE: This was discussed very briefly  
6 yesterday, and Dr. Van Zee mentioned it again, that  
7 one of the problems or worries about REMS is not the  
8 program itself, but that it could easily be  
9 overwhelmed entirely by various kinds of marketing  
10 promotional activities.

11           This is a summary. The data are from drug  
12 topics, which is a random sample of thousands of  
13 retail pharmacies and prescriptions filled in a given  
14 year, in millions. And the point of this is to  
15 connect the marketing activities of Purdue -- and I'm  
16 afraid the deadly elephant in the room is not  
17 necessarily the present Purdue people, because I have  
18 no reason to think that they were involved in what  
19 happened back when. But the company was convicted of  
20 criminal activity. And it was based on what they did  
21 between the time when the drug was first marketed and  
22 the end of 2001. And what they did is overstate the

1    benefits, understate the risks. And the predecessor  
2    of what we're talking about here on extended, long-  
3    acting opioids is a risk management program that the  
4    FDA and Purdue agreed upon in 2001.

5            As you can see in the upper left-hand corner  
6    of the slide, Purdue was supposed to stop false  
7    marketing claims, and they adopted a risk management  
8    plan. Somehow or other, after this was adopted, they  
9    kept selling huge amounts of Oxycontin. And in the  
10   beginning of '03, the FDA wrote them a strong warning  
11   letter about what they had done, in clear violation of  
12   the risk management program.

13           This is a letter January 17th, '03 from the  
14   FDA to Purdue. In fact, it was to one of the people  
15   who pleaded guilty to criminal charges himself.

16           "Your journal advertisements omit and  
17   minimize the serious safety risks associated with  
18   Oxycontin and promoted for uses beyond which have been  
19   proven safe and effective. Specifically, your journal  
20   advertisements fail to present, in the body of the  
21   advertisement, any information from the box warning,"  
22   and so forth; grossly overstate the safety profile of

1 Oxycontin.

2           So in the middle of a period of time where  
3 they are, A, under a risk management program, and  
4 after the justice department, a year earlier in 2002,  
5 had begun their criminal investigation, their  
6 investigation of the company, they were still doing  
7 things to help to sell their drug.

8           It's interesting this morning in this  
9 discussion, people mentioned dealers, that the REMS  
10 program doesn't affect dealers. Where do the dealers  
11 get their pills from? I think maybe a small amount  
12 may be stolen, but they are buying them from other  
13 people who are needy, financially, who get  
14 prescriptions written and sell them.

15           The point is that a huge amount of this drug  
16 has been in traffic. And in May of 2007, the company  
17 pleaded guilty, was convicted by the U.S. Department  
18 of Justice; paid \$600 million to settle criminal and  
19 civil litigation, and signed a corporate integrity  
20 agreement with the Office of Inspector General and  
21 HHS.

22           We have been trying to get what has



1 happened, the progress of this agreement. I hope the  
2 FDA has it. I raised this a couple years ago. We've  
3 gotten a copy, 90 percent of which has been redacted.  
4 We are very eager to see what has happened in this  
5 agreement that the company made, having been caught  
6 once again for earlier activities.

7           The summary of this slide is there's been --  
8 in terms of Oxycontin itself. There's generic  
9 oxycodone available. This is just Oxycontin itself.  
10 There's been a huge increase, tripling, since the year  
11 when the company pleaded guilty to criminal charges in  
12 a number of prescriptions.

13           The next slide shows the same thing, in  
14 terms of retail sales. This is again, drug topics.  
15 The company gets, not obviously all of this --  
16 probably a quarter, a third, but the amount of money  
17 that they have gained since the criminal conviction,  
18 and sales of this drug far exceeds the amount that  
19 they paid. I debated the U.S. attorney on the  
20 NewsHour after this conviction, arguing why did no one  
21 go to jail, and why did the company pay only money  
22 under activities through the end of 2001.

1           Summary is we've got to pay huge attention  
2 to marketing promotion. This includes the funding of  
3 a large number of pain societies, some of which  
4 testified this morning. The individuals who testified  
5 themselves have no reason to think they got money from  
6 the company. But certainly, many pain societies --  
7 this was in the 70-page indictment by the U.S. Justice  
8 Department, many of these pain societies were funded  
9 by Purdue, and probably other companies.

10           So we have to pay attention to this. This  
11 company seems to have bounced back since, and it was  
12 convicted criminally, sold more drugs, Oxycontin, and  
13 way more prescriptions are in there. The figures that  
14 were given were something like 7 or 8 million  
15 prescriptions in 2009 of all extended-release  
16 oxycodone, of which the majority is Oxycontin.

17           So I'm very worried about this. I'm sure  
18 I'm not the only one that's worried. And I just think  
19 that it needs to be part of the discussion. Even  
20 though we're focused on, as we should be, REMS, these  
21 kinds of efforts can just swamp out everything in REMS  
22 unless these companies, any company that does this, is

1 properly penalized, which they were not the last time.  
2 And people who have engaged in criminal activity  
3 actually go to jail as opposed to paying out of their  
4 own pockets, which three of their officials did, \$30  
5 million or so, but didn't have to go to jail.

6 We're not going to have enough deterrent for  
7 this kind of activity. This is another sort of  
8 deterrent of the industry. Thank you. I'd be glad if  
9 there are any questions at all on this.

10 DR. KIRSCH: Yesterday, there was a number  
11 of questions related to advertising. And it's my  
12 understanding that FDA has made available Tom Abrams.

13 Is Tom Abrams here? I'd ask him to come to  
14 one of the microphones, and I'll allow members of the  
15 committee to ask Mr. Abrams. Mr. Abrams is in charge  
16 of advertising for FDA.

17 Are there questions for Mr. Abrams?  
18 Dr. Farrar?

19 DR. FARRAR: I guess one of the things that  
20 would be important for the committee to understand is  
21 the authority that the FDA would have with regard to  
22 the implementation of warning labels or other things,

1 with regard to the opioids. And it's very clear in  
2 the television advertisements that they have to run  
3 through the litany of potential issues. I don't think  
4 I've seen an advertisement for opioid on television  
5 for quite a long time.

6 But I wondered what the authority is in  
7 terms of the paper and advertisements and the  
8 brochures that are produced, and so on, if the REMS  
9 was approved and there was some need to place a box  
10 warning or something else that says, "Potential for  
11 Abuse," et cetera.

12 MR. ABRAMS: Hello, everyone. I'm Tom  
13 Abrams, director of the Division of Drug Marketing,  
14 Advertising, and Communications at the Food and Drug  
15 Administration. Our authority would extend to all  
16 promotional materials. That would include TV  
17 advertisements, any other materials directed to  
18 consumers and patients, as well as healthcare  
19 professionals.

20 Specifically, with your questions, the  
21 regulations would require a fair balance of risk  
22 information. That would include serious warnings,

1 including the box warnings, which are in the opioid  
2 labeling. It would also include elements of the REMS,  
3 which would be put into place. That would be one of  
4 the requirements that the companies would have to  
5 adhere to.

6 DR. KIRSCH: Sid?

7 DR. WOLFE: Tom, this question was asked  
8 yesterday, and you weren't here, and I think you can  
9 probably answer it now.

10 With the REMS now having been part of FDA  
11 law through the 2007 FDAAA, do you have any additional  
12 authority that you did not have now, to impose  
13 sanctions on companies, specifically in the area of --  
14 well, in this case, it's the opioid REMS. But do you  
15 have any more authority now than you had before, in  
16 terms of fining or any other sorts of sanctions  
17 against companies?

18 MR. ABRAMS: One of the new authorities that  
19 we have in place, apart from FDAAA, is the Food and  
20 Drug Amendments Act of 2007. That gave us the  
21 authority to impose civil monetary penalties on  
22 manufacturers for misleading direct-to-consumer

1 advertisements. Most of the promotion is directed to  
2 healthcare professionals, I note.

3           However, our existing authorities include  
4 issuing regulatory warning letters and untitled  
5 letters, as well as seeking injunctions, and seeking  
6 seizures if necessary, as well as working with the  
7 Department of Justice. The testimony before  
8 referenced a case that the Department of Justice  
9 worked on and imposed on the manufacturer of  
10 Oxycontin. FDA was very intimately involved in the  
11 investigation and work-up of that case.

12           DR. WOLFE: Just a quick follow-up question,  
13 which is, yesterday, when this was raised, someone  
14 said, and I guess you've confirmed it, that the 2007  
15 FDAAA did not confer authority on you to impose civil  
16 monetary penalties for journal advertisements.

17           The warning letter that you all sent in 2003  
18 to the company was for a journal advertisement. And  
19 so you're saying that because that wasn't direct to  
20 consumer, you do not have any authority to impose  
21 civil monetary penalties on journal ads or any other  
22 professional advertising; is that correct?

1           MR. ABRAMS: The civil monetary penalty  
2 provision that was included in FDAAA is for direct-to-  
3 consumer advertisements that would appear in consumer  
4 magazines. It would not include journal  
5 advertisements appearing in medical journals.

6           DR. WOLFE: Thank you.

7           DR. KIRSCH: Dr. Morrato.

8           DR. MORRATO: Thank you. I think it might  
9 also help the committee, perhaps, if you could explain  
10 a little bit as to how launch materials or  
11 advertising's actually reviewed, because I think  
12 there's some parallels to some regard with how the  
13 safety data is being discussed, in terms of core.

14           What I'm thinking there is, it's my  
15 understanding that a company, when they're getting  
16 ready to launch, they'll provide what would be their  
17 launch advertising so that it's checked against what  
18 the label is, and that it's representative of what the  
19 full launch materials will actually be, and that the  
20 company then has the ability to execute that message,  
21 if you will, in multiple media formats.

22           So maybe you could explain that process.

1 And what is the process then for self-regulation of  
2 when someone may be veering off in the execution? The  
3 content may be there, but really, the delivery of the  
4 message, the art of the advertising, and how that kind  
5 of comes to your attention.

6 MR. ABRAMS: There's no requirement for most  
7 drugs to submit their draft promotional materials  
8 beforehand. The law is clear that all promotional  
9 pieces have to be submitted to the agency at the time  
10 of initial dissemination. We receive about 76,000  
11 promotional pieces a year, just to give you an idea of  
12 what comes in.

13 One of the exceptions is for drugs approved  
14 under Subparts E and H, the accelerated approval  
15 provisions. In those materials, for those drugs  
16 rather, all the materials have to go and be submitted  
17 to FDA 30 days prior to use. There's no requirement,  
18 however, that the company has to incorporate FDA's  
19 comments. It's not a pre-clearance or a pre-review  
20 provision. It's a pre-submission requirement.

21 One thing I have to add to that. The  
22 regulations allow for the voluntary submissions of



1 proposed launch materials. FDA encourages the  
2 submission of these materials, especially for drugs  
3 which have serious risks, such as for opioids. We  
4 encourage companies to submit the materials. We make  
5 it a high priority to get comments back to the  
6 company. We work very closely with the medical review  
7 divisions to do that. And our hope is to prevent  
8 misleading messages from first occurring.

9 DR. KIRSCH: Dr. Craig. Dr. Turk.

10 DR. MICHNA: I think they were referring to  
11 a question I had earlier. And this goes to Mr. Wolfe.

12 I'm a little confused by the chart that he  
13 presented and what the purpose of it was. To me, the  
14 scripts have been very consistent. There was a dip,  
15 but -- somebody could correct me if I'm wrong. But  
16 that was when Oxycontin went generic. And they lost  
17 to generic competition. It then became a branded  
18 product again, and there was no other generics.

19 So in looking at this, my impression is  
20 Oxycontin prescriptions have been consistent, if not a  
21 little lower. Sales are up probably because they  
22 raised the price. So I was a little confused of what

1 the purpose of the graph was.

2 DR. WOLFE: Well, it was just to show the  
3 Oxycontin, the brand name itself. I mentioned that  
4 before, in the data shown yesterday, the total number  
5 of oxycodone extended-release prescriptions for, I  
6 guess 2009, was maybe 7 or 8 million. So it is the  
7 majority now. I mean, I think that Oxycontin has  
8 become a brand name in a very unfortunate kind of way,  
9 and I think there's probably a lot of attraction to  
10 get back to more prescribing Oxycontin. The company  
11 has tripled its sales, tripled its prescriptions since  
12 the time that this criminal conviction occurred.

13 DR. MICHNA: Well, it really hasn't, only  
14 because it was a situational thing, where it was  
15 generic, and it went back to the branded product. So  
16 I don't think you can draw that conclusion now.

17 DR. WOLFE: The conclusion is simply that  
18 Oxycontin is selling more, the brand name Oxycontin.

19 DR. MICHNA: And I think the reason that  
20 there was an increase, and it hasn't been consistent -  
21 - look, I'm not a supporter of industry, but I don't  
22 want to mislead the facts here. The facts, I think,

1 reflect the fact that it went generic, and then it  
2 became a branded product again, not that there was an  
3 increase in marketing that produced an increase in  
4 sales.

5 I mean, I think we have to be clear when we  
6 present data, as to what it's actually saying. I  
7 don't want to mislead anybody here. And it seems like  
8 the scripts have been very consistent. And being a  
9 clinician, obviously, a product, whether it's been  
10 abused or not, there is a clinical need for it. And  
11 obviously, physicians with all the knowledge and all  
12 the issues with the misuse, still feel it's an  
13 effective drug for a consistent number of their  
14 patients, for whatever reason. That's all I'm saying.

15 DR. WOLFE: But just a quick response is  
16 that the "need" for probably more extended release is  
17 warranted by the situations that probably immediate  
18 release was created by this company. It's been  
19 sustained, if that's what you're saying. I think the  
20 company has done a good job sustaining the massive  
21 prescribing that they caused for a five-year period  
22 until they got caught by the FDA.

1           Yes. There's been a decrease because of  
2   some generic, but they are back in business again. It  
3   sold way more than they have paid in criminal  
4   penalties.

5           DR. MICHNA: Well, I think --

6           DR. KIRSCH: I think that we have data that  
7   was presented with two sides of understanding of what  
8   the data shows. And I think we could debate that for  
9   a long time, but we won't.

10          Dr. Denisco?

11          DR. DENISCO: Relative to promotional  
12   activities, in epidemiology, it's always difficult to  
13   find what causes what; what is the causality? What  
14   caused it and what is just merely associated? This is  
15   a situation where that case exists.

16          If we go back to the 1990s, certainly there  
17   were many calls by the WHO, by many pain societies, by  
18   individuals to relax the regulation of prescription  
19   opiates. However, if you look epidemiologically, the  
20   points of upturn in the morbidity and mortality data,  
21   it seems to be clearly related to sales of Oxycontin.  
22   And it's this whole problem, that is the number two

1    cause of accidental deaths, that seems to be able to  
2    be tracked back to the illegal promotion of this one  
3    medication, which had an effect of publicizing the  
4    desirability of prescription medications with front-  
5    page ads, front-page publications on both Time and  
6    Newsweek.

7                Because of the serious nature of this and  
8    the close relationship of this to marketing, I, number  
9    one, wonder if you have looked at the marketing data,  
10   and would agree with me, relative to the epidemiologic  
11   data. And number two, based on the fact that, prior  
12   to this, it was possible to get by with an immediate-  
13   acting opioid product or a very strong-acting product  
14   such as Dilaudid for a short period of time, until you  
15   can switch a patient over to a longer acting  
16   medication.

17               It seems with this high morbidity and  
18   mortality, that a program of protection, greater than  
19   what we have seen yesterday, would be warranted and  
20   would not unduly delay the treatment of patients to  
21   register somebody or for the physician to check a  
22   database. It does not appear to me that there was any

1 significant morbidity and mortality prior to the mid-  
2 1990s, when the problem, the morbidity/mortality  
3 problem, and the marketing of Oxycontin shot up.

4           There was no problem related to people  
5 getting medication immediately. And if it meant for a  
6 day or two, the nursing staff would have to run and  
7 get some more doses of medicine to administer to the  
8 patient until everything was clear. We did not hear  
9 any data that this was causing any problems, but we do  
10 hear data that the current situation is causing  
11 problems to the rate of second only to motor vehicle  
12 accidents.

13           Would you agree with that, based on your  
14 analysis of the promotional data?

15           MR. ABRAMS: A number of issues here.  
16 First, it is a complex issue. Part of your question  
17 is for practice of medicine, evolution of practice of  
18 medicine, or how it turns, and FDA obviously does  
19 regulate the practice of medicine.

20           Then, another part is for correlation of  
21 marketing data or sales data to the promotional  
22 efforts. And there's so many factors that go into the

1 sale and prescribing of prescription drugs, it's  
2 difficult. I have not seen anybody who's been able to  
3 tease out a promotional activity and have a direct  
4 correlation.

5 I think there's two main points here, as far  
6 as promotion. First, FDA's charged with ensuring that  
7 promotion of prescription drugs is not false, is not  
8 misleading, and is balanced, balanced with the serious  
9 toxicities, or risk which may be associated with the  
10 drug, as well as other material information, comments,  
11 and adverse events.

12 There's no limitation. FDA does not have  
13 any authority on the extensiveness of promotion. I  
14 often hear people saying, "Well, there should be a  
15 limit on how much a company can spend on promotion or  
16 how far it can do it." FDA does not have that  
17 authority. What we look at is the messages, whether  
18 they are accurate and balanced.

19 DR. DENISCO: Just quickly, that's where my  
20 point is exactly, that the initial messages, starting  
21 back from the 1990s, were not balanced. I don't care  
22 how much they choose to market. But the marketing was

1 false, and in some large way, contributed to the  
2 problem we're dealing with today, due to an unbalance  
3 of the advertisement, is my problem.

4 MR. ABRAMS: Just another comment on that.  
5 I think it's hard to correlate the promotion to what  
6 may have happened. But I think a more important point  
7 is, the agency has acted when it has seen misleading  
8 promotion. It has issued regulatory letters in the  
9 '90s. It has also issued a warning letter that  
10 Dr. Wolfe referenced in his comments. So when the  
11 agency does detect misleading promotion, we are  
12 prepared to act against it.

13 DR. KIRSCH: Dr. Flick.

14 DR. FLICK: Another questions regarding  
15 promotion. I just want to be clear.

16 Does FDA have the authority to require that  
17 this class of drugs marketing be cleared prior?

18 MR. ABRAMS: No, it does not.

19 DR. FLICK: Okay.

20 MR. ABRAMS: I may reference somebody from  
21 our legal department, if they want to add something to  
22 that.



1 DR. FLICK: Do you have authority to review,  
2 at some time, or require review of all the marketing  
3 materials?

4 MR. ABRAMS: We do not have the authority to  
5 pre-clear materials. We do have the authority, in  
6 certain cases, of Subpart E and H drugs, to require  
7 pre-submission. That would give us the opportunity to  
8 review the draft materials before use and then provide  
9 comments. We do not have the authority to require  
10 pre-clearance. That means approve. We do not approve  
11 actual promotional pieces before they go out in use.

12 DR. FLICK: But currently, this class of  
13 drugs, you do not require pre-submission of marketing  
14 materials?

15 MR. ABRAMS: That is correct.

16 DR. FLICK: Do you believe it should be the  
17 situation?

18 MR. ABRAMS: I would have to discuss that  
19 with other people in the agencies and respond later.

20 DR. KIRSCH: Okay. The next question is  
21 from Dr. Markman.

22 DR. MARKMAN: My question pertains to

1 several of the presentations from yesterday, regarding  
2 the so-called balloon effect. The balloon effect was  
3 referencing the -- related-to-access-to-care issue  
4 with regard to patients and prescribing of opioids.

5           It was sort of alleged or hypothesized that  
6 making education mandatory would, for physicians and  
7 prescribers and other clinicians, limit access to  
8 care. We heard in the public session today from two  
9 speakers, Dr. Katz and Mr. Porada, who have data to  
10 suggest that that's not the case, or that hypothesized  
11 balloon effect may be, in fact, imaginary.

12           So I was just interested in hearing from  
13 folks at the agency who presented yesterday, or any of  
14 the other presenters, any data to support the  
15 likelihood of that balloon effect occurring.

16           The reason I ask this is because, as a  
17 clinician in practice, who like workers in every other  
18 industry, I'm required virtually every month to take  
19 some sort of training test, whether it's to give  
20 conscious sedation or for infection control or to  
21 reduce my malpractice premiums, to show that I can  
22 safely make decisions and communicate with patients

1 and other colleagues. So it's virtually an ongoing  
2 process, to protect patient privacy.

3 So I just want to understand whether those  
4 things don't inhibit my ability to wash my hands or to  
5 give conscious sedation. In fact, they enhance my  
6 confidence that I can do it well. I invariably learn  
7 something, and it changes my practice.

8 So I just want to understand better, the  
9 evidence for a dampening effect on prescribing for the  
10 most prescribed drugs in America, if there's any  
11 evidence for that.

12 DR. RAPPAPORT: The access group went  
13 through this in quite a bit of detail, and looked at  
14 every submission from every stakeholder who had  
15 comments related to this, including data. I should  
16 say, when we asked for this a year and a half ago, we  
17 asked publicly for submission to the docket, of as  
18 much data as possible. We heard a lot of people say  
19 they had data. We got not a lot of data in the docket.  
20 We got a lot of opinions.

21 But based on the data in the docket and  
22 based on the opinions that were presented in the

1 docket and at the public hearings -- and that's all  
2 summarized in your background material -- the  
3 conclusion of the access working group and the overall  
4 REMS working group was that there could possibly be an  
5 effect that would be negative on access and that might  
6 cause the balloon effect to result in patients being  
7 treated with other drugs that might have worse  
8 outcomes.

9           Now, that's the conclusion based on the  
10 information we had. There may be additional data.  
11 And we do have, I believe, data from both Dr. Katz and  
12 Porada that has been looked at as well. So I think  
13 part of your charge today is going to be to assess the  
14 data that you have from us, that we summarized for  
15 you, and to consider whether additional data is  
16 needed, and then to make a decision about whether this  
17 is appropriate, that our conclusions are correct, or  
18 whether we need more information, or how to move  
19 forward.

20           DR. MARKMAN: That's helpful. Thank you.

21           DR. KIRSCH: So I'm going to go back to the  
22 list of individuals who raised their hands from

1 yesterday who we couldn't get to. I'd ask that the  
2 members of the committee, when I call on your name, if  
3 the question's already been answered, to pass.

4 I'd ask for the FDA, that maybe Dr.  
5 Rappaport could be the person who can assign the  
6 questions to the appropriate person, since many of the  
7 people from yesterday or some of the people from  
8 yesterday may not be here. And we'll do the best we  
9 can to answer the questions that the committee has.  
10 So the next question comes from Dr. Ballantyne.

11 DR. BALLANTYNE: I actually had a question  
12 from yesterday's presentation by the industry working  
13 group. And it was concerning, actually, Dr. Davis's  
14 presentation on education, particularly the education  
15 of prescribers. And the first item on the list, under  
16 education for prescribers, was, and I quote, "proper  
17 patient selection."

18 So I think that patient selection is such a  
19 critical issue. And in terms of the outcomes we've  
20 all been looking at, we seem to be focused on  
21 catastrophic outcomes. But in fact, there is another  
22 disastrous outcome, and that is failure to meet

1 treatment goals. I realize that we're not considering  
2 that so much here. But proper patient selection is  
3 critical to achieving the goal of a good outcome, in  
4 terms of pain treatment or improvement in quality of  
5 life.

6 My question really was, will this segment,  
7 in teaching prescribers through the REMS, be focused  
8 on how to select patients specifically for extended-  
9 release and long-acting opioids, or will it be in  
10 terms of selecting patients for opioids in general?  
11 Because I see that, actually, it could go both ways.  
12 It could be helpful, in that it helps us select the  
13 right patients for the treatment, or it could actually  
14 be unhelpful or negative, in that it encourages us,  
15 particularly if the drug companies are involved, in  
16 actually selecting people inappropriately for the  
17 treatment.

18 DR. KIRSCH: So there are a number of people  
19 in the front row over there from the industry working  
20 group, and I would ask if any of the individuals from  
21 that group would feel comfortable coming to the  
22 microphone to answer the question. And I'll remind

1 the individuals who come to the microphone to please  
2 introduce yourself prior to answering the question.  
3 Thank you.

4 DR. DAVIS: Eric Davis, with the IWG. And  
5 as far as the educational goals for the prescribers,  
6 this is one area where the IWG believes that we bring  
7 in third parties, the learned societies, those that  
8 are familiar with this topic and pain medications to  
9 assist us in forming the best training and educational  
10 program that we can. So the IWG doesn't propose any  
11 kind of training program on its own, but gets the  
12 material through the learned societies and the  
13 stakeholders.

14 DR. RAPPAPORT: Can I add something?

15 DR. KIRSCH: Please.

16 DR. RAPPAPORT: The choice of patient  
17 selections of the proper patient for opioid use is  
18 obviously a key component of how to properly prescribe  
19 these, and should be a key component of the  
20 educational program. And I agree that this is going  
21 to be written and created by the experts, not by  
22 anybody from industry, and not by us at FDA, just with

1 our oversight. And I want to remind you all that we  
2 will have the oversight to make sure that it's done  
3 right, and to not have it used until it is.

4 DR. BALLANTYNE: Thank you for that. It  
5 seems clear to practitioners that it is such a highly  
6 critical issue, and it's where we all struggle. I  
7 mean, I wouldn't even pretend we know how to select  
8 patients appropriately, but we certainly need to find  
9 out how to do that. And what concerns me is that it  
10 can only be done by our educational efforts outside  
11 this process, that this process cannot be unbiased,  
12 whereas what we do outside this process can, in terms  
13 of selection.

14 DR. KIRSCH: Dr. Deshpande.

15 DR. DESHPANDE: Thank you. This question's  
16 for the FDA.

17 The REMS proposal is focused on the word --  
18 I read the words education, voluntary, and encourage.  
19 And the question I have is, is education in this  
20 setting -- two questions. One is, is education in  
21 this setting the same as training, and is encourage  
22 the same as require?



1 DR. RAPPAPORT: We are requiring that  
2 education be for prescribers. Prescriber education is  
3 required. What we're not requiring is that they be  
4 tested for that and proven to show that they have  
5 reached a certain level of competence. But what we're  
6 doing is asking and requiring of the sponsors that  
7 they survey to make sure that a reasonable percentage  
8 of the prescriber population has been appropriately  
9 trained.

10 DR. DESHPANDE: As a follow-up, one of the  
11 proposed REMS does not include the mandatory patient  
12 education. And I was just going to make a comment  
13 based on two presentations we heard. I think it was  
14 Dr. Savage and Dr. Brason, that the loop for an  
15 effective solution, in their presentations, if I heard  
16 it right, included physician, pharmacist, and  
17 community or patient education as part of the total  
18 loop.

19 So I wanted to find out why, at the end of  
20 the day, this was left out of the recommendation.

21 DR. RAPPAPORT: I think when you look at the  
22 feasibility of requiring patients to be enrolled in

1 some kind of a program -- and you're talking about --  
2 I think the number we estimated was around 4 million  
3 patients. And to capture that information in some  
4 kind of closed system that's going to guarantee that  
5 those patients have been enrolled, and therefore  
6 properly educated, that whole system appeared to us,  
7 and appeared to most of the stakeholders, which is  
8 what we based our decision on, to be so overwhelming  
9 to the public health system that it really was not  
10 feasible. And there are additional issues of  
11 stigmatizing patients and such.

12 Now again, we are open to hearing if people  
13 think we ought to step this up at this point, but we  
14 don't want to step out there with something that is so  
15 overwhelming to the public health system that it's  
16 going to collapse the whole process before we even  
17 test this out. It might be that we do have to go  
18 there eventually if what we proposed doesn't work.

19 DR. JENKINS: If I could add to that? Going  
20 back to Ms. Axelrad's presentation yesterday, let me  
21 remind you that our REMS authority is to regulate the  
22 sponsor of the application for the product. So

1 anything that we exercise has to be affected through  
2 the sponsor or the manufacturer of the product.

3           So some of the considerations that go into  
4 that type of a system is the feasibility and the  
5 desirability of having the sponsor in charge of those  
6 activities. So we did seriously look at the question  
7 of having every prescriber individually registered  
8 into an opioid REMS prescribing system, where they  
9 would be individually enrolled, tested, certified, and  
10 then they could prescribe the drug. We looked at  
11 having individual patients enrolled, so that they  
12 could be educated and certified that they could  
13 receive the drug. We also looked at having real-time  
14 verification of that prescriber training, patient  
15 enrollment at the pharmacy level.

16           Those types of systems do exist for certain  
17 products, like isotretinoin, where it's a much smaller  
18 scope of the number of prescribers and number of  
19 patients involved.

20           In the end, based on all the considerations  
21 you heard, we decided that that was not the direction  
22 we thought was appropriate for this program, keeping

1 in mind that one of the statutory requirements we have  
2 to meet is that it not be unduly burdensome on the  
3 healthcare delivery system and patient access to  
4 therapy.

5 So that's the judgment we made when we put  
6 this all together, and that's why we're putting  
7 forward the program that we are. You know we're  
8 interested in hearing your feedback on whether we  
9 didn't get that balance right.

10 We also were reluctant to create a  
11 registration system for prescribers of scheduled  
12 products when there already exists a registration  
13 system for prescribers of scheduled products. So if  
14 we created it through the REMS, the manufacturers of  
15 these products would have to create that registration  
16 system for prescribers.

17 We were concerned about whether that was the  
18 appropriate way to go when there is already a  
19 registration system. And as Dr. Rappaport said in his  
20 presentation, the more efficient pathway arguably  
21 would be to link it to the DEA registration. As  
22 you've heard, that's something that would require

1     legislation. We cannot do that under the REMS  
2     authority that Congress gave us under FDAAA.

3             DR. KIRSCH: Dr. Flick.

4             DR. FLICK: One thing that we have not  
5     discussed through these past hours is the cost. And I  
6     don't know whether cost is something that is under the  
7     committee's review. But I wonder what do we estimate  
8     the cost of this REMS program, and who will bear that  
9     cost. I see Dr. Neuman is here from Covidien. He  
10    might be able to give us some insight into what the  
11    REMS cost is for EXALGO.

12            DR. KIRSCH: Dr. Neuman.

13            DR. NEUMAN: Herbert Neuman with Covidien  
14    Pharmaceuticals. We don't split out the cost for  
15    EXALGO REMS by itself. We keep the cost for all of  
16    our risk management activities across our entire  
17    product portfolio. I can tell you our investments in  
18    that area are growing on a yearly basis, but for  
19    competitive reasons, I really can't get into our exact  
20    budget.

21            DR. FLICK: Thank you.

22            Dr. Rappaport, do you have a sense of what

1    this will add to the cost of caring for these patients  
2    and providing long-acting narcotics?

3               DR. RAPPAPORT:  I don't, and I don't have a  
4    number in my head.  But I can tell you it's going to  
5    be expensive any way we do this.  Most of the cost  
6    will of course be borne by industry, but you know  
7    where that's going to get passed on to.  And the more  
8    we do, the more cost.

9               And I'm not saying -- we don't take cost  
10   into consideration in making our public health  
11   decisions, but that is a reality that the more  
12   restrictive, the more costs there will be, because the  
13   expense of having registries and systems in place to  
14   monitor those registries would be quite high.

15              DR. FLICK:  Thank you.

16              DR. KIRSCH:  Dr. Woods.

17              DR. M. WOODS:  Thank you.  I'm not sure why  
18   you picked on me at this time.

19              DR. KIRSCH:  I'm sorry.  I got the wrong  
20   Woods.  I'm sorry.  I had the wrong Woods.  If you  
21   have a question, you can ask it and I'll ask the other  
22   Dr. Wood after.

1 [Laughter.]

2 DR. J. WOODS: I'll be happy to make a  
3 comment, if you don't mind.

4 DR. KIRSCH: I'd love to hear it.

5 DR. J. WOODS: I want to go back to  
6 yesterday. It speaks a little bit to the issue of  
7 patient selection and how we can offer better care and  
8 prevent overdosed deaths. Tom McClellan told us  
9 yesterday that there were a couple of studies that  
10 suggested that overdose deaths occurred right after a  
11 script was written. They occurred if someone also had  
12 a script for benzo and if they had some history of  
13 overdose.

14 I'm wondering if we couldn't take the  
15 appropriate sponsors for those folks who have these  
16 scripts, ask them to stratify restrictions and  
17 agreements with their practitioners in ways that would  
18 help us prevent the specific problem associated with  
19 overdose, and actually design interventions, together  
20 with the sponsor, that would reduce the problem. In  
21 other words, deal very specifically with putting a  
22 patch on the hole.

1           In addition, this isn't in any way to speak  
2   against the more general issues that were discussed  
3   with the REMS, but it's something that I've been  
4   grappling with, in thinking that in some ways we're  
5   dealing with very general kinds of things that are  
6   dictated by the restrictions in ways that we have to  
7   move to satisfy laws, et cetera; at the same time, not  
8   dealing very specifically with the public health  
9   problem that's before us.

10           So that's what I was thinking about when you  
11   asked.

12           DR. KIRSCH: Thank you.

13           The other Dr. Woods?

14           DR. M. WOODS: Thanks. I have a couple of  
15   questions. The first, I don't know that will have an  
16   answer. But with respect to the epidemiology of the  
17   epidemic, so to speak, do we have any data to tell us  
18   to what extent the deaths and adverse events occur in  
19   the inpatient setting versus the outpatient setting?

20           DR. RAPPAPORT: Actually, folks from SAMHSA,  
21   do you have any -- No?

22           DR. KIRSCH: Please use the microphone and



1 please introduce yourself.

2 DR. DORMITZER: For deaths --

3 DR. KIRSCH: Please introduce yourself.

4 DR. DORMITZER: Okay. My name is Dr. Cathy  
5 Dormitzer. I'm an epidemiologist in the Division of  
6 Epidemiology in the Office of Surveillance in  
7 Epidemiology.

8 We did not present death data, but there is  
9 death data via the medical examiner data. And if it's  
10 in the medical examiner, those are deaths that are  
11 unattended. So they were outpatient deaths, not  
12 inpatient deaths.

13 DR. M. WOODS: Okay. I suspected we didn't  
14 have great data.

15 I have some questions related to the REMS  
16 program itself and how it might roll out. As I  
17 understand it, with the patient education materials,  
18 prescribers at the time of prescribing the medication,  
19 would provide patients with education material;  
20 correct?

21 DR. RAPPAPORT: Yes.

22 DR. M. WOODS: Then when the patient goes to

1 the pharmacy, they would again be provided that same  
2 material; correct?

3 DR. RAPPAPORT: At the pharmacy, they would  
4 get a Med guide, which would be similar but different.

5 DR. M. WOODS: Okay. When patients are  
6 admitted to the hospital, presumably stabilized on the  
7 medication, would it be required that the pharmacy at  
8 the time of admission provide them the Med guide?

9 DR. JENKINS: You're asking a very complex  
10 question. In general, the medication guide regulation  
11 was written for outpatient dispensing. And generally,  
12 they are not distributed in the inpatient setting.  
13 But there have been, I think, some exceptions where in  
14 fusion centers or other types of environments,  
15 medication guides have been distributed. But in  
16 general, no. They're not distributed in an inpatient  
17 hospital setting.

18 DR. M. WOODS: Thanks.

19 DR. KIRSCH: Dr. Terman.

20 DR. TERMAN: Frankly, I'm a little saddened  
21 by the last couple of days of discussion. Assuming  
22 that I get the education to treat my carefully

1 selected patients with exactly the right amount of  
2 pain medicine, I'm not sure how that is going to help  
3 get rid of abuse and misuse, diversion, addiction, and  
4 most of the deaths, according to the data.

5           When I talk to my opiate expert colleagues,  
6 like my realtor, she tells me that when she's  
7 scheduling an open house, the first thing she asks is  
8 whether people are on pain medicines so to avoid  
9 people participating in the open house, also going  
10 through medicine chests and finding things they're  
11 looking for.

12           So there's been some talk about storage and  
13 almost nothing about disposal. And so, most of the  
14 patients I prescribe opiates for have a long-term goal  
15 of getting off those opiates. I'd just like to know  
16 where we stand in terms of takeback or buyback  
17 programs to try and encourage people, when they do  
18 stop taking their medicines, to be able to get rid of  
19 their opiates in their security cabinets.

20           DR. THROCKMORTON: This is Dr. Throckmorton.  
21 Let me take a shot at that. It is a part of what  
22 we've been talking about in the last couple of days.

1 But you're right; we perhaps haven't focused on it as  
2 much as we could have.

3           It's part of a much larger initiative, that  
4 the FDA and several of the partners that spoke  
5 yesterday are working together on to try to make a  
6 difference. We are trying to minimize people keeping  
7 these drugs longer than they need to, minimize getting  
8 more of the drugs than they needed at the time.

9           How to affect that and how to use the REMS  
10 to make that more effective is one thing we'd like to  
11 hear your thoughts on. I would say, however, the  
12 other piece that we've talked about these last couple  
13 of days, is another aspect of it. The Safe Use  
14 Initiative that Karen Weiss spoke to yesterday is  
15 about groups working together to try to do this kind  
16 of thing more effectively. And at least, my own  
17 personal view is that that's much more likely to be  
18 effective than trying to use a program targeted like  
19 the REMS to achieve it by itself.

20           DR. JENKINS: This is John Jenkins. If I  
21 could also go back to some of my opening remarks  
22 yesterday in some of the context that the REMS fits

1   into? This is clearly a broad, societal problem with  
2   multifactorial causes that are involved in misuse,  
3   abuse, diversion, addiction to prescription opioids.  
4   We tried to make clear that we understand that the  
5   REMS cannot be the solution to all those  
6   multifactorial causes.

7           As I said in my opening remarks, our REMS is  
8   focused primarily at that doctor/patient interface, to  
9   try to help make sure that the doctors are selecting  
10  the correct patients, prescribing the right dose,  
11  educating the patients on safe use and appropriate use  
12  and disposal, et cetera, giving patient education.

13           We then see that there are kind of  
14  concentric circles of household contacts, neighborhood  
15  contacts, illegal activities that go beyond the scope  
16  of what we can really hope to achieve in the REMS.

17  But we did notice in some of the data that  
18  approximately half of the product that ends up in the  
19  hands of people who are using it for non-medical  
20  purposes originated from that doctor/patient  
21  interface. Again, we regulate that area of this scope  
22  of problem, and that's where we're focusing our

1 attention.

2 Dr. Rappaport showed a slide at the end of  
3 one of his presentations yesterday that was a spectrum  
4 of parties involved in this issue. On the left-hand  
5 side was the prescriber, in the middle was the  
6 patient, and on the far right was labeled others,  
7 others meaning household contacts, neighborhood,  
8 illegal activities, the whole scope of others. And if  
9 you go back and look at that slide, the REMS banner  
10 was over the prescriber, and the safe-use banner was  
11 over on the right side for the others.

12 So it has to be a multifactorial  
13 intervention. So we're not under any presumption that  
14 the REMS program will solve all of those problems.  
15 It's just really focused on trying to make sure that  
16 doctors are prescribing appropriately, educating  
17 patients appropriately, and patients are behaving  
18 appropriately in how they use the drug and how they  
19 store it and don't share it.

20 That's where we're trying to intervene.  
21 Will it solve the entire problem? No. Hopefully, it  
22 will have some impact as part of a multifactorial

1 program under safe use, with the other partners, with  
2 DEA, to focus on the illegal activities. So just keep  
3 that context in mind as you're thinking about the  
4 proposal.

5 DR. KIRSCH: Dr. Craig. Dr. Todd.  
6 Dr. Carter.

7 DR. CARTER: I just wanted to agree with  
8 some of the comments that were made by Dr. Woods and  
9 Dr. Terman, that I'm quite concerned that we haven't,  
10 up to this point, identified any unique risks that are  
11 associated with this class of extended-release drugs;  
12 that is risks that are neither outcomes, like death,  
13 or risks that differentiate this class from the  
14 immediate-release opioids. And I think until we have  
15 those risks identified, it will be very difficult to  
16 implement mitigation strategies that can address these  
17 very specific risks, particularly in light of the fact  
18 that we've seen data thus far that the prescriptions  
19 for the extended-release compounds have been  
20 increasing, and increasing at a faster rate, and that  
21 the problems, per number of prescriptions for this  
22 class, are greater than those for the immediate-

1 release drugs.

2           So I think, until we identify the unique  
3 risks that are pertinent to this class, it'll be  
4 difficult to generate these specific mitigation  
5 strategies to address those risks.

6           DR. KIRSCH: Dr. Kosten.

7           DR. KOSTEN: Thank you. Perhaps, some of  
8 these are summary points rather than addressed to  
9 specific people who have testified. But the things  
10 that are striking to me as we're talking about  
11 voluntary training or voluntary -- not even training -  
12 - voluntary education, when the pharmaceutical  
13 industry has plenty of data to indicate how worthless  
14 that is as influencing physician behavior. And that  
15 academic detailing, in many ways of making and  
16 influencing physician behavior, are very well known to  
17 the pharmaceutical industry and very well utilized,  
18 yet, all of that's being avoided, as far as I can  
19 tell, in any of this discussion, of what the  
20 pharmaceutical industry could actually contribute to  
21 this.

22           The second concern that I have is that



1 implementing best practices in medicine has, in fact,  
2 a very strong set of principles involved in  
3 implementation science. The Veteran's Administration  
4 has, in fact, done quite a bit in this over the last  
5 10 years. And yet, I hear very little about how the  
6 FDA's going to make any use of that expertise in  
7 implementing a program or a project, that the aspects  
8 of which are very well articulated, in a system that's  
9 been in place for a long time, including things that  
10 have been mentioned by several of the presenters that  
11 didn't represent the pharmaceutical industry.

12           The third thing is that we should be  
13 targeting bad prescribers, and that seems to be an  
14 issue that the DEA could be of great help to us. And  
15 while I did hear some discussion of putting the  
16 advisory group of the various federal agencies back  
17 together again -- I think that was from Dr. Schnoll --  
18 I don't see anything in these documents that suggest  
19 these kind of interagency collaborations are going to  
20 occur, or that in fact the state registries of who may  
21 be your problematic providers are going to be utilized  
22 in any way.

1           Then finally, as, again, several people have  
2   said, I see no distinction between the immediate-  
3   release and the extended-release types of opiates.  
4   And at least, in Texas right now, the biggest problem  
5   that we have with an opiate is an immediate-release  
6   one, Vicodin. It is making millions of dollars for  
7   several hundred physicians in the state, who don't  
8   seem to be pursued by the criminal justice system.  
9   And I find that despicable. I think the cooperation  
10   level between the agencies seems to be outrageously  
11   uncoordinated.

12           So I think there are very serious issues  
13   there, but I'm quite concerned that we're not dealing  
14   with them.

15           DR. KIRSCH: Thank you.

16           Dr. Covington?

17           DR. COVINGTON: Thank you. I think I'd most  
18   like to express a concern. You know, we're relying  
19   here on voluntary education, and it's hard for me to  
20   come up with a scenario in which we can have an  
21   authoritative answer as to exactly what education  
22   we're going to be providing.

1           We've heard that people taking over 100  
2 milligrams a day of morphine equivalence are more  
3 likely to die. I think Dr. Ballantyne showed that  
4 there was essentially no evidence supporting use of  
5 over 195 milligrams of morphine a day in chronic use  
6 for non-malignant pain.

7           Our background materials tell us that the  
8 typical dose is 300 milligrams of oral morphine a day,  
9 and all of our experts who give us lectures tell us  
10 that there's no ceiling. We're being told, too, that  
11 there's hazard associated with combining opioids and  
12 benzodiazepines because of increased death. And yet  
13 we have literature showing that benzodiazepine use is  
14 actually a predictor for chronic opioid therapy.

15           We're told about the special hazards of  
16 prescribing opioids to people who have a pre-existing  
17 addictive co-morbidity. And yet the insurance data  
18 from the Pacific Northwest tells us convincingly that  
19 an addictive disorder predicts, number one, a  
20 likelihood of an opioid prescription, number two, that  
21 it's likely to be a Schedule II, number three, that  
22 it's likely to be in high doses.

1           So we really have a huge amount of sort of  
2   discrepancy in what people believe about opioids,  
3   based largely on the fact that we have very poor data  
4   and lots of biases with different ones of us, in terms  
5   of which answer we would think is correct.

6           Finally, it seems to me, in some of my  
7   forensic work from years gone by, is that the people  
8   who are doing the most egregious practice were the  
9   ones who thought they were best educated about opioid  
10   pharmacology. So that raises a question as to whether  
11   anything voluntary is going to be useful.

12           So I guess the two questions, is how can we  
13   come up with something authoritative in an area where  
14   there's so much ambiguity? And number two is, is  
15   voluntary physician education really going to do the  
16   job? Thank you.

17           DR. RAPPAPORT: I'll respond to that. Now,  
18   you know what we face pretty much every day. There  
19   isn't a lot of clear-cut data out there. And there  
20   are a lot of very strong opinions from some very well  
21   meaning, and some very highly educated and experienced  
22   people, many of whom are in the room today.

1           So when we have this type of a situation,  
2 this is exactly when we need to come to an advisory  
3 committee meeting and have an appropriate mix of the  
4 experts, sit around the table and discuss this  
5 information, and make some recommendations.

6           I think we did a pretty good job this time  
7 in pulling together a group of you who have a broad  
8 expanse of experience in pain management, in  
9 addictionology, in the interface between the two, and  
10 in related safety issues.

11           So that's why you're here today. And the  
12 second question you asked is one of the ones we're  
13 putting to you.

14           DR. JENKINS: If I could just add to that,  
15 we've heard some discussion about the voluntary nature  
16 of the prescriber training on the individual  
17 prescriber. Keep in mind, what we're proposing is  
18 that the sponsors will be required to make the  
19 training programs available to the individual  
20 prescribers. They will be FDA approved for content,  
21 and then they will be expected to meet certain  
22 performance goals for demonstrating that prescribers

1 have, in fact, completed the training and that there's  
2 evidence that we're hopefully seeing some increase in  
3 the awareness of the appropriate prescribing  
4 practices.

5 We're hoping that there will be take-up of  
6 this through CME programs. That's why we had those  
7 speakers here yesterday. We've also heard from  
8 partners at the federal and state medical boards, the  
9 CME that's related to the REMS could be required for  
10 licensure in individual states.

11 So we're looking for ways to leverage that  
12 voluntary training for prescribers to become not so  
13 voluntary, but not directly through the REMS program.  
14 We've heard from the Federation of State Medical  
15 Boards that their members might actually require that  
16 physicians take the training and have evidence that  
17 they've completed it in order to maintain their  
18 license.

19 So it is voluntary on the individual  
20 prescriber. It's mandatory for the sponsors to make  
21 that training available. And they will have  
22 performance goals under the REMS to meet, to show that

1   prescribers are in fact taking the training. We're  
2   looking for incentives through CME. And we're hoping  
3   to partner through safe use with other stakeholders,  
4   who can help us nudge that training out of the  
5   voluntary space and into the required space.

6           Keep in mind, the only way that we could  
7   require an individual prescriber to be trained would  
8   be to have some way to keep track of every individual  
9   prescriber and check off that they have in fact  
10   completed the training. That means that you have to  
11   enroll every prescriber into the program, and you've  
12   heard why we considered that and in the end, decided  
13   not to go there.

14           You may tell us that that's a way you think  
15   we should go. But that's trying to help understand  
16   voluntary for the individual, mandatory for the  
17   sponsors. And we're hoping to leverage through  
18   partners and other activities to make the voluntary  
19   individual training not so voluntary.

20           DR. COVINGTON: May I follow up on that  
21   point?

22           DR. KIRSCH: Yes.

1 DR. COVINGTON: So I think one of the  
2 potential pitfalls with the voluntary training or  
3 education is that if we can agree that participating  
4 in such education is a responsible activity, and if we  
5 can agree that prescribers exist along a spectrum of  
6 responsibility, then I think that it's likely that  
7 those that are least responsible will participate in  
8 the education and the training.

9 So even if you can show that a high  
10 proportion of prescribers are participating in  
11 education and training, I think the individuals or who  
12 those people are in the proportion that are not  
13 participating will be critically important. And I  
14 think this is a significant concern with regard to  
15 voluntary training and education.

16 DR. KIRSCH: The FDA has given us lots of  
17 material to discuss in our questions. But before we  
18 discuss them, I turn the floor over to Dr. Rappaport  
19 to charge the committee in our discussion of these  
20 questions.

21 DR. RAPPAPORT: Thank you.

22 Okay. So you've heard about the problem of



1 prescription opioid abuse and misuse, not just here  
2 today, yesterday, but you've all heard about it for a  
3 long time from many different sources, including your  
4 own work. And you've heard about the benefits of  
5 these products and how important maintaining access to  
6 them is to many patients in this country. You've  
7 heard from a lot of experts and from a variety of  
8 speakers at the open public hearing today, who had a  
9 variety of opinions about where our proposed REMS is  
10 right and where it isn't right.

11           Given the goals of reducing addiction,  
12 overdose, and death, I think we can probably all agree  
13 on those, but we would like to hear if you think that  
14 we shouldn't be trying to reduce those or if there are  
15 other goals that we should be focusing on. But given  
16 those goals, and the goals of maintaining access and  
17 not overburdening the healthcare system -- again,  
18 recall that those are mandated by the statute. And  
19 given the feasibility -- and you need to keep this in  
20 mind as well -- of implementing a REMS that will cover  
21 over 700,000 prescribers and somewhere around 4  
22 million patients, we're now going to ask you to

1 discuss a number of issues, beginning with your  
2 thoughts and concerns regarding this proposed REMS.

3           Then, after some general discussion, you'll  
4 be asked to vote on whether you agree with our  
5 proposed REMS or not. Following that, whatever way  
6 the vote goes, we're going to continue the discussion  
7 and ask you to discuss, even if you voted against  
8 having this particular REMS, how best to implement the  
9 educational components of a REMS. And finally, how to  
10 measure the impact of a REMS on both abuse and misuse,  
11 as well as access.

12           This is, granted, a daunting charge to you.  
13 But it is really essential that we and the public hear  
14 clearly from you, because that's the point of calling  
15 you together day. As I said a little earlier, in  
16 response to Dr. Covington's comments, there are no  
17 easy answers. If there were data out here that was  
18 clear cut, we probably wouldn't need to have you  
19 giving us input; we would be able to make a decision  
20 clearly.

21           So without that, we need your expertise and  
22 your experience to help us. Whether we're on the

1 right track or not is going to be what we would like  
2 to hear from you. And if we're not on the right path,  
3 we need to hear from you how we should modify the path  
4 that we're on. And I want to thank you in advance for  
5 what's going to be quite an effort today.

6 DR. KIRSCH: So I'm going to read the  
7 questions, and then we're going to discuss the  
8 questions. And then, I'll do my best to summarize the  
9 discussion for the FDA. And when I do my summary,  
10 please correct me if I'm misrepresenting the group  
11 opinion. As I look at the list of the 36 members of  
12 this committee that we have, I'm a little bit  
13 concerned about getting a consensus opinion, but we'll  
14 do our best.

15 So the first question is, please discuss the  
16 problem of misuse and abuse of the extended-release  
17 and long-acting opioid analgesics and its impact on  
18 public health. We're going to start a new list.

19 Dr. Wolfe?

20 DR. WOLFE: I'm going to refer back to  
21 Dr. Denisco's remarks because it's right on the point.  
22 There's been a change in culture over the last 15

1 years or so, certainly led by Purdue and other  
2 companies have followed, to shift a larger proportion  
3 of opiate prescribing to extended release from  
4 immediate release.

5           So I think that part of the problem of  
6 misuse and abuse has to do with this ratio shifting.  
7 I mean, the data that were in the briefing package  
8 were very clear, measured by DAWN, emergency room  
9 visits or almost anything else, that the dangers of  
10 the extended release far swamp out the immediate  
11 release.

12           So if the overall endpoint of the goal is to  
13 reduce the amount of abuse, et cetera, et cetera, an  
14 intermediate step to that would be changing this  
15 ratio. So I think that the problem as evidenced by the  
16 harm is clear, differential between what we're  
17 discussing, because we're not discussing changing  
18 immediate release; we're talking about what can be  
19 done about the extended release.

20           I think that the problem is there, and the  
21 impact on the public health is much more over time  
22 than it used to be, and the over-time than it used to

1 be is largely related to the increased use and  
2 percentage of opiates that, even though it's the  
3 minority of use, the rate of growth, as a couple of  
4 people have alluded to, is enormous. In direct  
5 proportion to that, we are seeing more deaths, more  
6 emergency room visits, and so forth.

7           So I think it's a well-documented problem,  
8 and I think that we need to expand from the list of  
9 REMS as to how to take care of it.

10           DR. RAPPAPORT: Can I just make a comment?  
11 It would be helpful, since what Dr. Wolfe just said is  
12 that there's a clear-cut more serious outcome seen  
13 with these long-acting, extended-release products.  
14 And some other people have said that, and yet there  
15 are a number of people around the table who have said  
16 there's no difference in the seriousness of the  
17 consequences of the immediate release, and that they  
18 should be included.

19           That's an important question for us, is to  
20 how broad this REMS should be. So I hope there will  
21 be some discussion between the two opposing thoughts  
22 on this.

1 DR. KIRSCH: Dr. Markman.

2 DR. MARKMAN: Would you prefer that we wait  
3 to speak to Dr. Rappaport's direct question here?

4 DR. KIRSCH: No.

5 DR. MARKMAN: Okay. So with regard to the  
6 question of the public health problem and the issue of  
7 balance here, balance between access and safety,  
8 access to care and public health safety with regard to  
9 these medications, I think from what we've heard,  
10 we're not currently in balance. We're out of balance.  
11 That's the status quo.

12 When these medications that we're talking  
13 about are contributing to the most common cause of  
14 accidental death in 10 states, and a number of which  
15 will likely increase and we maintain the status quo, I  
16 would argue that the current state is not one of  
17 balance.

18 Equally important as a practitioner, I feel  
19 that we currently operate -- and someone who  
20 prescribes these medications, that we operate in an  
21 environment of voluntary education for the most part  
22 with regard to these medications. And what's being

1 proposed is a continuation of voluntary education.

2 And I don't think that that will change the status  
3 quo, which is unacceptable.

4 DR. KIRSCH: Dr. Farrar.

5 DR. FARRAR: With regards to the very  
6 specific point about extended versus immediate  
7 release, from my perspective, the issue revolves  
8 around dose. What makes extended release more  
9 dangerous is that if you chew it, you get an acute  
10 dose of up to 80 milligrams of Oxycontin, or now with  
11 the long-acting hydromorphone, et cetera. And so I  
12 think the issue, from my perspective, is that concern.

13 Clearly, if the REMS is imposed in whatever  
14 form for extended release only, it will reduce the  
15 amount of extended-release use, and I would expect a  
16 concomitant increase in the use of the short acting.

17 There's a second issue, which is that over  
18 the course of years, there's been a very strong push  
19 to try and get dosing to be given less often. There's  
20 excellent evidence that dosing that's given less often  
21 increases compliance. That's important for your blood  
22 pressure medicine. That's important for your

1 antibiotic. I have no evidence specifically, but I  
2 would be willing to bet that most of the people around  
3 the table agree with the fact that there's no problem  
4 with compliance with pain medications.

5 In fact, if you're going to give something  
6 that doesn't work, give it frequently because it works  
7 better. As a neurologist, I call that the placebo  
8 effect. But in opioid use, there's been a push to try  
9 and get the long acting to be taken. And there's  
10 concern, physiologic concern, again no clinical data,  
11 that long acting may induce more level tolerance, and  
12 that in fact, short acting might actually be better  
13 for many kinds of pain. We don't have data, however,  
14 on that, adequate to know that.

15 My concern in limiting this to the long  
16 acting is that I think that the short acting has an  
17 equally potentially dangerous problem, and I would  
18 actually strongly encourage including both of those in  
19 the REMS program.

20 That said, we have to start somewhere. And  
21 in the interests of trying to move this all forward, I  
22 would hate to have it all get stalled for years based



1 on that discussion, and would be very much in favor of  
2 moving ahead with the implementation for long acting,  
3 assuming that long acting is a measure or is some sort  
4 of a way of getting at at least some of the population  
5 who use the drugs acutely.

6           So my argument basically would be summed  
7 this way. I would hope that in fact, these programs  
8 would cover all of the opioids, long and short acting,  
9 but that in terms of the requirements for things,  
10 those could be imposed for the long acting as a place  
11 to start, with the clearly intended goal of extending  
12 them once we had more data.

13           DR. KIRSCH: Dr. Boyer.

14           DR. BOYER: I feel that it would be  
15 incorrect to omit immediate-release products from a  
16 REMS. I think that it should be included. You're  
17 correct. I can kill you just as dead with an  
18 immediate-release product as I can with an extended-  
19 release product. If there's a perception that they're  
20 safer products, it may be because deaths are coded a  
21 different way. It's difficult. Every medical  
22 examiner discussion I've heard is that it's difficult

1 to code an oxycodone product as being from one  
2 formulation or another in determining a cause of  
3 death.

4 I think they're also coded a different way.  
5 People who die of immediate-release products may die  
6 of respiratory depression, but they are also at risk  
7 for dying from fulminant hepatic failure. And that's  
8 sometimes lethal, if it's not caught in time, or if  
9 it's not treated properly. But I'm not convinced,  
10 given the low value of the data surrounding the whole  
11 milieu of opioid-related fatality, that anybody can  
12 say with confidence one group is safer than another;  
13 one group should be eliminated on that data.

14 DR. KIRSCH: Dr. Beardsley.

15 DR. BEARDSLEY: I also am concerned about  
16 not including the immediate-release product under this  
17 REMS for much the same reasons that have been iterated  
18 already. But also, another consideration is that if  
19 we don't include the immediate-release REMS under this  
20 current REMS, we'll be back next year or in two years,  
21 discussing a special REMS for the immediate-release  
22 products. These REMS are just going to proliferate

1 and eventually become a very onerous burden on the  
2 healthcare system.

3 So I think we should really consider  
4 including at least the immediate-release product under  
5 this current REMS to prevent that sort of imposition  
6 on the healthcare system in the future.

7 DR. KIRSCH: Dr. Morrato.

8 DR. MORRATO: Thank you. I wanted to echo  
9 similar concerns raised with not including the  
10 immediate release. And the point I'd like to make is  
11 that, in addition to the dosing considerations, et  
12 cetera, I think it's confusing to patients and the  
13 public to make a distinction between it's the form and  
14 it's not the active.

15 So it's the same therapeutic agent, same  
16 pharmacological properties, and it's a somewhat  
17 artificial distinction in how it's actually being  
18 dosed. And considering that I'm not a pain  
19 specialist, but I would expect that it's a natural  
20 progression for a patient with chronic pain to maybe  
21 have started out with the immediate release and  
22 perhaps progressed to extended release over time for

1 reasons of convenience and pain management, et cetera.

2           So I think it creates an artificial,  
3 suddenly you now get the extended-release product and  
4 you have this education, whereas there was none of  
5 that type of education at the point of starting  
6 opioids in general. I can appreciate the logistical  
7 challenges of doing this on a broad scale. And I  
8 would agree with Dr. Farrar, it's better to get  
9 started with something as opposed to arguing it.

10           But I think if you go with just extended-  
11 release and long-acting, then there really needs to be  
12 very careful thought of how you communicate the why  
13 we're doing it there, and not leaving the unintended  
14 implication that the other forms are better, and  
15 that's why they're not having the same amount of risk  
16 management.

17           DR. KIRSCH: Dr. Denisco.

18           DR. DENISCO: I think, just as a practical  
19 matter, we know that the extended-release products are  
20 where we think we're seeing the most problems. And  
21 immediate release may well be involved in that, but  
22 clearly, the overwhelming problem is due to extended

1 release.

2           Historically, it was thought that extended-  
3 release products would be safer and have less  
4 addiction. However, that has not been borne out to be  
5 the case. I did not see any slides yesterday that  
6 showed that they are more effective. So what we're  
7 left with is a medication that's not more effective,  
8 and is of higher risk. But nonetheless, it is where  
9 the higher risk is, and we should sort of get started  
10 somewhere.

11           The problem with any of these is that I  
12 think good people are going to do the right thing,  
13 good patients, good doctors. And if the gentleman  
14 from the DEA is here, I'd love a comment. Nothing  
15 that we've seen is going to address the proliferation  
16 of pain clinics in south Florida. And this is on CNN.  
17 This is on any of the local news channels down there.  
18 The DEA said we had a closed system, so they know  
19 where every pill is. If that's the case, then they  
20 should know the huge number of pills that are being  
21 dispensed out of a clinic, which is very unusual.

22           They showed pictures in the bathrooms of

1 Oxycontin, with the comments, "Ask for it by name."  
2 If you go to CNN, or maybe it's on YouTube or  
3 whatever, or just, "pain clinics south Florida," in  
4 Google, you'll see this, and it's just an unbelievable  
5 thing.

6           These are the problems. This is where I  
7 wish the REMS would attack. We don't want to make it  
8 more difficult for well-meaning patients and well-  
9 meaning doctors to make it a pain in the neck. I  
10 would think we would want to make it difficult for the  
11 doctors who are running these kind of pain clinics --  
12 I hate to even call them that -- and the poor patients  
13 who have become ensnared in an addiction, due to these  
14 very unscrupulous and I would say immoral doctors.  
15 That's what I would like to see a REMS do.

16           Just a brief comment to the FDA council. I  
17 have truly nothing -- I did not mean any implication  
18 or any negative comment to the FDA. I have nothing  
19 but the utmost respect. But as was said, the laws are  
20 such that it must be a reactive situation. It's very  
21 difficult to be proactive. And to be proactive would  
22 mean the FDA would need to know a problem's going to

1 exist, and then try to react to it, which would  
2 require a crystal ball. So that's just unrealistic.  
3 But there's nothing but the activities.

4           The same goes with Purdue. The people who  
5 were in charge of Purdue back in the criminal days are  
6 not the same people that are there now. But  
7 nonetheless, the consequences that the actions of  
8 those people have wrought is still bothering us and  
9 killing people and causing a great deal of human  
10 suffering.

11           We talk about morbidity and mortality, but I  
12 have to put a plug in for the horrible life-destroying  
13 events around a case of addictive disorder, and how  
14 many families have been destroyed, and how many people  
15 have gone to prison and lost all kinds of things.

16           DR. KIRSCH: I think we need to go onto the  
17 next person.

18           DR. DENISCO: Okay.

19           DR. KIRSCH: Dr. Deshpande?

20           DR. DESHPANDE: I've got a couple comments.  
21 The question to the committee on number 1 is it a  
22 public health problem? My answer is yes. And I agree

1 with the other members of the committee that wanted to  
2 include the immediate release because this is an issue  
3 for the class of opiates.

4 My concern for the extended -release and  
5 long-acting group in particular is that of dose, as  
6 somebody mentioned before, particularly for the  
7 pediatric patient. One pill will kill you, or can  
8 kill you, depending on the size and the metabolism of  
9 the patient. So if we're starting somewhere, then  
10 this is a good place to start.

11 The second part of this for me is that we  
12 heard yesterday from Dr. Bickel the response about the  
13 SES and ethnicity in this problem, that there are  
14 specific populations that are at even higher risk for  
15 the problem. And as the REMS is being clarified, I  
16 want to make sure that those issues are addressed so  
17 that we don't have something that feels good but  
18 doesn't do good.

19 So finally, I think it's necessary but not  
20 sufficient to address the total problem, and it may be  
21 the first step, as Dr. Farrar said.

22 DR. KIRSCH: Dr. Rappaport?



1 DR. RAPPAPORT: Yes. I just want to put one  
2 thing on the table so everybody's aware of it. I  
3 think it's part of this conversation. We've already  
4 taken the first step with the REMS that we've been  
5 working on for the oral transmucosal fentanyl  
6 products, which are considerably more restrictive and  
7 have registries for patients and for prescribers.

8 DR. KIRSCH: Dr. Berger?

9 DR. BERGER: Actually, I have a few things.  
10 I, like some others at the table, like Dr. Terman,  
11 have actually been quite sad these two days, being a  
12 pain and palliative care doctor. I mean, when this  
13 was just put up, I'm like, okay, well, that's kind of  
14 nice. But with this REMS, how is REMS and education  
15 going to help this huge public health issue?

16 Nobody believes more that pain education  
17 needs to be done, because physicians know nothing  
18 about pain management. I mean, absolutely nothing.  
19 And physicians know nothing about opiates. That, I  
20 would absolutely agree. But we have a huge public  
21 health issue. But in this whole discussion, I'm still  
22 very unclear in the epidemiology, like how many

1 patients have died, and how many are those who are  
2 people who have taken drugs because they got them off  
3 the street or from family members or not patients who  
4 have taken the drugs illicitly. I'm not clear from  
5 these two days what that number is.

6 With those people, we need to then figure  
7 out if educating the physicians is really going to  
8 make the difference. And I'm not sure that's going to  
9 make the difference. We then need to figure out what  
10 kind of steps need to be taken to stop that problem,  
11 which I think is going to be more than one or two  
12 steps.

13 We then need to address some of John's  
14 issues about safe storage of the drugs and things like  
15 that; the transmucosal fentanyl issue that Bob, you  
16 just raised, and that was one of the things I had  
17 thought about. Having been involved in many of those  
18 studies early on, I don't know that much about  
19 addiction. But it seems to me, that's not something  
20 in these two days that we've heard about being a huge  
21 problem in the addiction world.

22 So is that because of access; is it because

1 of dosage; was it because of the lockboxes; is it  
2 because of the education?

3           Should we maybe retrospectively look at why  
4 has that drug not been a problem? And just even from  
5 an FDA point of view, can we learn something from that  
6 experience, and what can we learn from that  
7 experience? I don't know, but is it worth maybe  
8 looking at what has been done from that drug, because  
9 that seems to be less of a problem than the Oxycontin.  
10 Why is that so different?

11           If training is going to be about opiates, I  
12 think it's going to be a problem. You know, the  
13 patient that came up spoke beautifully about, "I went  
14 there not only to get opiates, but I went to have my  
15 pain treated." And pain management is more than just  
16 opiates. So if you're going to teach us about  
17 opiates, and not about psycho-, social, spiritual  
18 issues, and about complimentary modalities, and  
19 everything else about pain management, the physician's  
20 not going to know what to do.

21           So if you're just going to teach about  
22 extended-release opiates, you're really not going to

1 get very far. And so, maybe we can discuss this in  
2 the afternoon when you discuss educational methods and  
3 what you want to learn about what you want us to talk  
4 about.

5           The other thing that I thought was  
6 something -- the other presentation that was  
7 discussed that I thought was very intriguing, and  
8 maybe should be raised, was by Mr. Brown, Carlton  
9 Brown from ONS, where he mentioned that maybe a pilot  
10 REMS should be introduced. Rather than bringing this  
11 huge REMS program out and saying this is what it is,  
12 bringing out some pilot, and looking at an evidence  
13 based, and starting to pilot something. Looking at  
14 some evidence based, rather than bringing out  
15 something big and not knowing exactly what we're doing  
16 might be something that we want to do.

17           DR. KIRSCH: Many of the comments that have  
18 been made by the last several members of the committee  
19 really have revolved around the issue of REMS and not  
20 really pinpointed the issue or question at hand. So  
21 I'm going to take the chair prerogative and try to  
22 summarize what I understand the committee is saying

1 about the question at hand, and then, move on to the  
2 next question, because I think that will address many  
3 of the issues related to REMS that had been  
4 appropriately discussed.

5           So, for the specific question about please  
6 discuss the problems of misuse and abuse of the  
7 extended-release and long-acting opioid analgesics and  
8 its impact on public health, I believe the consensus  
9 of the opinion of the committee is that our country  
10 has a huge problem right now with abuse and misuse of  
11 the extended-release and long-acting opioid  
12 analgesics, and it has a huge impact on public health  
13 in the United States.

14           I think there's a good consensus on that. I  
15 think there's less consensus about the effect or the  
16 role of the immediate-acting analgesics, opiate  
17 analgesics. And I think there's a real concern about  
18 the immediate-acting analgesics, but not the same  
19 level of concern as there is for the extended-release  
20 and long-acting drugs.

21           If I misrepresented what the consensus of  
22 the committee is, please provide me with some

1 feedback.

2 Dr. Kerns.

3 DR. KERNS: I hope this speaks to the point.

4 I like the way this was phrased, putting the focus on

5 impact on public health. I think a key message that

6 I've learned from my public health colleagues is

7 something about message bringing, and the simpler,

8 more direct and sustainable the message -- less

9 complex messages are important.

10 I think, therefore, from public health, in

11 trying to do something at a public health level, two

12 things I would make. One is, it's about opiates.

13 Don't exclude or try to be specific about extended

14 release, long acting versus the opioid class more

15 generally. And the other is that within the context

16 of REMS, I hear a lot about targeting prescribers,

17 pharmacists, and then, patients. But I don't hear a

18 lot about an expenditure of resources at the level of

19 a public health campaign. And I would like to see the

20 REMS initiative, if it's possible, within the scope of

21 the legislation, to I guess, encourage or require

22 industry partners to engage in an ambitious public

1 health campaign to address this issue.

2 DR. KIRSCH: So to restate my summary, I  
3 think the wording is important. So the consensus of  
4 the committee is that the use and misuse and abuse of  
5 opiates is a huge public health problem for our  
6 country. We believe, however, that the largest  
7 concern exists with the extended-release and long-  
8 acting drugs.

9 No? Okay. I'll make it more strong based  
10 on the feedback of the committee.

11 We believe, as a committee, that there is a  
12 very significant problem with misuse and abuse of  
13 opiates in the United States, both extended-  
14 release/long-acting and immediate-acting opiates. And  
15 this problem has a huge impact on public health.

16 Dr. Krantz.

17 DR. KRANTZ: I agree. But I really think  
18 that the thought behind the FDA, to sort of target in  
19 on long acting, is a real important one, because I  
20 think, although we've heard from the Office of  
21 Epidemiology, that there's a linear relationship  
22 between the amount of opioid put into the market by

1 us, the prescribers, and the number of deaths.

2 I think there is some example of  
3 disproportionate levels of death, despite the  
4 prescriptive use. I think we've seen the data from  
5 the DAWN, where clearly, you had a relatively higher  
6 risk associated with the long-acting opioids -  
7 specifically, Oxycontin.

8 As an addiction physician back in a prior  
9 life, there is one specific medicine -- I think  
10 industry got it right. We want to be sure we have  
11 enough focus on methadone as its own unique  
12 pharmacologic agent. In Utah, if I recall, there's  
13 about a 500 percent increase in the prescription, yet  
14 about a 1,500 percent increase in the deaths. So  
15 there is something unique, and I think Doug certainly  
16 knows about methadone's properties. It's got complex  
17 PK in terms of PD. I think PD can cause arrhythmia.

18 So I'm not saying that we have to eliminate  
19 the short acting, but I think starting with the long  
20 acting is a very prudent first step.

21 DR. KIRSCH: So I think FDA has heard the  
22 concerns of individual members of the committee.



1 Based on the feedback that I got from my summary,  
2 we'll stay with that summary and ask the FDA to also  
3 take into consideration of the individual views that  
4 have been expressed.

5 The second question is to please discuss the  
6 goals of the proposed REMS, the appropriateness of the  
7 REMS components to address the misuse and abuse of  
8 extended-release and long-acting opioid analgesics,  
9 and the potential burden of the proposed REMS on the  
10 healthcare system, and patient access to these  
11 analgesics.

12 Based on the consensus of opinion on  
13 question one, I'd ask the FDA that we restate the  
14 question and make it apply to all opioid analgesics  
15 because the committee feels that there's significant  
16 risk for both groups of analgesics.

17 So that being the question, I'll open it up  
18 to further discussion.

19 Dr. Gray.

20 DR. GRAY: I guess I'm somewhat cynical that  
21 volunteer training is going to make much of an impact.  
22 As others have said, the biggest problem in Tennessee

1 are the prescribers, the mercenaries that are willing  
2 to write these scripts. And if they can't find them  
3 in Tennessee, there actually is a shuttle that goes  
4 from northeast Tennessee down to Broward County twice  
5 a week. It costs \$40 round trip and the bus is full  
6 every time they leave.

7 My guess is that the doctors in Broward  
8 County will not take the course. If they do, they'll  
9 continue business as usual. So really, to make an  
10 impact on this, somehow, we have got to deal with the  
11 dishonest providers that are willing to write these  
12 prescriptions. These doctors are sometimes referred  
13 to me by the Board of Medical Examiners. And they  
14 say, "Well, they need to go to a prescribing course."  
15 And I say, "They don't need a prescribing course.  
16 They know a lot about writing prescriptions. What  
17 they need is a course in ethics or a conscience. And  
18 unfortunately, they don't have a conscience. I can't  
19 give them a conscience."

20 DR. KIRSCH: Thank you.

21 Dr. Vaida.

22 DR. VAIDA: I'd just like to start off by

1 saying one question I wanted to ask yesterday and  
2 didn't get the opportunity was we didn't see any error  
3 data presented. And I think that what would have just  
4 at least been interesting hearing some of the  
5 questions, especially with today, how many deaths and  
6 what is it from.

7           There's a lot of information out there,  
8 depending on how big you want the numbers, where  
9 people have died from inappropriate prescribing. I  
10 mean, people have received fentanyl patches post-  
11 dental. They've received fentanyl patches. They've  
12 left them at home and their kids got them. There's a  
13 lot of preventable information out there on the use of  
14 opioids, both long acting and short acting.

15           So I think, with that in mind, I'd just like  
16 to make a few comments on this question, and just say  
17 that there is that information out there, too, that I  
18 think we should remember that it does exist. And we  
19 may not need big numbers when we're talking about  
20 preventable. So when we look at inappropriate, I know  
21 we're breaking out inappropriate and misuse. But many  
22 of us in the safety field put those together, just as

1 the IOM had those together back in '99, misuse  
2 included errors and preventable.

3           Prescriber education. I believe we do need  
4 that. It's on the inpatient and outpatient side.  
5 There is more than enough information that we have.  
6 There's a big inpatient issue with the use of opioids,  
7 and a lot of it is misprescribing these drugs. So  
8 although my colleagues here from ASHP had said that it  
9 may not be needed, I think it's certainly needed. And  
10 it should be across the board.

11           With the mandatory, I think heard from FDA  
12 is that, yes, I mean, you make it mandatory for  
13 license renewal. And I think you had the players here  
14 in the room yesterday that will put that into place.  
15 I mean, this happened years ago with when I had to  
16 renew my license. And HIV was big, and all of a  
17 sudden, it became that I needed X amount of credits in  
18 that. So it became mandatory, and I think that is  
19 something that you have the people in the room to help  
20 with that.

21           Another thing is that I think that hearing  
22 on the abuse side -- and again, I don't think how deep

1 we could get into that -- and hearing from the FDA,  
2 saying that part of these elements of safe use  
3 includes the drug may be dispensed only in certain  
4 healthcare settings. And we've seen that with some  
5 restrictive programs. I think you should strongly  
6 consider that a prescriber can't dispense Schedule II  
7 narcotics.

8 I mean, what that would take, how that would  
9 be put into place -- would that solve the Florida  
10 problem? Now, I don't know if it would solve that,  
11 but the majority of those are actually being dispensed  
12 by the prescriber. And this is a Class II narcotic,  
13 and you need a safety net.

14 Now, would you have pharmacists out there  
15 dispensing these things? Maybe. But you do need that  
16 safety net, which I'll just talk about in a minute.  
17 And I don't think the burden is yet a question. I  
18 don't think any of this is a big burden that you'd put  
19 on because everyone needs CME to get license renewal.  
20 I think the important thing is - and not to jump ahead  
21 -- is that it's specific. It does have to talk about  
22 pharmacology of these drugs, pharmacokinetics, and it

1 does have to talk about how to educate patients, and  
2 be specific from what we heard today, too, on storage  
3 and disposal and having a safe or like real specific  
4 items.

5 Same thing does with pharmacist's education.  
6 I believe that it should go beyond that, that  
7 pharmacists do need education, once again, inpatient  
8 and outpatient, because the errors we get, we wonder  
9 how were those drugs dispensed. So I think  
10 pharmacists do need the education in this. And once  
11 again, it is something that should be through license,  
12 that there should be so many credits for license  
13 renewal. That includes medication safety, and it  
14 includes safe use of opiates. Once again, very  
15 specific.

16 Another thing I think you should seriously  
17 consider is mandatory patient counseling at the  
18 outpatient pharmacies. I mean, I think this is  
19 something we've seen. Several states have it. The  
20 state of Arizona has mandatory counseling for all new  
21 prescriptions. And I'm not talking about the CMS, the  
22 over counseling where you could sign off. This is

1 every patient that gets a new prescription -- we've  
2 done observation studies -- get counseling, and the  
3 pharmacists take it seriously.

4           The burden? I'm not sure what the burden  
5 is. But I'll tell you, every large chain that has a  
6 store in Arizona does it. They may not do it in  
7 Texas, but they found a way to do it in Arizona.

8           So I think this is an opportunity here of,  
9 once again, pharmacists acting as that safety net,  
10 through prescriber education, pharmacists education,  
11 and also mandatory counseling for opioid  
12 prescriptions. We consider this a high-alert drug.  
13 And that means, when it's misused, when it's  
14 improperly used, it could cause more harm than any  
15 other drug. And you know, we don't have a lot in  
16 those categories, but I think that's something that's  
17 very important.

18           Then finally, with the abuse, I think that  
19 the Safe Use Initiative is something that the FDA  
20 should look for the partners, push that out, and also,  
21 look toward the industry to help support some of that  
22 as part of the public service, although it'd be driven

1 by the FDA. Sorry for going on so long.

2 DR. KIRSCH: Thank you.

3 Dr. Farrar.

4 DR. FARRAR: I think this is a tremendously  
5 complex issue, and I would ask my fellow committee  
6 members to try and keep separate some of the issues  
7 we're trying to address. We've heard about Broward  
8 County. And frankly, Broward County needs to be  
9 addressed by the law. We've heard about accidental  
10 overdose by people taking too much because they didn't  
11 understand it. That can be addressed by patient  
12 education. We've heard about getting it from your  
13 friends, stealing it from your mother or your  
14 colleague or from a friend that you have. That might  
15 be addressed by lockboxes.

16 It seems to me that the devil really is in  
17 the details, and if we talk broadly about sort of this  
18 and that and the other thing, without keeping it clear  
19 what we're trying to prevent, it's going to be very  
20 confusing.

21 In terms of the specifics, they're asking  
22 this question. Clearly, there is going to be some



1 cost to doing this, and who ends up bearing that cost  
2 is going to be somewhat controversial. It seems to  
3 me, though, that, in fact, as was suggested by  
4 Dr. Ballantyne and others, good training about pain  
5 care with a focus on helping to prevent the accidental  
6 overdose and abuse, but with the initial piece of it  
7 being good pain care, could actually improve pain care  
8 as an outcome of this project, as opposed to reducing  
9 the use because of the ways it's imposed.

10           Clearly, the devil again being in the  
11 details. It needs to be checked. There needs to be  
12 data collected. And there are ways to do that without  
13 imposing significant costs, and I'll address those  
14 when we get to the next question. But it seems clear  
15 to me that if it is done wrong, there will be  
16 significant costs, and it will limit the amount of  
17 care, perhaps, in a way that would be detrimental.

18           If it's done in a way that makes sense,  
19 which is appropriate education, I think with a  
20 requirement, although how that's implemented I think  
21 needs to be discussed --if there's appropriate  
22 education for physicians, for patients, and for the

1 public, that it could in fact benefit the overall care  
2 of patients with pain.

3 DR. KIRSCH: Thank you.

4 Dr. Flick.

5 DR. FLICK: We're being asked to address  
6 question 2, discuss goals. I think the goals, as I  
7 understand them here, are to improve the  
8 appropriateness of prescribing this class of  
9 medications. I think the REMS, as the FDA has  
10 written it, is appropriate in that.

11 However, as proposed, I think the REMS is  
12 unlikely to have a significant impact on that goal.  
13 And as to the third portion of that question, the  
14 burden, I think that there is certainly some burden.  
15 As Dr. Rappaport described, there will be a  
16 significant amount of expense associated with this.

17 I'm not sure whether the results that will  
18 be achieved through this can justify that burden.  
19 However, I do recognize that this is an incremental  
20 process, and that we should proceed down that  
21 incremental pathway toward something that at some  
22 point is likely to have a positive impact on the

1 public health.

2 DR. KIRSCH: Thank you.

3 Dr. Michna.

4 DR. MICHNA: What I wanted to discuss was in  
5 the proposal, should this voluntary system fail, then  
6 there was words to the effect that a mandatory system  
7 connected to your DEA.

8 Based on what's been said by Dr. Jenkins and  
9 others, in terms of your working with the boards of  
10 medicine, and more to the point of my colleague next  
11 to me, I could understand at the beginning why tying  
12 it to the DEA would have been an easier way of going,  
13 given if we were under the pressure of doing that.  
14 But if indeed we're going to have an interim period  
15 where we're going to have voluntary, why not then  
16 propose that should it fail, then we will go to a  
17 broader education system tied to your medical license  
18 with the boards of medicine?

19 I think a more global approach to education  
20 is important, even for those that don't prescribe,  
21 which was what was stated yesterday, that even if  
22 you're not prescribing these, you're still going to be

1 affected by the patients with this in your practices.

2           So my question is, basically, is the FDA  
3 rethinking that part of it, and would they consider,  
4 if this fails, to consider a more broader approach  
5 tied to your medical license, and eliminate all the  
6 potentials for the opt-outs, the secondary unintended  
7 consequences that have been discussed.

8           DR. JENKINS: This is John Jenkins. I'll  
9 try to address some of that.

10           We have to operate within the authority that  
11 Congress gives us through the laws, so we don't have  
12 authority over licensing physicians for practicing  
13 medicine. We don't run the DEA registration system  
14 for prescribing controlled substances.

15           What we were referring to is if this program  
16 were not to be successful, and we wanted to go to a  
17 more required-type of a program for training or  
18 whatever, that would be under the REMS program. So we  
19 would be executing that through the manufacturers. So  
20 our ability to escalate this would be to require the  
21 manufacturers to build those registries that  
22 individual prescribers would have to be enrolled,

1   trained, certified, and patients would have to be  
2   enrolled, trained, whatever, like was done for  
3   isotretinoin. That's the authority that Congress has  
4   given us to operate under.

5           As we said, we acknowledge -- and I think  
6   it's probably in our reports -- that a more efficient  
7   approach might be to, if you wanted to go that  
8   direction, link it to the existing DEA registration.  
9   DEA registration requires that you have a valid  
10   medical license but doesn't require any specific  
11   training beyond that in prescribing controlled  
12   substances.

13           Essentially, as it was described yesterday,  
14   you demonstrate that you have a license, you fill out  
15   the form, and you pay your fee, and you get your  
16   registration number. It's really a tracking system,  
17   more than it is a system designed to try to oversee  
18   the appropriateness of the prescribing in that sense.

19           So that's what we were referring to. If  
20   this doesn't work, this incremental approach doesn't  
21   work, then our authority would allow us to work  
22   through the manufacturers, the sponsors of the

1 applications, to build that parallel system. And we  
2 were very concerned about the burden of that parallel  
3 system. But also, we heard a lot of feedback from  
4 patients and other stakeholders about, do we really  
5 want to have the manufacturers of these products be  
6 the ones who are in charge of that system to register  
7 prescribers and patients?

8 But to answer your question, that would be  
9 how we would escalate the REMS, would be through the  
10 sponsors having greater requirements to develop these  
11 systems. Any linkage to the DEA registration system  
12 is something that would require legislation through  
13 Congress, not something we can do under our authority.

14 DR. KIRSCH: Thank you.

15 Dr. Hatsukami.

16 DR. HATSUKAMI: I too was a little bit  
17 skeptical in terms of the effectiveness of a voluntary  
18 approach. And I'm not really sure what would be the  
19 best mechanism, whether it be the DEA registration or  
20 working with other stakeholders like the state medical  
21 licensing boards to actually get to a point where it  
22 would be more mandatory.

1           But I think what we also need to take a look  
2 at, carefully, too, is the nature of education that  
3 will be provided to the prescribers. Dr. Gallagher  
4 had said yesterday that what doesn't work are the CME  
5 lectures, seminars, and readings. And so the FDA  
6 certainly needs to pay careful attention to how that  
7 education will be provided to the prescribers. It  
8 appears that more of an interactive approach might be  
9 effective, and perhaps, using an online interactive,  
10 innovative educational approach should be considered.

11           The other issue is whether -- I'm not really  
12 clear, based on research, since the research seems to  
13 be limited, whether the education that is provided,  
14 whether it be innovative or not, whether that's going  
15 to translate to actual change in behavior in the  
16 physicians' prescription methods or the way in how  
17 they inform their patients.

18           So, I think we need to really carefully  
19 maybe do some pilot testing or something prior to  
20 implementing the REMS to assure that there is some  
21 kind of translation of their education into actual  
22 alteration in behavior.

1 DR. KIRSCH: Dr. Porter.

2 DR. PORTER: My comment goes back a little  
3 bit in the conversation to several speakers. And I  
4 think that Dr. Farrar and Dr. Flick caught the essence  
5 of what I wanted to say, that we were addressing the  
6 potential burden of the proposed REMS on the  
7 healthcare system. And then, clearly, somehow, it's  
8 going to trickle down to the insurance companies, to  
9 the patients themselves. But perhaps the committee  
10 could address what the relative benefits are to that  
11 system as far as saving dollars to the healthcare  
12 system and dropping addictive programs, and that those  
13 kinds of things might be something we should consider  
14 when we go down to the metrics; something that would  
15 be included as far as the success of the program goes.

16 DR. KIRSCH: Thank you.

17 Dr. Wolfe.

18 DR. WOLFE: I'm concerned about time lost by  
19 having voluntary education, particularly in the hands  
20 of the company. I realize and agree fully that that's  
21 within the limits of FDA's authority. And when I  
22 asked Dr. Rappaport yesterday, he gave a predictable



1 and correct answer; they cannot support legislation  
2 unless it's been cleared.

3 But I think we could take a stand that would  
4 cause this to happen sooner rather than later, to have  
5 this involved with DEA. DEA is the logical. That's  
6 not to say that state medical boards couldn't also get  
7 involved. But it would seem to me that such a large  
8 national problem with an already existing controlled  
9 substance act created agency, the DEA, that we should  
10 discuss as part of this question what can be done now,  
11 as opposed to saying, well, if this voluntary doesn't  
12 work. I mean, voluntary generally doesn't work for  
13 almost anything having to do with health. So I would  
14 just put forth that.

15 In terms of the burden on the healthcare  
16 system or access part of this question, I agree with  
17 Dr. Denisco. I don't think the access question has to  
18 do with the ratio of extended release to instant or  
19 immediate release. I think that people would still  
20 have access, who need them, to opiates, that a larger  
21 proportion of people than are now using the IR form  
22 would be using it if we retrained people. So I wanted

1 to introduce the phrase "retraining people" because a  
2 lot of people have gotten untrained and detrained from  
3 appropriately using IR to using ER because of all the  
4 campaigns.

5           So just to summarize, two things. I think  
6 we should discuss, maybe not under this question, the  
7 idea of recommending from this panel that the process  
8 of starting to move towards legislation that would  
9 empower DEA to add this to what they have to do. And  
10 secondly, I think the access question is contrived in  
11 the sense that if you're saying someone would not have  
12 any access to opiates, that would be a big problem.  
13 And I don't think that's where we're dealing here.  
14 It's the relative and inappropriate proportion of  
15 people that are getting ER opioids.

16           DR. KIRSCH: Dr. Turk.

17           DR. TURK: In addressing the question, the  
18 first part that we're presented with, please discuss  
19 the goals of the proposed, I think if the goals are to  
20 reduce morbidity and mortality associated with opioid  
21 prescribing, I don't think anyone could disagree, and  
22 Mom and apple pie would be about the statement. So I

1 think we would all agree that, yes, the goals are  
2 commendable.

3 I think it's important that we realize, and  
4 I think Dr. Farrar mentioned this, alluded to this,  
5 that we're talking about at least two, maybe three,  
6 different populations here. We're talking about  
7 trying to prevent inappropriate prescribing by  
8 unscrupulous providers. And I don't think anything in  
9 the REMS or any REMS we could come up with is going to  
10 do that. So we're not going to be able to eliminate  
11 problems.

12 Can we reduce the problems? Then we're  
13 talking about the prescribers who might benefit from  
14 greater information, education and for patients who  
15 get greater information. And the patients who get the  
16 greater information would potentially trickle down to  
17 the potential family members and other people getting  
18 access to their medication.

19 So I think that if we keep those two apart,  
20 contrary to -- I think Dr. Vaida said something about  
21 lumping them together. I think we really need to keep  
22 those two things separate, and I think we drift when

1 we start trying to solve everything, by looking at  
2 these as being one group.

3           Then, if we look at the comments that we've  
4 received from some of the people from the FDA, it's  
5 that we hope, we may, they may, they might do better,  
6 or they might be incentivized by CMEs. That, for some  
7 reason, doesn't give me a great deal of comfort that  
8 that, in fact, is going to be the case. I think it  
9 was Dr. Katz who mentioned that he was here eight and  
10 a half years ago when REMS were first begun to be  
11 talked about. We've had many attempts along the way.  
12 There are huge numbers of educational programs, and we  
13 see the numbers are getting worse.

14           So I don't think that the REMS, as being  
15 presented, is likely to have a huge benefit. It's  
16 definitely not going to affect the unscrupulous  
17 providers. It might have some marginal benefit -- I  
18 don't think a huge benefit -- on the current, "good  
19 prescribers" and the patients that are there.

20           I think that the discussion we've had  
21 repeatedly about voluntary versus mandatory, I think  
22 that discussion is something we really have to come

1 back to. I think, in the past, voluntary efforts have  
2 not done very well. Voluntary efforts in the area of  
3 opioids have not done very well. It is not for lack  
4 of CMEs being available.

5 DR. KIRSCH: I'm going to ask one other  
6 person to speak, and then I'm going to try to  
7 summarize the comments so that we can, after the  
8 summary, after we agree on the summary, have lunch and  
9 come back for the vote.

10 Dr. Brull.

11 DR. BRULL: Thank you. I'll try to stay on  
12 focus and be short. I, too, agree that the REMS are -  
13 - the goals are very good. But I don't know that we  
14 know the potential impact is known yet. We don't have  
15 any data. So I'm in somewhat of a dilemma, because on  
16 one hand, REMS is a reasonable first step to increase  
17 patient safety, but since we don't have any data, we  
18 may not want to pass anything. But not doing anything  
19 is also not reasonable. So I think that even though  
20 the REMS may not be sufficient at this point, I think  
21 it's a reasonable first step.

22 Back to the first question, I don't know

1     that the two statements or the dichotomy was  
2     necessarily that the two things were mutually  
3     exclusive. I think we can say that the problem is for  
4     all opiates, whether they're immediate or extended  
5     release. But at this point, we opted to, or the FDA  
6     opted to, focus on the extended release.

7             There are two other points. I don't know  
8     that we know the decay of knowledge of the REMS. And  
9     I think that this is something that we may want to  
10    advise on starting a demonstration project. I mean,  
11    how often do we have to do this? Will a single REMS  
12    be sufficient? How often do you repeat it?

13            Finally, I think that we need a realistic  
14    assessment of the time that's required for prescribers  
15    and patients. Again, we don't think that it's going  
16    to have much of an impact. But I don't know that we  
17    have hard data to base our judgment on this. So  
18    before we continue to pile on additional time  
19    requirements, I think that we should actually see  
20    whether it's realistic or not, especially as  
21    healthcare changes are underway.

22            DR. KIRSCH: Okay. I'm going to try to

1 summarize the opinion of the committee. You guys  
2 don't make it easy. So I think we will all agree that  
3 the goals of the proposed REMS are laudatory. They're  
4 certainly appropriate. However, it's unclear whether  
5 the REMS components are adequate, particularly in  
6 their voluntary nature to address the issue of misuse  
7 and abuse of extended and long-acting analgesics.

8           The potential burden of the REMS, although  
9 it may be significant, must be balanced by the  
10 potential benefit of the REMS, both in human health as  
11 well as in savings and expense in other areas of the  
12 healthcare system. And that's my assessment of what I  
13 heard.

14           Any corrections or additions to what I've  
15 said?

16           Yes, Dr. Vaida?

17           DR. VAIDA: I think that summed it up. I  
18 think the only comment, at least that I'd make, is the  
19 last part with the burden. I really didn't feel that  
20 I heard a lot of people say the elements we're talking  
21 about would be a big burden right now. And I don't  
22 know if that's just me, but I mean there would be a

1 big burden in cost or whatever. Probably the only  
2 thing is with the DEA. So I don't know if we should  
3 soften that to just say that going forward it may not  
4 be as big a burden as we think. I just throw that  
5 out.

6 DR. KIRSCH: Well, I think what we heard  
7 yesterday and what we heard a little bit about from  
8 industry today is that there is going to be a  
9 significant financial burden in implementing this REMS  
10 program. It will cost a lot of money; however, the  
11 education and training and determination of competency  
12 occurs, that will cost a significant amount of money.  
13 So I think tempering that cost with improvement in  
14 human health and savings in other programs might be  
15 necessary because of the current abuse problem that we  
16 have. I think that sends the same message.

17 Dr. Farrar.

18 DR. FARRAR: The FDA cannot ask us to  
19 recommend, or about the recommendations, that we try  
20 and encourage the U.S. government to move towards a  
21 more cohesive approach to this problem. And I'd like  
22 to just echo what Dr. Wolfe said and actually ask the



1 committee whether adding to the summary would be that  
2 we would strongly encourage the collaboration between  
3 FDA and other groups within the government, and that  
4 this committee recommends that some of that  
5 collaboration and cooperation be written into law.

6           The FDA cannot do anything with that, but I  
7 think it would be an important step in trying to  
8 handle some of these issues. I don't know if it's an  
9 appropriate motion, but it seems to me that -- I  
10 certainly feel strongly that putting a little bit of  
11 teeth into this thing would be a good idea, and I  
12 don't know how best to do that. But certainly, I  
13 think we should encourage that that step be taken.

14           DR. KIRSCH: I think it's appropriate, and,  
15 certainly by the comments I've heard the committee  
16 make, that the committee strongly encourages the FDA  
17 to collaborate in moving forward on this project with  
18 the other important governmental agencies.

19           Ms. Krivacic.

20           MS. KRIVACIC: With regard to the burden  
21 question, I think one of the things -- and maybe this  
22 follows onto what Dr. Farrar is talking about, is we

1 haven't really understood the cost benefit of this.

2 And that's what it speaks to, is there hasn't been a  
3 cost-benefit analysis put in place.

4 Perhaps, the FDA working with various other  
5 agencies or even some outside foundations to look into  
6 that, some type of cost-benefit analysis as it relates  
7 to implementing a REMS, whichever REMS we decide on.

8 DR. KIRSCH: Dr. Kerns.

9 DR. KERNS: Yes. Building on Dr. Farrar's  
10 comment, I agree and would further extend that to -- I  
11 think he was mentioning legislative action where it's  
12 needed. And also, I really am impressed, in this  
13 entire meeting at the call for more science. And  
14 although the REMS plan calls for evaluation, I think  
15 it's incumbent on FDA to call on its partners in NIH,  
16 VA, other funding, research funding agencies to  
17 establish this or call for this topic to be a priority  
18 for science.

19 DR. KIRSCH: Dr. Nelson.

20 DR. NELSON: Given that this drug amounts to  
21 the second most frequent cause of preventable death,  
22 it sounds like in this country, I think the threshold

1 to consider something to be unduly burdensome is  
2 fairly high. And I would suggest that it does depend  
3 a little bit on which patient population or which  
4 professional practitioner or whatnot you're talking  
5 about. The need to protect the patients, the public,  
6 and particularly the children and teenagers who are  
7 really involved in a lot of these issues, I think is  
8 striking, and the threshold should be fairly high.

9 DR. KIRSCH: Dr. Flick.

10 DR. FLICK: I wonder if we could ask the  
11 Chair to specifically address Dr. Farrar's point after  
12 the vote and after lunch. I think my sense is that  
13 there are many members of this committee who believe  
14 that the REMS approach is, as defined by the FDA, too  
15 narrow a focus on a very broad problem that needs to  
16 be addressed from a variety of directions. And I  
17 think it's important for us as a committee to express  
18 that sense and have that sense reflected in the  
19 minutes of this committee, so that the FDA may use  
20 those comments. So I think it's important we address  
21 that at some length but not at this point.

22 DR. KIRSCH: I would agree. And maybe it

1 would be appropriate for Dr. Rappaport or legal  
2 counsel for FDA to come back after lunch and maybe  
3 remind the committee what's within the realm of your  
4 abilities or authority in the FDA. I know it's been  
5 talked about on several occasions, but it keeps on  
6 coming up, so we can discuss it more extensively.

7 DR. FLICK: Dr. Kirsch, if I may, I wonder  
8 if the question that we could pose right now is would  
9 it be helpful to the agency for this committee to  
10 express its views as to the breadth and depth of the  
11 problem and the approach.

12 DR. KIRSCH: Will the FDA comment?

13 DR. JENKINS: I think this discussion is  
14 very useful, not only for us, but also for the other  
15 observers of this process. We ourselves cannot change  
16 the law to have DEA-linked educational training if  
17 that's what you feel is needed. So this is a public  
18 advisory committee meeting. If you feel that's the  
19 way the law should be changed, then you're free to  
20 state that.

21 Hearing that from you is useful for us, but  
22 I think there are other stakeholders and listeners who

1 can hear that as well. So if that's the way you want,  
2 take a poll and get some advice, I think that's fine.

3 DR. KIRSCH: Thank you.

4 Dr. Kosten.

5 DR. KOSTEN: Thank you. I certainly agree  
6 that it's hard to imagine how you could make this  
7 overly burdensome on providers, considering the damage  
8 that's being done. But I really do think -- I've  
9 heard this several times and I'm not sure it's sinking  
10 in much -- to roll out a national program with no  
11 pilot programs, with no data back, with essentially  
12 blind, is just absurd. There needs to be pilot  
13 programs. They need to have a timeline, perhaps of a  
14 year or so, to see how they work. There are multiple  
15 very good ideas here.

16 There's also programs that exist already.  
17 Buprenorphine had a rollout, had a mandatory training,  
18 had a DEA cooperation. There's legislation behind it.  
19 There are things that are in the laws already. There  
20 are examples. I don't see quite evidence of that  
21 showing up in this. And yet, the models are there.  
22 There's a whole other set of -- again, I regret to say

1 this, but in spite of being abused by the VA for many  
2 years, the VA does have examples. They've used it,  
3 it's been effective, and there have been evaluations,  
4 and implementation science is a science, and there's  
5 data on how you implement things.

6 I am just struck by, as I said, pilots,  
7 pilots, pilots. I mean, why are we sitting still?  
8 Thank you.

9 DR. KIRSCH: Dr. Jenkins.

10 DR. JENKINS: I heard some calls from the  
11 committee that you wanted to hear more from our  
12 regulatory experts and legal experts on authority.  
13 Ms. Axelrad is here and can't be here after lunch. So  
14 I just wanted to let you know, if you'd like for her  
15 to address that point, now would be a good time.

16 DR. KIRSCH: Ms. Axelrad, could you provide  
17 us with a summary of what your authority is and where  
18 your authority does not extend so we can discuss it  
19 afterwards?

20 MS. AXELRAD: Yes, I can do it, yes, very  
21 briefly.

22 Basically, as Dr. Jenkins indicated, our

1 authority runs to the regulated party, which is the  
2 sponsor who holds the application for the approved  
3 drugs. And our authority under the statute is that we  
4 can require the sponsor to implement a REMS when we  
5 determine that a REMS is necessary to ensure the  
6 benefits of the drug outweigh the risks.

7           Once we make that finding, in accordance  
8 with the statutory criteria that I described  
9 yesterday, then we would send a letter or letters to  
10 the sponsors, asking them to implement a REMS program.  
11 They would submit a program. We would review it and  
12 approve it.

13           I think that the issue of pilot programs is  
14 somewhat complicated, given the way the statute is  
15 written, because it doesn't say that we have authority  
16 to require any kind of a pilot program. And once we  
17 make the finding that a REMS is necessary to ensure  
18 the benefit of the drug outweigh the risks, I think it  
19 would be difficult to justify only trying something  
20 out in one place and not having it apply to all the  
21 drugs that are out there. It would be difficult to  
22 justify that under the statutory standard.

1           So one of the things that we've talked  
2 about, we in our discussions have also talked about  
3 pilot programs. And there have been a number of  
4 programs in various states and across the country  
5 where things have been tried. And I think that  
6 looking closely at those data to see what has worked  
7 and what hasn't worked might be the best thing that we  
8 can do in terms of a pilot program.

9           I would also say that, as I've said, the  
10 REMS, all REMS, have to have a timetable for  
11 assessment in them. And if we initiate some parts of  
12 a REMS program, or a REMS program such as the one that  
13 we've proposed, we will be assessing it on a regular  
14 basis. And to the extent that we're able to develop  
15 meaningful metrics that would allow us to see how well  
16 that program is working, it can function, in a way, as  
17 a pilot program because it can be broadened or  
18 extended or made tighter, depending on the results of  
19 that assessment.

20           DR. KIRSCH: So further questions for  
21 Ms. Axelrad before she goes?

22           Dr. Farrar.



1 DR. FARRAR: The statement I made before is  
2 that the buprenorphine situation might lend an  
3 example. And I wonder if you could help us to clarify  
4 that, because in fact, a special license is required  
5 for that. That's in some ways what we're talking  
6 about, thinking about, with opioids. And if you could  
7 compare that, that would help us to understand it.

8 MS. AXELRAD: Yes. I am not an expert.  
9 Bob, or perhaps one of the people in the division can  
10 speak directly to the details of the buprenorphine  
11 program. But we have looked at it as a model, and we  
12 have talked to various people about what has worked  
13 and what has not worked about that program.

14 DR. JENKINS: I think the most important  
15 distinction is that was specific legislation. That  
16 was the Drug Abuse Treatment Act of 2000 that  
17 specifically allowed for that outpatient treatment of  
18 patients with drug dependence, but it also set up the  
19 procedures that required DEA to establish a separate  
20 registration number and required that people seeking  
21 that registration number had to have a certain amount  
22 of training. I think it's eight hours of training.

1           So it's specific legislation for that  
2 situation. That's the biggest distinction, I think,  
3 between that and a REMS.

4           Taking it to the next step, there's been  
5 conversation about linking this training, that you  
6 think is needed for opioid prescribing, to DEA  
7 registration. That analogy is why we keep saying it  
8 would require specific legislation to require that  
9 prescribers who want a DEA registration number would  
10 have to demonstrate training and competence in opioid  
11 prescribing.

12           DR. KIRSCH: So I'm going to hold further  
13 conversation, as it is time for lunch and ask the FDA  
14 whether the summary that's been provided is clear  
15 enough, with the addition of the last comment, which  
16 is that in addition to the committee urging the FDA to  
17 work with the other appropriate agencies, as a public  
18 statement, as I know it's not within the purview of  
19 the FDA, but we believe that appropriate legislation  
20 should be generated in order to protect patients who  
21 are being prescribed these dangerous medications.

22           Last comment. Dr. Deshpande?

1 DR. DESHPANDE: I like your summary with one  
2 exception. I think what I've heard is that the word  
3 "burden" is different from the word "cost" in a lot of  
4 our minds, so that if we said that, yes, there may be  
5 additional or substantial cost, the summary may more  
6 reflect what I heard, which is different from the  
7 impression that the word "burden" gives.

8 DR. KIRSCH: Okay. We'll change the word  
9 "burden" to "cost," still being offset by the  
10 potential benefit of improving the human health, as  
11 well as improving the cost or decreasing cost in other  
12 areas of healthcare.

13 With that, we're going to break for lunch.  
14 We'll come back from lunch at 1:15.

15 (Whereupon, at 12:16 p.m., a lunch recess  
16 was taken.)

A F T E R N O O N S E S S I O N

DR. KIRSCH: Committee members, I'd ask if you take your seats, we're going to have a vote.

Okay. I assume that the vote will be electronic.

Has the FDA staff prepared the electronic system for the electronic vote?

I'll read the question. Please vote on whether you agree with the agency's proposed REMS for extended-release and long-acting opioid analgesics and discuss the rationale for your vote.

So, for those of you on the committee who have not voted previously on this committee, let me interpret the question as I understand it and tell you how the vote's going to work.

So the interpretation of the question is if you vote yes, that means that you agree with the content of the proposal that the FDA put forward yesterday on the details of what the REMS would include. If you vote no, that does not mean that you disagree with the idea of REMS in general, but just that you're disagreeing with the details of the REMS as is currently proposed by the FDA.

1           What will happen is they'll get the  
2   electronic system working. You'll vote yes or no, or  
3   abstain. After everyone has voted, they'll put a list  
4   up on the screen that has all of our names with how we  
5   voted, yes, no, or abstain. And then we'll go around  
6   the table one by one and explain why you voted how you  
7   voted.

8           So for example, if you vote no, and said, "I  
9   believe that a REMS program is important, but I don't  
10  agree with this detail or that detail," that's your  
11  opportunity to explain how you voted.

12           Anybody from the FDA want to clarify what I  
13  said or disagree with what I just said?

14           DR. JENKINS: No. I think we agree with  
15  that framework.

16           DR. KIRSCH: Okay. And is the FDA staff --  
17  I don't see anything flashing here.

18           Is the electronic system working?

19           Dr. Todd?

20           DR. TODD: Yes. Just one question. So this  
21  will be the only vote we take today; is that correct?

22           DR. KIRSCH: Yes.

1 DR. TODD: Thank you.

2 DR. KIRSCH: Any other questions about the  
3 vote?

4 Yes, Dr. Wolfe?

5 DR. WOLFE: Since it is written in a sort of  
6 absolute way, I am interpreting it to say you need to  
7 agree with everything in the REMS in order to vote  
8 yes.

9 DR. KIRSCH: That's my understanding as  
10 well.

11 DR. WOLFE: Everything? Right. Okay.

12 DR. KIRSCH: Everything in the proposed REMS  
13 that was presented by Dr. Rappaport yesterday.

14 For the FDA staff, are you ready for us to  
15 vote?

16 So again, everyone must vote. We won't be  
17 able to see the results of the vote until everyone  
18 pushes yes, no, or abstain. FDA will tell us when  
19 everybody has voted.

20 DR. KOSTEN: Is there any way for us to know  
21 that it's registered?

22 DR. KIRSCH: If it's not, FDA will tell us

1 as it was said.

2           TECHNICIAN: You can feel free to press the  
3 button more than once.

4           DR. KIRSCH: The last button that you push  
5 will be your vote.

6           [Voting.]

7           Has everybody voted?

8           TECHNICIAN: We're still missing one vote.

9           DR. KIRSCH: So everyone push their vote  
10 again, please.

11          [Voting.]

12          DR. KIRSCH: Okay. So for the record,  
13 voting yes was 10; voting no is 25; abstain is zero.  
14 And here are the details of who voted yes and no.

15          So we will start with Dr. Bickel. The idea  
16 is to express why you voted like you did. And if your  
17 sentiments have already been expressed by someone  
18 else, you can say, I have nothing to add.

19          DR. BICKEL: I voted no because I didn't  
20 think that the REMS, as proposed, was adequate to  
21 produce change in the nature of the problem. I'm  
22 concerned about the approach of sort we know that

1   there are some bad actors. We know that there are  
2   particular patient populations that are particularly  
3   susceptible to the adverse consequences, but what  
4   we're going to do is one size fits all instead of  
5   trying to identify the nature of the problem and  
6   specifically gear the solution to that problem. And  
7   to me, that seems to be both a waste of effort and  
8   energy, and wrong focus of our attention.

9           DR. KIRSCH: Dr. Denisco.

10           DR. DENISCO: Yes. I voted no. The reason  
11   is much the same as my colleague, and also that,  
12   essentially, this will be an expensive project. And  
13   whether we call it expensive or a burden, it's going  
14   to be a very resource-consuming project. And that is  
15   eventually going to be borne, not by a system of  
16   health, but rather by the patients. One way or  
17   another, it will be borne 100 percent by the patient.  
18   And I feel that this is not going to make any  
19   significant effect and is really just window dressing.

20           DR. KIRSCH: So if you could clarify for the  
21   record, is it that you don't believe a REMS program at  
22   all would be appropriate or that a different type of



1 REMS program would be most appropriate?

2 DR. DENISCO: I'm sorry I wasn't clear. I  
3 do believe a REMS program would be appropriate, but  
4 not this program, because it's not dealing with the  
5 specific problems sufficiently.

6 DR. KIRSCH: Dr. Krantz?

7 DR. KRANTZ: Yes. I voted no. I would  
8 first acknowledge Bob Rappaport and his team. I  
9 thought they did a really good job sort of balancing a  
10 very complex and nuanced issue that we're facing. But  
11 I guess overall I felt like the data, that education,  
12 communication plans, medication guides are effective  
13 in mitigating serious risks is almost nil, to copy  
14 Denisco's point.

15 I think, in this sense, "we have to match,"  
16 as Thomas Jefferson said, "the hole with a  
17 commensurate patch," to use -- I think, Dr. Gallagher  
18 gave that lecture on day one. And really, when you  
19 look at 14,000 people dying on an annual basis, that's  
20 more than we've lost in Iraq and Afghanistan since  
21 2001 in active duty. This is a big public health  
22 concern.

1           So I really think that the components of the  
2   REMS need to be stronger, including elements of safe  
3   use that are a little bit more declarative and  
4   restrictive. So again, I support the REMS in spirit,  
5   but I think it has to have a little bit more of a  
6   robust implementation plan.

7           DR. KIRSCH: Dr. Markman?

8           DR. MARKMAN: I concur with Dr. Krantz's  
9   statement. And again, I would like to acknowledge the  
10   agency's outreach, which I thought was excellent  
11   throughout the process. But the implementation and  
12   the follow-up, and the educational requirements, I  
13   think need to be more robust as a first step.

14          DR. KIRSCH: Dr. Gray.

15          DR. GRAY: I also voted no for the reasons  
16   already stated. I'd also like to see the immediate  
17   release included.

18          DR. KIRSCH: Dr. Ballantyne.

19          DR. BALLANTYNE: Yes. I voted no, and I  
20   also concur with the previous statements. My  
21   particular reasons for voting no were that I think  
22   that the process should include the immediate-release

1   opioids as well as the extended release. And I also  
2   have concerns about the educational piece in  
3   particular, which I feel should be more confined to  
4   risk management and not so much how we manage pain, or  
5   particularly, how we use opioids for pain. I think  
6   that belongs in a different process.

7               DR. KIRSCH: Dr. Boyer.

8               DR. BOYER: I voted no. I believe a REMS  
9   program is appropriate, but I don't think this is  
10  appropriate in scope.

11              DR. KIRSCH: Dr. Kosten.

12              DR. KOSTEN: I voted no. I agree with all  
13  the reasons that were given, in spite of running up  
14  against a congressional opposition or whatever, or  
15  takes an act of Congress, I still think a pilot study  
16  or two would be worth doing, and using some of the  
17  examples, for example, buprenorphine. And I also  
18  thought that leaving out an audit and feedback-type of  
19  mechanism that targets individual providers is very  
20  weak. And as one of the other speakers, one of the  
21  guests said, this needs to be a training program, not  
22  an educational program, and it has to be mandated.

1 DR. KIRSCH: Dr. Berger.

2 DR. BERGER: I voted no; agree with all the  
3 other speakers. I think we also need to understand  
4 how much of this is patients versus those not  
5 prescribed the medications. I think this is a huge  
6 public health problem in terms of abuse, but I'm not  
7 sure how much of this is the non-patient problem,  
8 especially coming from the palliative care approach.

9 I strongly believe that this needs to start  
10 with a little bit more of an evidence base, and we  
11 should start with demonstration pilot projects to get  
12 a little bit more of an evidence base, and understand  
13 what we're doing.

14 DR. KIRSCH: Dr. Mark Woods.

15 DR. M. WOODS: I voted yes. And I believe  
16 that the program as proposed was a good start. While  
17 it certainly was not perfect, I think we've seen lots  
18 of evidence that we have an epidemic.

19 I also want to respond to one of the things  
20 that I've heard that I think I have a little bit  
21 different opinion on, than others in the committee.  
22 While I understand that there's interest on the part

1 of other committee members to include the immediate-  
2 release products, I'm supportive of first focusing on  
3 the extended-release, long-acting products because,  
4 number one, they are novel drug delivery systems; and  
5 number two, they contain much higher amounts of drug  
6 per individual dosage units. Because of those two  
7 unique features, I think they probably do deserve some  
8 extra attention and education.

9           So while I understood people wanted to  
10 include the immediate-release products, I think the  
11 complexity of those dosage forms maybe deserves extra  
12 attention.

13           DR. KIRSCH: Dr. Terman.

14           DR. TERMAN: I voted yes. I agree with the  
15 FDA Scope working group, that this public health  
16 problem is not just about long-acting opiates, despite  
17 the fact that that is all the current REMS plan  
18 addresses. Nonetheless, any successful teaching of  
19 the patient assessment, drug safety, and careful  
20 follow-up for physicians prescribing long-acting  
21 opiates will generally also apply to immediate-  
22 release, short-acting opiates.

1           Further, such teaching will remind  
2   prescribers that opiates are only one tool in  
3   appropriate pain management, and that opiates, sadly,  
4   can be part of the problem, rather than always part of  
5   the solution. Ideally, this prescriber training would  
6   be mandatory. But I have come to the belief that the  
7   FDA, by itself, cannot implement such mandatory  
8   training. And as we've seen, this problem of opiate  
9   abuse and misuse cannot simply wait, without action,  
10   until appropriate databases are constructed or  
11   coordinated.

12           Federal agencies, such as the DEA or NIH,  
13   come alongside the FDA in this effort, or researchers  
14   get funding for conducting published studies on  
15   appropriate metrics for this problem. REMS are  
16   legislatively mandated to be dynamic, and this is a  
17   start.

18           Sadly, the real start needed is not as easy  
19   as training prescribers to use opiates appropriately,  
20   if that's easy. Somehow we must convince the public,  
21   including each of us and those we love, that opiates -  
22   - and prescription drugs for that matter, for the most

1 part -- are not the cure for their problems, but evils  
2 frequently necessary to help mask symptoms, and should  
3 never be shared, hoarded or kept unsecured anymore  
4 than we would allow access to our explosives.

5 DR. KIRSCH: Thank you.

6 Dr. Brull.

7 DR. BRULL: Thank you. My heart said yes;  
8 my head said no. So I guess I'm heartless; I voted  
9 no. Although I strongly support the idea of REMS, I  
10 think that the qualifier was, do you agree with  
11 everything that was proposed. And I think that that  
12 was imbalanced and what made me vote no, although I do  
13 fully agree with the idea of a REMS.

14 I don't think that it addresses some  
15 important issues of prescriber training, which should  
16 be mandatory, public education about safe storage and  
17 disposal, cost, and evidence of the effects. So I do  
18 think that we need pilot studies. Thank you.

19 DR. KIRSCH: Dr. Hatsukami.

20 DR. HATSUKAMI: Yes. I voted no. And  
21 although I do believe that a REMS is appropriate, I  
22 don't think that there was sufficient evidence to

1     convince me that the program that was proposed would  
2     have a significant impact on public health. And I  
3     also thought that we should include the immediate-  
4     release formulations.

5             DR. KIRSCH: Dr. Carter.

6             DR. CARTER: I voted no as well. I agree  
7     that a REMS is a good idea in this case. I voted no  
8     on the basis of I felt that there was inadequate  
9     identification of specific risks to the opioid class  
10    in general and the subset of opioids that we refer to  
11    as the extended-release or the long-acting opioids,  
12    risks that lead to the outcomes such as addiction and  
13    death, and also, on the basis of the seemingly  
14    ineffective and voluntary educational and training  
15    strategies.

16            DR. KIRSCH: Ms. Krivacic.

17            MS. KRIVACIC: I voted no. And while I  
18    don't dispute the seriousness of the risks associated  
19    with opioids, I want to commend the FDA on acting  
20    quickly to want to put something in place. And  
21    especially, I do agree that a REMS is necessary.

22            However, I do believe that we need to be



1 very cautious and deliberate when we move forward in  
2 trying to implement something, especially something of  
3 this large a scale. Dealing with a public health  
4 crisis is the way I would describe this, especially  
5 since as Americans, that 80 percent of the consumers  
6 of opioids are Americans. So this is really a key  
7 problem that we have.

8 I do believe in rolling out something like  
9 this. We have to understand the underlying causes,  
10 and that way we can put in place effective approaches  
11 to dealing with this and in the end have successful  
12 outcomes. And so I also agree a pilot program is  
13 warranted.

14 DR. KIRSCH: Dr. Covington.

15 DR. COVINGTON: I voted yes, which I think  
16 in part represents a triumph of hope over evidence. I  
17 mean, I think the REMS as proposed is severely flawed.  
18 I agree with all the people who voted no in that  
19 regard. On the other hand, I think we not only have  
20 an epidemic of drug abuse. It comes at the end of  
21 what everybody acknowledges was an epidemic of  
22 misinformation. And I think one way to correct an

1 epidemic of misinformation is to create our own  
2 epidemic of better information.

3 I have hope that we can put together a group  
4 of scholars who can come up with, if not reasonable  
5 guidelines, at least reasonable -- you know, this is  
6 the likelihood your patient will die if you do X. And  
7 I think that sort of information will ultimately,  
8 potentially be transformative to some extent, and it's  
9 a start.

10 DR. KIRSCH: Dr. Vaida.

11 DR. VAIDA: Yes. I voted no. And I  
12 mentioned before, I wish there was some little bit  
13 more strength in it. But I'll just take the approach  
14 of what would have made me vote yes. And I would have  
15 voted yes if it extended beyond just extended release  
16 and if it included pharmacists' education.

17 DR. KIRSCH: Dr. Michna.

18 DR. MICHNA: I voted yes. This is a huge  
19 problem. And, unfortunately, I don't think it's one  
20 that the FDA or these type of regulations are going to  
21 resolve.

22 That being said, I think when you balance

1 all the things that could have been against all the  
2 things that it is, I think this was a fairly balanced  
3 rational first step in this whole area.

4 Do I think the REMS as proposed is going to  
5 have the impact that's expected? No. But we're  
6 missing data on so many areas of this whole problem,  
7 that I think it would be, in my estimation, a good  
8 first attempt.

9 DR. KIRSCH: Dr. Kerns.

10 DR. KERNS: I voted no. With due respect to  
11 my colleagues in the FDA, I felt that the presentation  
12 and the proposal fell far short in terms of meeting an  
13 acceptable first step. So I disagree with my  
14 colleagues who voted yes. I thought that the plan  
15 could be much more clearly informed by the science  
16 that we do have and data that could more specifically  
17 inform even the first steps in a plan, as articulated  
18 by the FDA.

19 I thought that it needed to include  
20 immediate-release products. I was not compelled by  
21 data that would argue otherwise. I thought that the  
22 plan should more specifically articulate a step-wise

1 approach to an ultimate goal of mandating training,  
2 not education. And then, in that context, the step  
3 that was proposed, related to education, could be  
4 appropriate, but it needed to be placed in that  
5 broader, step-wise plan.

6 I thought they needed to or could expand and  
7 explicate the evaluation plans, and more clearly and  
8 specifically, speak to issues about plans for  
9 incorporating implementation science, and a step-wise  
10 approach to implementation, as well as just simply an  
11 articulation of the goals or the endpoints for  
12 evaluation.

13 Then, I was particularly disappointed with  
14 the scope of or the explication of the public health  
15 campaign. I view this as a serious, most serious  
16 public health problem, and I think that the efforts  
17 should be equally distributed, in terms of development  
18 of a plan, targeting providers, consumers, and the  
19 public more broadly.

20 DR. KIRSCH: Dr. Morrato.

21 DR. MORRATO: Elaine Morrato, and I voted  
22 yes. And I just want to echo what some others have

1    said.  I commend the FDA for exercising their expanded  
2    authority under FDAAA to help address this public  
3    health problem; it's very critical.  And I commend  
4    them for the tremendous effort to obtain the extensive  
5    stakeholders' input and feedback, and their  
6    thoughtful, transparent consideration of that  
7    feedback.

8                I ultimately voted yes because I believe we  
9    cannot not act, and it's a reasonable place to start.  
10   Educational training will be the foundation of any  
11   REMS, and we should get going on doing that, and doing  
12   it with consistency and with excellence.  And I also  
13   appreciated the perspective that the agency shared  
14   regarding the practicality and feasibility of  
15   executing a REMS within the FDAAA legislation that  
16   they're working with and appreciated that the REMS is  
17   just a component of a much needed and important safe-  
18   use initiative and other stakeholder.

19               Now ultimately, I would agree, though, with  
20   the other colleagues that I would endorse ultimately  
21   mandatory physician education.  I believe it's very  
22   important, as was mentioned, that there's ultimately

1 very strict performance guidelines such that if the  
2 voluntary is not working, that it quickly rolls over  
3 into mandatory. I would also ultimately like to see  
4 that it's targeting both immediate release as well as  
5 extended release and long acting. And I had the same  
6 concerns as many committee members, in terms of the  
7 sufficiency of the education.

8 I just wanted to add a couple comments  
9 because I wasn't able to during the discussion  
10 section, because the way I interpreted the proposal  
11 from FDA is we do have some flexibility in detailing  
12 what exactly is education. So I would echo Dr. Kerns'  
13 comments and suggest that we really reframe and  
14 elevate education to a scale of a multifaceted and  
15 integrated promotional public health campaign.

16 So I agree with the FDA's concept of having  
17 an approved core content. As we heard from DDMAC,  
18 this is a departure from traditional educational  
19 promotional oversight, so I think this is a very good  
20 thing, that we have consistency in message. However,  
21 what we heard from both the agency and the industry  
22 working group is that I'm very worried that the way

1 education is being currently framed, it's not  
2 sufficiently funded, nor will it be conducted with  
3 state-of-the-art training and promotional methods that  
4 are required for maximal effectiveness to actually  
5 change behavior.

6 I think we should tackle this the same way  
7 that you tackle commercial marketing. We should  
8 market the drug safety behavior with the same degree  
9 of sophistication, scale, and timeliness that's done  
10 in the commercial sector.

11 What does that mean? That means that we put  
12 in the investment to do the formative research, that  
13 we understand accepted physician and patient beliefs,  
14 the norms, intent, and behaviors before you design;  
15 that you pilot test the materials; that this all gets  
16 built in as part of the development; that you give  
17 careful consideration to prescriber and patient market  
18 segmentation, and the different educational messages  
19 are tailored accordingly, whether that's by specialty,  
20 clinic setting, or social economic characteristics;  
21 that we actually think about not just listing features  
22 of what's safe use in a Med guide, but we actually

1 think about this, is how do you translate these  
2 features into ultimate end-user benefits that would be  
3 such to motivate someone to actually change their  
4 behavior; and that the FDA really require that there's  
5 careful thought, just like you do with a promotional  
6 advertising plan, what is the reach, what's the  
7 frequency of the message, what is the media mix of the  
8 message, are we doing it of sufficiency in terms of  
9 shared voice relative to promotional activities, that  
10 there's sufficient share of voice in safety; and that,  
11 ultimately, it's imperative that there's a timetable.

12 I believe there's a unique public health  
13 opportunity here for the FDA to set the bar high on  
14 what world-class safety education can and should be.  
15 And often we say time is money in a private sector. I  
16 believe in the public health sector, time is people's  
17 lives, and we should get on with it and not have  
18 another seven years of debating the need for this.

19 DR. KIRSCH: So I voted no. And I echo all  
20 the comments that have been made with regards to the  
21 concerns. Although I certainly support a REMS  
22 program, I think a critical element that's missing in



1 this REMS proposal is the requirements for provider  
2 learning, definitive competencies, assessment of those  
3 competencies, so that we don't come back eight years  
4 from now and say this is an inadequate program. I'd  
5 rather get it in a better place now, rather than  
6 trialing something that is, I believe, inadequate to  
7 meet the need.

8 Dr. Farrar.

9 DR. FARRAR: I voted no, and I agree with  
10 some of the things that were said by everyone and not  
11 everything that was said by everyone. So to be clear  
12 about it, I support REMS as a process. I simply think  
13 that there needs to be substantially more teeth in the  
14 process.

15 One thing that has not been said, clearly,  
16 training for a REMS program could also improve the  
17 overall quality of pain care in general, and I'm very  
18 excited about that as a possibility.

19 I think the focus on long acting is actually  
20 not a bad place to start because it does identify  
21 patients in general, currently, who are more chronic  
22 users and because of the higher dose. But at the end

1 of the day, it's really about dose. And I think that,  
2 hopefully, if it did start with long acting, it would  
3 have to progress to include the short-acting  
4 medications as well.

5 A major flaw is that I heard almost nothing  
6 about data collection. There were some general  
7 comments about how they would try and monitor and use  
8 databases and use radars and things. In fact, I think  
9 a whole new data collection system needs to be  
10 installed in order to do this and have some very  
11 specific comments about how that might happen.

12 I think that under the current legislation,  
13 it's possible to implement something that has a good  
14 deal more teeth, and that the pharmaceutical industry,  
15 which is the group that you're targeting, can be  
16 charged with doing things and being successful and  
17 meeting metrics in order to be successful, and that  
18 that requirement would cost a bit of money, but  
19 nowhere near the profits that are currently being  
20 made.

21 To do so requires making it in everyone's  
22 best interest to comply. People don't do things

1 unless you twist their arm, and that's one way of  
2 handling it. On the other hand, if you simply give  
3 them something that they were striving for, you make  
4 it in their best interests to do so. So we all use  
5 our credit cards and our cards at the local  
6 supermarket because we get a discount if we do so. So  
7 we give them information about us so that they know  
8 what we buy, and then they can do something with that.  
9 We can use the same when we do a REMS program.

10           For example, the drug companies are very  
11 good at marketing. They're able to convince  
12 physicians to use our products, their products. They  
13 can invest a little of that expertise in figuring out  
14 how to get the physicians to use it correctly and to  
15 demonstrate that they're actually successful. They  
16 measure how successful they are at marketing the  
17 product. They can and have the capability to measure  
18 whether they're successful at training physicians to  
19 do the right thing.

20           They're very good at giving coupons to  
21 encourage patients to use their product. Instead, you  
22 give a patient a coupon to fill out a form every time

1 they go to the pharmacy. They don't have to, but they  
2 get a coupon if they do. You pay the pharmacy \$5 for  
3 every form they collect or data that they collect.  
4 It's in their best interests to do it. They don't  
5 have to, but they will, and the pharmaceutical  
6 companies could be held to that.

7           The last issue here is about the limitations  
8 of the REMS legislation, which is that I very strongly  
9 believe, after this meeting, that this group needs to  
10 send a message to our legislature, that the ability  
11 that they have given the FDA to control this problem  
12 is insufficient. They have a model, as we were  
13 discussing before, buprenorphine, which probably has  
14 problems. But if they use that model and implement it  
15 in a way to promote adequate training, not just in the  
16 safety of opioids, but in how to do it right, how to  
17 treat pain right, I think we can make a huge impact.  
18 And I think that my vote for no is clearly related to  
19 trying to send that message.

20           DR. KIRSCH: Dr. Nelson.

21           DR. NELSON: I believe education has a role  
22 in many things we do and is able to change certain

1 behaviors and influence certain outcomes. But as a  
2 sole measure to improve the problems that we've been  
3 discussing now for two days, I think is destined to  
4 fail. Education has a role and has some limited  
5 success, perhaps, in improving seatbelt use, in  
6 reducing smoking, but it's had devastating failures in  
7 improving seatbelt use and reducing smoking as well.  
8 So depending on your perspective on a lot of these  
9 things, education either works or it doesn't. My  
10 sense is that in this particular issue, there'd be  
11 very little benefit to doing it.

12 I think we really need to focus the REMS,  
13 which I do support of course, on the different  
14 factions of people that are involved. I mean, clearly  
15 the prescribers and the dispensers need to be trained,  
16 and they need to be validated and proven to be  
17 competent and capable. There are many ways that have  
18 been thrown out as a potential way to do that,  
19 including linking to the DEA and other databases. I  
20 think that the prescription data collection programs  
21 seemed like a really easy way to collect data on  
22 inappropriate prescribing and inappropriate use of

1 drugs, of opioids.

2 I think patients need more than education.

3 I think they really need a system to work within that  
4 provides an adequate chance, an adequate likelihood  
5 that they will use their medication safely and  
6 appropriately.

7 I think probably most concerning to me, as I  
8 kind of alluded to before, is really protecting the  
9 vulnerable populations. When you look at the data on  
10 who abuses and who dies from these immediate- and  
11 extended-release opioids, it's quite scary when you  
12 see eighth graders and tenth graders and twelfth  
13 graders and teenagers making a substantial impact on  
14 that list. And these are people who I think we really  
15 need to protect.

16 In the eyes of many of these patients, in  
17 many of these abusers, opioids that we're talking  
18 about today are essentially legal heroin, and we need  
19 to think about how we would construct a REMS if we  
20 were going to be marketing heroin. And this is the  
21 patient population that we're trying to protect. Of  
22 course, I'm not saying we actually go and market

1 heroin, but I do think that the kind of link to the  
2 significance of this drug in the lives of people  
3 really does amount to that same level. And the  
4 population that uses it and that suffers from it is  
5 extremely vulnerable and really needs to be protected.

6 DR. KIRSCH: Dr. Olbrisch.

7 DR. OLBRISCH: I voted yes, not that this is  
8 perfect, that these REMS are perfect or will even make  
9 a difference, because we're talking about something  
10 outside. We're talking about abuse that happens  
11 outside of the population that you're meant to impact  
12 here. And I think that maybe is not within the scope  
13 of the FDA.

14 There is, perhaps, even some hopelessness  
15 here about whether you can impact that or whether  
16 that's in the purview of other agencies; whether it's  
17 a public health problem that needs to be addressed  
18 elsewhere or whether it's a law enforcement issue.  
19 But certainly it's not something that we shouldn't try  
20 to do.

21 I'm also concerned here that I hear people  
22 saying no because they think we should regulate more

1 in the area of immediate-release opiates. And I'm not  
2 happy to hear that because there are so many people  
3 who would be going home every day from surgery with a  
4 short-term prescription for immediate-release opiates  
5 or would not be able to do that without Al Gore having  
6 moved into their house with a lockbox.

7 I think that we need to be very careful  
8 about overregulation of things for which there is not  
9 the same kind of problem as there is for these longer  
10 acting. And there's a lot of overregulation in  
11 healthcare, and I don't want to see that  
12 overgeneralization happening either. But I do think  
13 that taking a first step here is worth doing.

14 DR. KIRSCH: Dr. Turk.

15 DR. TURK: Thank you. I voted no. I  
16 strongly agree with the REMS process, however, I  
17 didn't see any convincing evidence that anything  
18 that's being proposed in the current REMS plan is  
19 going to have any impact at actually making a change  
20 in the behaviors that we're concerned about.

21 I think I saw things that were very loose,  
22 superficial, expecting voluntary approaches which have



1 failed in the past. I saw no effort to consider any  
2 of the research that's available on behavior change,  
3 on implementation science, on marketing and  
4 advertising, which could have contributed to what  
5 might have gone into this plan.

6 Dr. Nelson mentioned the seatbelt example,  
7 and it reminded me that when I lived in Ontario,  
8 Canada, at the time that they were switching, they  
9 were adding on seatbelts, making them mandatory, for  
10 the first year that they were mandatory, they had 21  
11 percent of the population were demonstrated to be  
12 wearing seatbelts. They then implemented a \$150 fine  
13 if you were caught not wearing a seatbelt, and they  
14 had a 98.5 percent increase in seatbelt wearing. So  
15 obviously, voluntary things don't always work.  
16 Sometimes, we have to come up with some other  
17 strategies.

18 I understand there are costs and a burden,  
19 and I think that the public health consequences are  
20 sufficiently severe that that burden and that cost is  
21 something that can be worked out to have a more potent  
22 effect. We heard some presentations of some different

1 groups of some strategies that are being tried, and I  
2 think those should be things we begin looking toward.

3 DR. KIRSCH: Dr. Todd.

4 DR. TODD: I voted yes, and it was a  
5 practical decision. I'm appreciative of the time and  
6 effort that FDA's put into this process thus far. I  
7 do think it's a huge public health problem. And I  
8 believe the option of doing nothing is unacceptable,  
9 and delayed action is also unacceptable.

10 But I do think a limited approach is  
11 cautious; it's deliberate. And I think that efforts  
12 to change behaviors start with education, although all  
13 of us I think are in agreement that that's not enough.  
14 I do think that education regarding the use of long-  
15 acting agents will have a spillover effect to  
16 immediate-release agents; that's a positive.

17 I think this is the beginning, or the  
18 middle, of a longer process, and I'm very interested  
19 to hear more about efforts that are beyond the purview  
20 of the FDA and involve interagency collaboration,  
21 because I think that's where the money is. The money  
22 is in what we can do between agencies and the

1 coalitions we can bring together, counter-measures we  
2 can bring together through that interagency  
3 collaboration.

4 DR. KIRSCH: Dr. Peairs.

5 DR. PEAIRS: I voted yes, and I share many  
6 of the concerns of the committee members who voted no,  
7 particularly in regard to the failure to include  
8 immediate-release opioids and the voluntary nature of  
9 the education.

10 But in regard to immediate release, I was  
11 concerned about the practicality of including it and  
12 how that would impact the prescribers of patients and  
13 the patients who have an acute orthopedic injury or  
14 are post-operative. And I felt, perhaps naively, that  
15 the educational component could still include  
16 immediate-release opioids. So I don't see how you can  
17 really talk about one class without the other.

18 In regard to the voluntary nature of the  
19 education component, I find that very concerning. I  
20 think whether we reach anyone or make an impact is  
21 questionable. And certainly, those that Dr. Kopelow  
22 described yesterday, as those who don't know what they

1 don't know, are not going to avail themselves of  
2 voluntary education.

3 But I see it as a step, and I rationalized  
4 my vote because the proposal does include a caveat  
5 that this may need to become mandatory; at least,  
6 that's how I read it. I think this is a first step.  
7 It's a piece of a puzzle that's much greater, to  
8 include the public health campaign and the interagency  
9 collaboration, so I did vote yes.

10 DR. KIRSCH: Dr. Craig.

11 DR. CRAIG: Thank you. I voted no,  
12 predominantly based on prescriber education and its  
13 voluntariness, and I felt that that was an important  
14 aspect that was not included, at least in the  
15 proposal. And although I recognize the significant  
16 amount of work that FDA has done and their workgroups  
17 have done, and resources have been put forth toward  
18 this proposal, I felt that it didn't have enough teeth  
19 as far as it didn't go far enough as requiring  
20 education for prescribers, which I felt was very  
21 vitally important.

22 The second caveat, which I felt contributed

1 to my no vote, was the entire class of the immediate-  
2 release versus the extended-release opioids. I  
3 practice in Florida, and so I see a lot of the pain  
4 clinics, which have been brought up here. The number  
5 one drug that they prescribed is immediate-release  
6 oxycodone.

7           So I felt very strongly that if we're going  
8 to try to address the problem of addiction, overdose,  
9 and death from opioids, that it should include the  
10 entire class. And I understand the mountainous effort  
11 that would be required to include the immediate  
12 release. In addition to the extended-release opioids,  
13 I felt that it should be more of a class effect versus  
14 carve out for the long-acting or the extended-release  
15 products.

16           DR. KIRSCH: Dr. Wolfe.

17           DR. WOLFE: I voted no because I think that  
18 in both briefing materials, the presentations, and in  
19 the constructing of the REMS, the FDA failed to  
20 adequately acknowledge what really has brought us  
21 here, which is the education campaign, criminally  
22 conducted by Purdue in the '90s, which led to this

1 huge increased use of dangerous, more dangerous than  
2 immediate release, extended-release opioids, Oxycontin  
3 specifically. What is to be learned from that is  
4 deficiencies in advertising, deficiencies in letting  
5 the education be done by a company, which is part of  
6 this program, and so forth.

7           So I would have liked more, since the FDA  
8 spent a year or two developing this, for them to have  
9 come here, not only with what they could do within  
10 existing REMS, but as John Farrar pointed out, a  
11 critique of existing REMS, and saying we would  
12 support -- and obviously would have to have gotten  
13 department clearance and so forth, but there should  
14 have been enough time to do that -- we would support  
15 an expansion of REMS to include, for instance, civil  
16 monetary penalties for all advertising, not just that.

17           They could have also in that period of time  
18 cleared to the department the idea that a mandatory  
19 educational program, as involving mandatory DEA  
20 connection with the education on this, would be  
21 supported.

22           In terms of retraining -- I've used that

1 phrase before, because I think at least that part of  
2 the problem -- that's the extended release -- involves  
3 retraining people back to where they were mistreated  
4 before they were mistreated in the late '90s and the  
5 early part of the 2000s.

6           So I think parallel to and a necessary  
7 complement to the REMS -- I also support REMS'  
8 expanded authority particularly. But complementary to  
9 it would have to be these other kinds of efforts, that  
10 they say, yes, we can do this much under REMS. We  
11 have already initiated the effort and gotten the  
12 department and the White House to support legislation  
13 that would bring the DEA part there. We've also done  
14 some other things so that we can do a much better job  
15 monitoring the industry.

16           Nobody thinks, even in the most expanded  
17 form, that REMS itself is going to do it. It is  
18 necessary to have REMS. I think that this could have  
19 been done better than it was, and I think that the  
20 education of this committee could have had much more  
21 of what lessons were learned from the disaster  
22 involving Oxycontin.

1 DR. KIRSCH: Dr. Deshpande.

2 DR. DESHPANDE: I voted no because we were  
3 asked to vote yes or no on the entire question. First  
4 of all, I want to thank the FDA for bringing a very  
5 important public health concern to the forefront and  
6 bringing this panel together. I think it's crucial  
7 that we discuss the issue and come to a resolution.

8 I am in favor of the REMS process and  
9 strongly support it. I think the devil is in the  
10 details, and the details we were asked to look at  
11 today don't go far enough.

12 What would make me vote yes, as Dr. Vaida  
13 said. I think that first and foremost is training,  
14 not voluntary education. I'm the chief quality  
15 officer for our hospital and find that throwing  
16 education at people in the daily stream of their work  
17 means that it's bypassed. Training is an important  
18 part, and mandatory training of prescribers and  
19 pharmacists, prescribers, and dispensers, I think is  
20 important.

21 We said that this was a public health issue,  
22 and public education or community education really



1 should be part of this as well. And it was pointed  
2 out that that is an effective component of the total  
3 education intervention triad.

4 The education really should be targeted for  
5 the audience or for the at-risk population, which is  
6 identifying the ethnic groups that are particularly at  
7 risk and the SES groups that are particularly at risk;  
8 and finally, making sure that we have a reasonable  
9 impact analysis so that we can follow and adjust the  
10 REMS as appropriate.

11 For the record, I'd request that the comment  
12 on Al Gore be stricken from the record. Thank you.

13 DR. KIRSCH: Dr. Porter.

14 DR. PORTER: I voted no, but with  
15 reluctance. I think this is an incredibly important  
16 program that should move forward without undue delay.  
17 I think the FDA has done a great job in getting  
18 started with this, pulling together a lot of really  
19 useful information and really setting a good  
20 foundation of what needs to go forward.

21 I think that the cost to the healthcare  
22 system, the burden that this kind of a program would

1 put on the stakeholders, including the sponsors, the  
2 physicians, the pharmacists who would have to go  
3 through the educational components, as well as the  
4 patients and the victims of diversion, would all  
5 benefit incredibly from a successful program. And so  
6 the benefit, if the program is done properly and is  
7 successful, could definitely outweigh the costs and  
8 the burdens.

9           The reason I voted no was that I thought the  
10 breadth of the program needed to be expanded, that the  
11 immediate-release opioids should be included. I  
12 think, on their own, they cause enough of a  
13 significant healthcare problem that, even if we  
14 weren't considering or there was no existence of the  
15 long-term acting drugs, that they should have their  
16 own REMS program.

17           I also thought that the educational  
18 component wasn't sufficient, that the training of the  
19 physicians should be mandatory and that the public  
20 educational programs should be really expanded to a  
21 large public health education campaign in order for  
22 the program to be successful.

1           So it's the scope, the mandatory nature of  
2   the training, and that the details, again, some things  
3   that might be included were better management of the  
4   drugs as far as storage, as far as identifying abusive  
5   prescribers and abusive consumers, that those are  
6   things that need to be sort of carefully detailed in  
7   advance. But I would like to, again, reiterate that  
8   this is something that should be expedited. The  
9   process, hopefully, will not be delayed by the no  
10  vote.

11           DR. KIRSCH: Dr. Flick.

12           DR. FLICK: I'd like to thank the chair and  
13  the FDA for the efforts that they've put into this. I  
14  think this has been a highly valuable discussion. I  
15  voted yes, not because I believe or have confidence in  
16  this REMS to have an impact; in fact, I voted yes  
17  because I have confidence in its failure. And I think  
18  that failure can be useful in bringing the agency and  
19  others to the realization that this problem is broader  
20  than something that can be approached by FDA. It  
21  needs to be approached in a more broad, comprehensive  
22  manner.

1           My concern is that we have voted this down,  
2   and we'll be back here as a committee in a year,  
3   looking at another REMS, created by FDA, within a  
4   regulatory environment that does not allow them to  
5   clearly address the issue. So, in fact, we will have  
6   delayed a process that really needs to move forward to  
7   become more comprehensive and inclusive.

8           DR. KIRSCH: Dr. Beardsley.

9           DR. BEARDSLEY: I voted no. I'm very much  
10   strongly in favor of the goals of the present REMS,  
11   but I just didn't feel that the proposed provisions  
12   will improve public health. I didn't see much data in  
13   support of any of the proposals, which I think  
14   underscores the need for pilot data to make proposals  
15   in the future, provisions in the future.

16           I wasn't confident that there exists  
17   baseline data to assess the effectiveness of any of  
18   the proposals in the future. And the whole idea of  
19   proposing multiple manipulations at one time, none of  
20   which really have adequate data to support them, would  
21   make future assessment impossible of any of the  
22   individual provisions.

1           Also, I was disappointed that the immediate-  
2 release opioids were not included in the present REMS  
3 proposals. As I said earlier, as I mentioned earlier,  
4 I think if it's not, then we're going to be back here  
5 in the near future with a REMS for the immediate-  
6 release opioids for themselves.

7           Finally, I thought that there needs to be an  
8 explicit way of behaviorally assessing the prescriber  
9 for his or her behavioral change, not just providing  
10 educational materials, much of which the information  
11 is contained in existing package inserts. But there  
12 needs to be an assessment of behavioral change that  
13 the prescriber has actually been trained to adjust his  
14 or her prescribing practices of the future so as to  
15 avoid the kinds of consequences that we've been  
16 talking about today. Thank you.

17           DR. KIRSCH: Dr. Morris-Kukoski.

18           DR. MORRIS-KUKOSKI: I voted no, and most of  
19 my sentiments have already been echoed. A couple  
20 reasons why that I'll just point out. One is the  
21 voluntariness for the education component. I believe  
22 that this is a very serious issue. I do believe in

1 the spirit of a REMS. But I do believe that education  
2 should be mandatory, and not just education, but  
3 training as well, to not just physicians, but all  
4 healthcare professionals.

5 We also need -- without looking at the  
6 component of other interagency collaboration, we're  
7 stuck with potentially educating and training people  
8 better so we can have decreased drug-drug  
9 interactions, and decreased adverse reactions based on  
10 drug disease, but we're still stuck with this big  
11 subset of a population that is misusing and abusing  
12 these substances. They are the people and they are  
13 the group that wind up being the overdoses and the  
14 toxicity. Without somehow regulating these  
15 physicians' bad practices, and regulating the  
16 pharmacies' bad practices, to continuing to fill these  
17 prescriptions, we're not going to have the end result  
18 that we want.

19 DR. KIRSCH: Dr. James Woods.

20 DR. J. WOODS: I voted yes because I felt it  
21 was necessary that we do something. I felt that the  
22 REMS is a good idea and insufficient to handle the

1 problem that we face. But I felt it was necessary to  
2 vote yes anyway, irrespective of its imperfections.  
3 Otherwise, I agree with just about 80 percent of the  
4 considerations that have been raised by those who  
5 voted yes and no.

6 DR. KIRSCH: Okay. We're going to go onto  
7 the next question, question 4, which reads, "Please  
8 discuss how we should work with sponsors to develop  
9 the necessary educational program for prescribers and  
10 patients. Include the following in your discussion.

11 First, how this might be achieved to avoid  
12 the concerns that have been raised regarding the  
13 manufacturers' involvement in the development of these  
14 tools; second, the value of a common set of  
15 educational materials for all products versus  
16 individual product-specific material, and third,  
17 potential initiatives to improve prescribers'  
18 participation."

19 Dr. Farrar.

20 DR. FARRAR: So I think it's important to  
21 understand that, at least, I think that it's possible  
22 to do this. However, there has to be a wall

1 constructed between the funding of the effort and the  
2 material that's then conducted in the effort. There  
3 are examples of this.

4           The first part of this question is how might  
5 it be achieved to avoid concerns raised about  
6 regarding manufacturers' involvement in the  
7 development of these tools. And what I would argue is  
8 that the IWG is a great organization. They ought to  
9 contribute the funding based on a certain payment per  
10 prescription written or something like that, and that  
11 there would then be set up a group of academic or  
12 knowledgeable experts who would receive proposals on  
13 how to conduct that education and make informed  
14 decisions about how to go about providing that  
15 education. So I do think that it's possible to do  
16 that.

17           I think there is value in the common set of  
18 educational materials, however, every person requires  
19 specialization. And so I think it would be really in  
20 the best interest of all groups to target the  
21 education based on the underlying knowledge of that  
22 group.



1           Also, frankly, someone suggested excluding  
2   certain groups like the people sitting around the  
3   table or people who are pain trained, and I'd actually  
4   argue against that. As much as we like to think that  
5   we know what we're doing, some of the more practical  
6   aspects could use some reinforcing and a little bit of  
7   updating on a five-year basis. As a requirement for  
8   my DEA license, that would make a whole lot of sense  
9   to me.

10           The potential incentives to improve  
11   prescriber participation, honestly, I think it needs  
12   to be required.

13           DR. KIRSCH: Dr. Ballantyne?

14           DR. BALLANTYNE: I actually agree with a lot  
15   of what Dr. Farrar just said. I think if we examine  
16   the failure of previous REMS, I would say that a lot  
17   of the failure can be put at the feet of the continued  
18   role of the drug companies in providing education  
19   about pain management, and that role actually became  
20   predominant to the point that many people around this  
21   table were concerned that the educational message was  
22   biased by the role of industry. In fact, I would say,

1 in my lifetime in pain management, there is no doubt  
2 that most of what I learned came from industry-  
3 sponsored education.

4           So I think that I agree with Dr. Farrar in  
5 that there needs to be some mechanism to put a wall  
6 between the drug companies, or the sponsors, and the  
7 people providing the education, which doesn't mean  
8 that they shouldn't be involved, but that there should  
9 be some mechanism to get between them and what ends up  
10 being the vital educational message.

11           In terms of part B, the common set of  
12 educational materials, I think it is a good  
13 foundation. Obviously, it needs to be modified  
14 according to who you're educating. But I think there  
15 are some fundamental principles, and it would be  
16 valuable to set them out.

17           In terms of incentives, I agree with many  
18 other committee members that it needs to be mandatory  
19 or it won't get done.

20           DR. KIRSCH: Dr. Nelson.

21           DR. NELSON: Maybe I kind of commented on  
22 this earlier. I really don't think that the system,

1 the way it's currently set up, is tenable at all. And  
2 I think that there should be some real effort placed  
3 by FDA into trying to see if we can't regulate this  
4 out of existence, such that FDA's charged with  
5 creating this broad educational material and not  
6 getting somebody else to do it and not giving that  
7 role to the sponsors. And that's the colloquial, the  
8 fox guarding the hen house, so to speak. It just  
9 seems to me to be a poor place to be.

10 If it has to be that way, then it would seem  
11 that the wall would be okay, but I would like it to be  
12 more than a wall, maybe like a ravine or an ocean or  
13 something between the two companies or between the  
14 two.

15 I guess one of the thoughts I've always had  
16 about CME, and the thing that's always troubled me is  
17 when you're given money by a company to produce  
18 something, and you have no obvious conflicts, the  
19 conflict that's built in there is the next contract  
20 that you're going to try to get. So you have to kind  
21 of satisfy the company to get the next contract.

22 So it would really be nice if that money

1   that they had allotted to do this was set aside and  
2   really used in a real, no-risk kind of way, that the  
3   people involved have no chance of satisfying the  
4   company in any ways, that they're not looking for the  
5   next contract. And their whole goal is to create a  
6   very valid set of educational material that could be  
7   used by providers and patients, whoever it's going to  
8   really be directed for.

9           I really think that rather than touting the  
10   benefits of the drug, if we really use this as a risk  
11   management tool, it should provide the other side of  
12   the coin. It should focus a little bit more on the  
13   risks, perhaps, because this is not promotional  
14   material to sell the drug; this is material to assure  
15   safe use and appropriate prescribing.

16           So I think the focus of the material has to  
17   be really set properly and has to be vetted through  
18   FDA and whoever else needs to do that. And incentives  
19   to prescriber, I mean, I think the only answer's going  
20   to be to mandate it.

21           DR. KIRSCH: Dr. Wolfe.

22           DR. WOLFE: One of the elements that was, at

1 least by this committee, voted down, in this package  
2 called REMS, is the medication guide. And this comes  
3 to mind because it sort of overlaps with the parts of  
4 question 4. There is no reason why the FDA can't  
5 develop a medication guide. There was a debate  
6 yesterday whether there should be one or three or  
7 whatever else. But a medication guide that's FDA  
8 approved, vetted, does not have to have any  
9 significant input from the company because by  
10 definition -- I mean, we've been involved in this kind  
11 of issue for about 30 years.

12           The FDA has the authority to require  
13 medication guides for certain dangerous drugs. Right  
14 now, maybe only 4 or 5 percent of all drugs on the  
15 market have medication guides. The other information  
16 that people get is just sort of willy-nilly,  
17 inaccurate. The FDA's done several studies showing  
18 how incomplete it is. So FDA has the authority and  
19 has recommended under REMS to do a medication guide.  
20 I think that would be very useful. It could be  
21 greatly increased, in terms of what it has in there,  
22 as opposed to now.

1           As far as the role of the companies -- and  
2 I'm not sure FDA has the authority to say to  
3 companies, "You put up the money, but we're going to  
4 have complete control over what's done with it."  
5 Ideally, that should be the case. It's a matter of  
6 undoing a lot of the damage that's been previously  
7 done, not just by Purdue, as I can keep focusing on,  
8 but other companies as well. You need to undo a huge  
9 amount of malicious education that's been done that  
10 has caused this kind of problem.

11           So I think, in terms of going beyond the  
12 medication guide in the way this is proposed, the FDA,  
13 outside of REMS in the safe medicine use talked about  
14 several things that they were doing. We would  
15 certainly welcome at least some of those, not as a  
16 replacement for the mandatory kinds of thing.

17           Again, part C, it has to be mandatory in  
18 terms of both the pharmacists, physicians or any other  
19 prescriber; otherwise, it's not going to work.

20           DR. KIRSCH: Dr. Jenkins.

21           DR. JENKINS: I'd like to hear some feedback  
22 from those members of the committee who have mentioned

1 that you think the training, education, whichever you  
2 prefer as the term, should be mandatory.

3 Are you thinking in context of the  
4 legislative requirement to be linked to the DEA  
5 registration, or are you thinking in terms of our REMS  
6 authority, where we would be working with the  
7 manufacturers to set up basically a system that  
8 prescribers would have to enroll in and be trained and  
9 certified in order to prescribe the drug, say, along  
10 the lines of isotretinoin?

11 It'd be useful for us to know, are you  
12 thinking legislative solution, linking to DEA  
13 registration? Are you thinking we should try to set  
14 this up as a parallel system through the REMS  
15 authority?

16 DR. KIRSCH: Dr. Berger, if it's to address  
17 this particular issue.

18 DR. BERGER: I would say, even whether  
19 through DEA or even through your licensure, would be  
20 the easiest thing to do. Then it doesn't have to go  
21 through FDA.

22 DR. JENKINS: Just remembering, licensure is

1 a state-based --

2 DR. BERGER: Then do it through DEA. That's  
3 how people have to write their opiates.

4 DR. JENKINS: Okay. So you're advocating  
5 that it be mandatory --

6 DR. BERGER: If it's possible, that would be  
7 the dream to do.

8 DR. JENKINS: Okay.

9 DR. BERGER: I mean, if it's a possible  
10 thing, that would be my wish. Whether that's true for  
11 people around the table, you need to ask that  
12 question. But that would be the dream.

13 DR. KIRSCH: I'd like to comment, actually.

14 So I'd like this not to be used as an excuse  
15 not to do it. So you all are the experts to know  
16 whether it's easier to do it through the REMS  
17 mechanism or to do it through the DEA and have  
18 legislative action. But it'd be my interest not to  
19 use this as an excuse. And if it's easier, mostly  
20 under your control, to do a REMS mechanism, then my  
21 request would be to have it done through the REMS  
22 process.



1 Dr. Kerns.

2 DR. KERNS: I actually remember  
3 Dr. Rappaport, I'm pretty sure, saying that it could  
4 be done within the legislation by FDA, but that it  
5 would be easier, and if there was a change in the  
6 legislation that allowed DEA to do this.

7 So I actually very strongly agree with the  
8 statement that was just made that this should be done  
9 by FDA and take steps to develop a method for  
10 mandating it and registering it now.

11 DR. KIRSCH: Dr. Flick.

12 DR. FLICK: Dr. Jenkins, correct me if I'm  
13 wrong. If this was done outside of a federal agency,  
14 like DEA, then FDA could require the sponsor to  
15 require the prescriber. FDA can't do that. It can  
16 require the sponsor to mandate education.

17 Is that right?

18 DR. JENKINS: I'm not quite sure I'm  
19 following the question. The way it would operate, if  
20 we were going to do it under the REMS authority, is we  
21 would require the sponsors to develop a training  
22 program and an enrollment system through which

1   prescribers would have to receive the training, become  
2   certified, and then you would have to link that  
3   information to the pharmacy to say that unless they  
4   have been enrolled and certified in the program, you  
5   can't dispense a prescription for whatever product you  
6   decide should be covered, be that extended release,  
7   long acting, or the entire class, similar to  
8   isotretinoin.

9           With isotretinoin, you have to be enrolled  
10   in the iPLEDGE Program. You have to be trained and  
11   certified and enrolled. And when your prescription  
12   goes to the pharmacy, they will not fill that  
13   prescription unless you're enrolled in the program.

14           That's how we would do it under the REMS  
15   authority versus the DEA authority where it would be  
16   you can't get your registration number to write the  
17   prescription that the pharmacy's going to fill unless  
18   you've completed a certain amount of training.  
19   Pharmacies already have the ability to check that your  
20   DEA registration is valid.

21           DR. FLICK: So as a prescriber -- and it is,  
22   I think, the statement of this committee that it

1    should not simply be long-acting narcotics; it should  
2    be all narcotics.  So every physician in the country,  
3    then, would have to be given permission to write  
4    prescriptions by sponsors for opiates, and I don't  
5    think that anybody in this room really wants that to  
6    happen.

7               DR. KRANTZ:  I don't think you speak for all  
8    the other committee members.  With all due respect, I  
9    think some of us are okay with allowing folks to write  
10   for short-acting opioids.  As a cardiologist, for  
11   example, I can't --

12              DR. FLICK:  No.  But I --

13              DR. KIRSCH:  Let me clarify that.

14              DR. FLICK:  Yes.

15              DR. KIRSCH:  As I understand, what Dr. Flick  
16   is saying, Dr. Flick is advocating that the sponsor  
17   should not be the group that determines whether or not  
18   we as prescribers are able to write the prescription  
19   for a particular medication.

20              DR. FLICK:  Exactly.  And that is what  
21   Dr. Jenkins is telling us.  It's that is the REMS  
22   system.  That is what the legislation requires, is

1     that if you or I want to write for methadone or  
2     Oxycontin, we would have to have permission, so to  
3     speak, from the sponsor.

4             Dr. Kirsch, correct me if I'm wrong, but the  
5     committee has already expressed its sense that this  
6     REMS should apply broadly to all narcotics. So if we  
7     follow those statements to their conclusion, then  
8     every physician will have to go to a sponsor to be  
9     allowed to write for an opiate.

10            DR. KIRSCH: Dr. Jenkins.

11            DR. JENKINS: Just a little bit of  
12     clarification. The requirements for what the training  
13     would be and the certification would be, under the  
14     REMS, would still be approved by FDA. So we would be  
15     saying what the requirements are. It would be the  
16     sponsors who would be standing up the system to  
17     implement that training and collect the information of  
18     who passed the test or whatever certification there  
19     would be.

20            So we would set the standards for the  
21     certification requirements; they would have to stand  
22     it up. So it's a little bit different from saying it

1 would be the sponsors who would be determining who  
2 could prescribe. They would be running the system.  
3 We would be setting up the standards.

4 DR. FLICK: But this would be an entirely  
5 new system in parallel to a system that exists  
6 currently?

7 DR. JENKINS: Exactly.

8 DR. KIRSCH: So to summarize Dr. Flick's  
9 opinion as I understand it is that he feels strongly  
10 that this authority should happen through the DEA and  
11 not through the REMS program.

12 DR. FLICK: Well, I think that that almost  
13 goes without saying, that the cost of this would be  
14 borne by our patients and by us. And it would be  
15 extraordinarily expensive and cumbersome, and would  
16 seem to be somewhat unnecessary since a system already  
17 exists.

18 DR. KIRSCH: Dr. Markman.

19 DR. MARKMAN: I think one argument for  
20 having this be -- two arguments, actually, for having  
21 this administered and reside within the FDA under the  
22 REMS authority is I think, number one, as we've talked

1 about and was the discussion earlier with regard to  
2 advertising, if it goes through this mechanism, in  
3 contrast to advertising, the FDA will be, in a  
4 prospective way, able to control or to regulate the  
5 content to some extent; whereas with advertising, that  
6 can only be done retroactively. So I do think here is  
7 a proactive mechanism for the FDA to be involved with  
8 controlling the messaging up front.

9           The second reason, presumably the FDA has  
10 the deepest understanding, and I think the agency  
11 certainly does, of many of the risks that go into not  
12 only the application but also into the phase 4 issues  
13 around these drugs. And I think to link the  
14 understanding of the phase 4 complications that are  
15 being collected in an ongoing way with the education  
16 is critical. And if this does reside within the DEA,  
17 they will basically have to go to the FDA to  
18 understand what the phase 4 issues are.

19           So I do think, in terms of the education  
20 coming from the experts with the deepest repository of  
21 knowledge about the compounds and about the ongoing  
22 real world implications of having those compounds out

1   there and being prescribed, the FDA is the natural  
2   home for this educational forum. I do understand the  
3   challenges that Dr. Flick raises regarding how  
4   cumbersome would this be and the fact that there would  
5   be duplication. But with regard to the specific  
6   content that prescribers need to have at their hands,  
7   which will inform the messaging on an ongoing basis, I  
8   think the FDA is a logical home.

9           DR. JENKINS: Just one point I want to add  
10   to that. The Drug Abuse Treatment Act did provide a  
11   role for SAMHSA in the content of the training that  
12   was required to get that special DEA number for  
13   outpatient treatment of opioid dependence. So there's  
14   nothing to say that legislation linking training to a  
15   DEA registration couldn't also have FDA in a role of  
16   helping to develop the training. So you could have  
17   both if the legislation were written to provide for  
18   that.

19           DR. MARKMAN: Hearing the rationale for the  
20   many members, or the several members who voted yes,  
21   their concern was that they felt a yes vote was a way  
22   to expedite some intervention. And some intervention

1 was better than no intervention, or the delay, as  
2 someone said, would be unacceptable.

3           So I think my only fear with letting the  
4 legislative process and that timeline drive this, is  
5 that, frankly, that could be a decade before that  
6 actually happens. I don't think a decade is  
7 acceptable to the yes voters or the no voters here.  
8 So to the extent that the DEA option requires a  
9 decade's worth of wait, I think it's not acceptable,  
10 from my point of view.

11           DR. KIRSCH: Dr. Wolfe.

12           DR. WOLFE: What I'm hearing here is a  
13 partnership. The part that is the check off by the  
14 company as to whether a doctor can write a pill is I  
15 think ridiculous. For isotretinoin, it's fine. It's  
16 one product. Here, we've got a dozen or two dozen  
17 companies and who knows how many different products  
18 there?

19           So again, I think that to wed the expertise,  
20 the unbiased expertise of the FDA and/or SAMHSA or  
21 whatever, with the authority to do the check off with  
22 the DEA, is I think a more logical way of doing it.



1           I was just looking at my notes, when Dr.  
2   Rappaport at 1:00 yesterday started off by saying,  
3   "The REMS does not have the following." The first  
4   thing was electronic verification of doctor training,  
5   because, he said this would be too difficult,  
6   complicated, whatever else, and then, he threw out --  
7   which is why I asked him whether he supported it --  
8   the idea of it going to DEA.

9           So I think the combination of the  
10   educational materials being developed by FDA, NIDA,  
11   SAMHSA, and then put into the training program, which  
12   someone would have to do in order to get their DEA  
13   license, would be something I would agree with, and I  
14   would wonder whether other people would agree with  
15   this as well.

16           DR. KIRSCH: Dr. Nelson.

17           Dr. Deshpande.

18           DR. DESHPANDE: I want to come back to  
19   Dr. Kirsch's point that we don't want to have this  
20   question delay a revision of the plans; that if the  
21   FDA has the authority through REMS, then I would  
22   recommend, as Dr. Markman also pointed out, that we

1 need to move ahead because this is a public health  
2 concern. And, therefore, if it can be done under the  
3 REMS authority sooner, while working with the other  
4 agencies for an eventual legislative fix, then it  
5 definitely is worth doing. And I think Dr. Vaida and  
6 several of us said that we would have switched our  
7 votes to a yes vote if mandatory training was included  
8 as part of the REMS.

9 DR. KIRSCH: Dr. Berger.

10 DR. BERGER: I would vote that industry  
11 definitely be kept out of training. And some form of  
12 ACCME, the pharmacy, ACCME, be used. In terms of a  
13 common set of educational materials, that's not very  
14 hard. A group of experts -- there are tons of  
15 educational tools in terms of opiates and pain  
16 management things already out there. Not hard. There  
17 are lots of organizations already doing tons of  
18 teaching. It would be very easy to pull together with  
19 groups of experts.

20 I think we just definitely need to keep  
21 industry out of it with using an ACCME-type model and  
22 clearly with potential incentives. It absolutely must

1 be mandatory both for physicians and for pharmacists,  
2 and for NPs and anyone involved in the prescribing and  
3 dispensing model.

4 DR. KIRSCH: I'm going to take the chair's  
5 prerogative and try to summarize what we have so far,  
6 and see if we can move onto question 5.

7 So we're intended to discuss how we should  
8 work with sponsors to develop the necessary  
9 educational program for prescribers and patients. I  
10 think, my sense from the committee is that as a  
11 committee, on average, we're uncomfortable with  
12 industry or the sponsors creating the educational  
13 program of understanding the needs of the FDA.

14 I think the committee would feel more  
15 comfortable if FDA created the content of the training  
16 or education program, or if necessary, to include the  
17 sponsors, to assure that extensive review occurred  
18 prior to approval for general use.

19 How this might be achieved to avoid concerns  
20 that have been raised regarding manufacturers'  
21 involvement, again, the best way to avoid it would be  
22 to have content developed by FDA in consultation with

1 experts in the field, but if necessary, to have the  
2 sponsors involved to make sure that before released in  
3 a prospective fashion, to have extensive review and  
4 ultimate approval.

5 I think the committee as a whole does value  
6 a common set of educational materials for the products  
7 or groups of products, rather than having individual  
8 educational materials for individual drugs. And I  
9 think overwhelmingly the committee believes that there  
10 is no need for incentives to improve prescriber  
11 participation, but rather this education or training  
12 should be mandatory, working either in concert with  
13 the DEA or through the REMS legislation.

14 Now, with that as a summary, I'll take  
15 additional comments.

16 Dr. Morrato.

17 DR. MORRATO: I didn't get a chance to add a  
18 bit. With regard to how to organize, I agree with  
19 what's been said in terms of a payment model that's  
20 like iPLEDGE. And there is just two points I wanted  
21 to say.

22 One is how do you figure out what's a fair

1 payment? We talked about linking it with the market  
2 shares, et cetera. But I think we should consider  
3 what is a standard promotional spending to do an  
4 adequate education program. So it's not a standard of  
5 what we typically have in federal grants to do an NIH  
6 study. It's not the standard of a public health  
7 program that's trying to scrap things together. It  
8 needs to be of a standard of funding that industry  
9 uses to do their advertising materials.

10           The other piece I just wanted to say is that  
11 I think it's important to bring experts from  
12 academics, but I think we also need to bring expert  
13 stakeholders who, as we've heard in the session, have  
14 a tremendous amount of practical hands-on experience  
15 designing these kinds of programs.

16           I would be careful -- I know we need a  
17 barrier, but I would be careful in throwing out the  
18 baby with the bathwater, in that many in marketing and  
19 advertising agencies have this very skill set that we  
20 need to be applying to these kinds of questions, with  
21 state-of-the-art knowledge, as well as the CME  
22 developers, of how to actually affect change. We can

1 keep barriers, but I think we don't want to totally  
2 exclude all of that expertise and hands-on knowledge.

3           And then with regard to -- I actually voted  
4 yes, so I just wanted to throw out that I think there  
5 are some incentives that you can do. In light of yes,  
6 it's important to institutionalize, you know, as we've  
7 been talking about the mandatory. But I think audit  
8 feedback, which we heard from I think the Missouri  
9 Medicaid program -- and systems like that have been  
10 used as ways to make visible what behavior change  
11 you're trying to do.

12           So the National Surgical Quality Improvement  
13 Program was trying to reduce mortality following  
14 surgeries. And they did an audit kind of program that  
15 was described in which you would see how your hospital  
16 ranked on this measure relative to others in your  
17 competitive set, if you will. And you actually do  
18 real-time tracking of what percentage of physicians in  
19 a particular region or particular specialty type have  
20 signed up for that, and you publish it weekly, so it's  
21 very visible. And you start tracking. Just like when  
22 you have a target campaign to raise money for some

1 sort of charity, you make it visible what your target  
2 it, and you make it visible how you're tracking  
3 against it, and you use the natural competitiveness of  
4 folks to not want to be the ones left out.

5 So we could create sort of surveillance maps  
6 in the same way that CDC uses maps to look at  
7 behavioral risk factors, survey or tracking obesity.  
8 Instead of those, we're tracking compliance with this  
9 kind of training.

10 So I'm not discounting that, yes,  
11 institutionalizing it by making it mandatory is  
12 obviously where you'd like to be, but there can be  
13 things that are done in the meantime.

14 DR. KIRSCH: Dr. Carter.

15 DR. CARTER: Yes. I just wanted to point  
16 out that 4B is phrased as a choice, and it might not  
17 have to be. There might be a possibility to allow a  
18 common set of materials and product-specific  
19 materials. The concern being is that with a common  
20 set, there may be an incentive to simply achieve a  
21 minimum. And there might be pathways or incentives  
22 that could be provided to allow that some companies

1 are looking to do something more innovative so that  
2 innovation is not stifled. But there may be a  
3 possibility to allow product-specific materials to try  
4 and improve this sort of approach.

5 DR. KIRSCH: Dr. Krantz.

6 DR. KRANTZ: I would agree completely. I  
7 think, in my mind, the framework that the industry  
8 working group laid out were three choices, the  
9 fentanyl, the methadone, and the long acting seemed a  
10 logical one. In my mind, for example, methadone is  
11 the only one I'm aware of that has significant  
12 cardiotoxicity. So to sort of lump it all together  
13 would really be very difficult and perhaps not in the  
14 patient or the physician's best interest.

15 So I would consider the question as do we  
16 decide whether we like the framework as proposed by  
17 IWG, and if so, how we move ahead.

18 DR. KIRSCH: Dr. Ballantyne.

19 DR. BALLANTYNE: I just wanted to comment on  
20 the way that you, Dr. Kirsch, just summarized how the  
21 committee feels about this. I think it would be very  
22 different if it only applied to extended-release



1   opioids, because then it would have the undesirable  
2   effect of people being trained to use these drugs, but  
3   in many cases preferring to use the drugs that were  
4   not controlled in this way because it's easier.

5               DR. KIRSCH:   Dr. Porter.

6               DR. PORTER:   So I don't have an answer to  
7   this question.   I don't know that there is one.   But  
8   how high is the wall between having sponsors enroll  
9   and going through the DEA?

10              Is there any creative way that there could  
11   be a partnership set up, where you don't have to  
12   actually set up the legislation to go through the DEA,  
13   but somehow, that information could be fed into them  
14   through something that the sponsors were to establish?

15              DR. THROCKMORTON:   I guess I'll just say  
16   that we have had discussions with our legal  
17   colleagues, who are not here, and we've been told that  
18   legislative change would be required.

19              DR. JENKINS:   Basically, somehow, you have  
20   to set up a system where you can't prescribe the  
21   products unless you've had the training.   One way is  
22   to link it to your DEA registration.   The other under

1 the REMS would be to set up an isotretinoin-like  
2 program. Those are the only two ways that we're aware  
3 of. And currently, we don't have the authority to the  
4 DEA link. That's the legislative requirement.

5 DR. KIRSCH: Dr. Olbrisch.

6 DR. OLBRISCH: I'd like to add that there  
7 are other aspects to pain treatment and pain  
8 management besides pharmacological, and that these  
9 should be components of any educational program for  
10 physicians. And when you focus on the role of  
11 industry, you start limiting yourself to pharmacology.

12 DR. KIRSCH: Dr. Vaida.

13 DR. VAIDA: I just want to briefly mention  
14 the last part of the statement that said the DEA or  
15 through the REMS. And I think we heard that we would  
16 rather maybe not have it go through the REMS; there  
17 may be too many manufacturers in that.

18 Just that the FDA's aware too, and I'm sure  
19 you are, is the DEA, that would be limiting to  
20 prescribers. I do not have a DEA number, and nurses  
21 don't have a DEA number unless they're nurse  
22 practitioners and prescribe; so other healthcare

1 professionals. So if you want to say DEA, or,  
2 ideally, it'd be the licensing bodies, because in  
3 order to get my license, medical license or pharmacy  
4 license, we need to have CE, and they could mandate  
5 what CE we have. So I'd just like to get that out and  
6 clarified, because there's so much emphasis on that  
7 DEA number.

8 DR. KIRSCH: I'd like to remind the  
9 committee that our comments are taken very seriously  
10 by the FDA, but our comments are advisory, not  
11 prescriptive, to the FDA. And so, I think it's  
12 important that they hear us, but we're not going to be  
13 able to define how the FDA actually acts on this  
14 matter or any other matters.

15 Dr. Denisco.

16 DR. DENISCO: It's being commented that  
17 there's only two ways to accomplish this, one through  
18 the DEA, and two, through a sponsor-organized  
19 registration plan.

20 There's a third way, and that's through the  
21 Federation of State Medical Boards. Now, there's no  
22 legislative way to adopt it, but they are very

1 interested in this problem. And if they were  
2 contacted, might well be glad to put this on as a CME  
3 requirement, much as was discussed as with the other  
4 boards, because to keep throwing it into the DEA, when  
5 the DEA has been involved with the buprenorphine  
6 issue, they've been heavy handed recently in the  
7 inspections. And they've admitted they've done this  
8 and are going to be more respective of physicians'  
9 rights.

10 So before it's advised to use the DEA, I  
11 would urge a lot of caution and think of considering  
12 the Federation of State Medical Boards, which as of  
13 yet has not abused its powers.

14 DR. KIRSCH: Dr. Jenkins.

15 DR. JENKINS: We have had lots of discussion  
16 with the Federation of State Medical Boards. We met  
17 with them recently, and I know they testified during  
18 the open public hearing that they're very interested  
19 in playing a role. There are 70 individual licensing  
20 bodies that are represented by the Federation of State  
21 Medical Boards. So as I understand it, each of those  
22 70 would have to adopt the requirements if you wanted

1 it to be universal across the country. Not saying  
2 it's not an approach, but the Federation is just that.  
3 They're a federation. They don't have any overarching  
4 authority over their member organizations, so you'd  
5 have to work individually through the 70 members. But  
6 it's clearly a pathway that we're interested in.  
7 We've been discussing with them linking training to  
8 licensure for your license to practice.

9 Let me mention one other thing that we  
10 haven't talked a lot about here, but it is important  
11 to bring this up since we've heard a lot of calls for  
12 expanding the REMS to include the immediate-release  
13 products as well.

14 While we presented this to you as a class  
15 REMS for the long-acting and sustained-release  
16 products, in reality under the law, we will be  
17 imposing a requirement for REMS on each individual  
18 sponsor that has an application for those products,  
19 and we've encouraged them to work together  
20 collectively. And for each individual product, we  
21 have to meet the statutory framework for being able to  
22 impose a REMS.

1           When we start bringing in the immediate-  
2 release products, you have a lot more products, a lot  
3 more sponsors, and we'll have to meet the statutory  
4 triggers for new safety information for each of those  
5 products as well. So it's not as easy as it might  
6 sound to say a class REMS, that you go from long  
7 acting and sustained release to the class of all the  
8 immediate release because I don't remember how many  
9 applications there are, but there are many, many more  
10 applications and sponsors, and we have to meet the  
11 triggers under the law for each of those applications.

12           So it is a big step from the legal standard  
13 to go from extended release, long acting, to immediate  
14 release, and that's part of why we chose not to  
15 include it in our plan. It's not the primary reason.  
16 The primary reason is we thought this is the major  
17 problem we were seeing with the product itself, having  
18 an inherent risk of the high dose, the sustained-  
19 release mechanism that could be easily defeated, and  
20 even in a legitimate patient cause a fatal outcome.

21           But I just wanted to make sure you're aware  
22 of that. It's not as easy as it sounds to go from the

1 constrained REMS that we've proposed to including all  
2 immediate-release opioids.

3 DR. KIRSCH: Last comment on this question  
4 is going to be Dr. Peairs.

5 DR. PEAIRS: I just wanted to say that if  
6 changing this to a mandatory education occurs, to me,  
7 that's a game changer, as far as leaving out  
8 immediate-release opioids. The way the proposal is  
9 written now, there really isn't a reason for a  
10 squeeze-the-balloon effect, where prescribers are  
11 going to shift to prescribing short acting. And as  
12 much as I think it should be mandatory, if I saw that  
13 proposal, I would vote no unless it included immediate  
14 release, because I think there would be a lot of  
15 unintended negative consequences to that.

16 DR. KIRSCH: Okay. Thank you. We're going  
17 to go onto question 5.

18 Question 5, I'll read. "Please discuss how  
19 to assess the impact of REMS. Include the following  
20 in your discussion: specific metrics that should be  
21 used, and sources for data on those metrics; the  
22 changes in those metrics that would constitute

1 evidence of success for the REMS; the changes in those  
2 metrics that would suggest a need to make changes in  
3 the REMS; the appropriate period of follow-up for  
4 initial evaluation and to determine if the REMS is  
5 working; how to distinguish the effects of REMS from  
6 other efforts to address misuse and abuse of these  
7 analgesics.

8 Dr. Farrar.

9 DR. FARRAR: I've said earlier, and so I  
10 won't repeat, but the collection of data is an  
11 absolutely vital part of this and is one of the  
12 devil's in the details piece of it.

13 I wanted to make sure that it was clear,  
14 that it is very important, from my perspective, that a  
15 whole new set of data be arranged to be collected --  
16 we do not have adequate measures currently -- and to  
17 be very specific that the data needs to be focused on  
18 the various categories that we have been talking about  
19 and that sometimes continue to get jumbled up in terms  
20 of considering how to affect the overall process.

21 Because, clearly, affecting how patients are  
22 prescribed medications, and even if they stored them



1 better and disposed of them better, there is still  
2 going to be a large number of patients, or a  
3 significant number of patients who get medications in  
4 Florida or elsewhere and will need to be dealt with in  
5 a very, very different way. So that the global  
6 measure of how many patients die because of overdose  
7 may not completely reflect the effects of the process.

8           It's specific, just to be very clear about  
9 it. I think that the information presented by  
10 Dr. Dormitzer about where people get their pain  
11 medication is an important slide for us to focus on,  
12 because it helps us to know where to focus the efforts  
13 that we undertake.

14           In terms of the metrics to use, to state it  
15 again, I think it's absolutely imperative that you get  
16 patient-level data on their use, or at least on their  
17 storing and on their perceived use of their  
18 medications. That data is obtainable at the source of  
19 the pharmacy. It is obtainable without requiring that  
20 they do it. It is obtainable by making it in their  
21 best interest to do it, as I said, by giving them a  
22 coupon for \$5 off their co-pay and providing a \$5

1 payment or some amount of money to the pharmacy for  
2 collecting those forms. I would bet that you would  
3 get substantial data that would help us to actually  
4 understand whether these medications work and also to  
5 say do you keep it in a safe or something.

6           Those questions and how those questions  
7 would be asked would have to be very short, have to be  
8 something to be completed very quickly, and could be  
9 changed over time, and should be generated from the  
10 FDA or from some organization that wants to define  
11 what needs to be known in a way that makes sense.

12           Clearly, in terms of the overall metrics,  
13 we've had a lot of data presented here about the  
14 number of deaths. and I think our ability to  
15 understand that is clearly growing. The one thing I  
16 would argue is that we heard in the public  
17 presentation the concept of actually labeling, being  
18 able to label pills.

19           For those of you who know me, I am  
20 inherently paranoid about the amount of information  
21 that's being collected on all of us. And what's very  
22 clear is that there's no limit to the amount of

1 information that can be collected on all of us -- all  
2 we need to do --so what we need to focus on is how  
3 that information is used.

4           Carrying that forward, if every pill is  
5 labeled with a little identity tag, then when a  
6 thousand Oxycontin are identified in a car, we know  
7 where they came from and we can do something about  
8 that. So I would argue that that is an important  
9 additional data source that is necessary for what we  
10 do.

11           Then in terms of the number of patients that  
12 die because of opioids, I think we talked before about  
13 the need to provide guidance at least and to do  
14 serious work about trying to figure out whether the  
15 opioids were simply there when they died or were the  
16 source of their death. And I think it's very hard to  
17 know. And it may be that we can't know that. But at  
18 least, we ought to be honest with ourselves to say  
19 that even death data is going to be sometimes hard to  
20 interpret, and we at least need to understand the  
21 variability there so that we can interpret it better.

22           Then, in terms of how often it should be

1 collected, honestly, it's an ongoing thing. I think  
2 there ought to be a dashboard that comes up and  
3 changes on a weekly basis, based on the data that's  
4 collected. There's no reason in the world, given the  
5 current ability to collect and move data in the  
6 marketing world, that we can't do it better in an  
7 attempt to try and improve care.

8           Then, the last question was distinguishing  
9 the effect of REMS from other efforts. Honestly,  
10 you're never going to be able to dissect that out. If  
11 things get better, everybody gets to claim credit, and  
12 if things get worse, we know it didn't work; that,  
13 with the stipulation that we would look at and dissect  
14 the data into the different groups that we were  
15 discussing before, i.e., unintentional overdose,  
16 purposeful overdose, drug abuse by drug abusers, and  
17 sort of the party, grab a pull out of the bottle-type  
18 of phenomenon. Thank you.

19           DR. KIRSCH: Oh, my gosh. I thought there'd  
20 be a million hands up for this one.

21           Dr. Nelson.

22           DR. NELSON: These are obviously very, very

1 complicated issues. The current sources that were  
2 presented here to provide data for us are all ongoing,  
3 and they have a long track record, which allows us to  
4 follow trends. Obviously creating a new data set  
5 would mean that you'd have essentially no track  
6 record, which would make it hard to know what any  
7 directional change meant, although obviously, you  
8 might be able to gauge up or down or something like  
9 that. It would obviously be very limited.

10           The one thing I thought that was really  
11 interesting, the hardest piece of data you have  
12 always, is death data. And John's comments were  
13 right, which is it's very complicated to figure out  
14 whether somebody died of a specific drug or whether it  
15 was incidental in their cause of death or in their  
16 death, period.

17           One thing that would be interesting, and  
18 something that's been talked about a lot in the med  
19 tox world and the forensic toxicology world, is trying  
20 to define a lot of these things and put some  
21 quantitation around meanings of numbers and post-  
22 mortem redistribution values and some things like

1     that.  And as best I know, nobody's ever really taken  
2     the lead in trying to organize this type of symposium  
3     or this sort of consensus discussion.

4             So this might actually be something that  
5     would be useful to think about, which would really be  
6     trying to figure out -- it's hard, but it's something  
7     that's potentially possible; but bringing together a  
8     group of people that would actually be able to set  
9     some definitions and standards about interpretation  
10    of, I guess, pre- and post-mortem drug testing when it  
11    comes to the opioids.

12            The other things I think, obviously, are  
13    much more complicated.  but death is definitely a hard  
14    endpoint.

15            DR. KIRSCH:  Dr. Terman.

16            DR. TERMAN:  I guess I'm not terribly  
17    surprised that we're having a little trouble with this  
18    metrics question when we've changed the whole idea of  
19    what we're doing.  Now, we're including immediate  
20    release or now we're including mandatory education.

21            So, of course, the metrics are going to  
22    change somewhat.  If there's mandatory education, then

1    what you're going to be looking at is how many people  
2    opt out of bothering with the DEA certification, for  
3    instance, deciding not to treat patients with pain.

4                When the FDA talks about that really the  
5    only thing they can do is to hand it back to industry  
6    for mandatory education, that sounds like more  
7    involvement of the industry in the education to me.  
8    In fact, what I'm really hearing is registries. And  
9    after reading hundreds of pages of people who thought  
10   that registries was not a good idea, after industry  
11   actually coming together as a working group to work on  
12   this, to send it back could destroy the industry  
13   working group in terms of actually working together.  
14   Now, you've got everybody for themselves, which I was  
15   actually kind of excited to see, for a change, was not  
16   taking place.

17               Now, I could be wrong on that. But it  
18   sounds like when the FDA's talking about what they can  
19   do without the DEA, without the medical boards in each  
20   state, all they can do is kind of tell the individual  
21   sponsors to do what's right and make sure there's  
22   education.

1           So, I think dealing with this metrics  
2 question, when we've changed the whole landscape of  
3 our suggestions, I for one am still very much against  
4 registries, and particularly for each individual  
5 product. That's a nightmare for treating my patients.

6           DR. KIRSCH: Dr. Kosten.

7           DR. KOSTEN: A few things. The first is  
8 that I'm afraid I disagree with this issue of getting  
9 the DEA involved or not involved. I think there are  
10 examples, particularly with Actiq, these fentanyl  
11 lollipops, of where the FDA did in fact have a process  
12 where they directly did interventions that have had a  
13 very nice impact on people don't abuse the lollipops  
14 very much. And that did not involve the DEA.

15           So I think they can do it if they want to.  
16 I think the persons who need to pay for it are the  
17 industry. I think it's very clear that they can  
18 extract money out of industry to get drug approvals;  
19 they can extract money out of industry for this.

20           I think that doesn't mean they don't control  
21 it. They do in fact control it. They control the  
22 standards. And in fact, one of the other things that



1 I think that they do control, and that they should  
2 insist upon, would be the audit and feedback kind of  
3 mechanisms. Those are in fact the most effective way  
4 to get things to happen. You don't have to do it on  
5 every single provider in the United States. You can  
6 pick subsamples of them, and you pick them randomly,  
7 and the DEA can control that also.

8 I think when they go into that, you'll get  
9 process measures. The problem is we're looking at  
10 outcomes, outcomes that are often a couple of years  
11 out; process measures, that is finding providers who  
12 don't do what they're supposed to do, including  
13 getting the training. You can figure that out usually  
14 within months. Again, I base that on experience out  
15 of a system in the VA that's big and national, and we  
16 do it.

17 I'm afraid I just see backpedaling for very  
18 easy things, when in fact, there are harder things to  
19 do, perhaps, but they need to be done. And there  
20 needs to be process measures. That would be feedback  
21 comes back sooner. They are different metrics than  
22 we've been discussing. And I think death and these

1 other kind of metrics are perhaps convincing and hard  
2 outcomes, but they're disastrous. I don't know why  
3 we're settling for outcomes that have to be so  
4 Draconian, when there are other ones that you can, and  
5 you can identify who are the problematic providers,  
6 and you can do something about them.

7 DR. KIRSCH: Dr. Kerns.

8 DR. KERNS: Just briefly, I get excited  
9 about this question because of specific interests in  
10 evaluation and methods. I think that there are  
11 opportunities here for specific partnerships,  
12 interagency partnerships, and including, in  
13 particular, NIDA and maybe other institutes.

14 I think, in fact, disagreeing with  
15 Dr. Farrar's conclusion about E, that it's impossible  
16 to do, I think that, in fact, well designed, mixed  
17 method, qualitative, quantitative approaches that are  
18 focused in more specific areas, a specific catchment  
19 area, a county here and there to study the effects of  
20 REMS in the context of other changes, and looking at  
21 collecting data from a variety of stakeholders, both  
22 quantitative and qualitative data, is the kind of

1 research that really could help inform, give answers  
2 to some of the questions that we're struggling with  
3 today and help inform future efforts in this  
4 direction.

5           So without being really specific, I think  
6 there are a lot of empirical questions embedded here  
7 and looking not only at more sophisticated modeling  
8 approaches to the data that we already have and  
9 trending those into the future, creating new -- I  
10 don't know if the answer is registry, but metrics.  
11 Population-based metrics would make sense, but also  
12 focused science, again, through our partnerships with  
13 the NIH would make sense to me.

14           DR. KIRSCH: I'd like to maybe provoke the  
15 committee a little bit. And as I listened to the  
16 comments, I hear about metrics over the outcomes of a  
17 REMS program, as far as whatever bad outcomes exist  
18 from this class of drugs or these classes of drugs,  
19 and the other metrics being around providers.

20           I think they are a bit different, and I  
21 think the committee is split on the idea of having  
22 registries that involve individual patients or

1 individual providers, or looking at more global data  
2 to look at an overall effect of a program. And I'd  
3 like to ask for a comment from the committee about is  
4 there a consensus or not about whether we recommend  
5 individual metrics about individual patients or  
6 providers versus a global evaluation of the program.

7 Dr. Ballantyne.

8 DR. BALLANTYNE: Well, I was just going to  
9 say that in addition to everything that's already  
10 being done -- I mean, there are a lot of processes for  
11 measuring these bad outcomes of opiate treatment, that  
12 the prescription monitoring system's absolutely vital  
13 in where we can go next. And prescription monitoring  
14 systems are actually de facto registries, and they do  
15 give us the information we need. And the existing  
16 prescription monitoring systems, as far as I know, not  
17 all of them make the information available to  
18 physicians. I don't think they do in Pennsylvania.

19 So I can't find out who else is prescribing  
20 to my patients, for example, and if I could, it would  
21 be very helpful. But I think prescription monitoring  
22 is a direction we need to go, and it does actually

1 produce some form of registry of patients and  
2 prescribers.

3 DR. KIRSCH: Dr. Turk.

4 DR. TURK: I think we may need to make a  
5 distinction between what are we predicting, what are  
6 the outcomes we're trying to change, and what are the  
7 metrics we're going to use to look at what the  
8 predictors are.

9 We know or we have some sense of the types  
10 of outcomes we're looking for, ultimately, which is we  
11 want to reduce morbidity and mortality, so say with  
12 opioids. So in one sense, it's like what are those  
13 outcome metrics, and then we could say what are the  
14 process metrics that will allow us to see if they  
15 affect or influence or predict what those outcomes  
16 are.

17 So I think we're mixing the dependent and  
18 the independent variables here to some extent. And I  
19 think, if we agreed on what the dependent variables  
20 are, then we could begin to start talking about what  
21 would be the metrics we would use to collect the  
22 independent variables.

1           For example, knowing the number of  
2 physicians who prescribe in a certain way, does that  
3 predict a change in the outcomes we're concerned  
4 about? Have we agreed on what the metrics are for the  
5 outcomes? I think that's where we have some problems,  
6 because the RADARS and the DAWN and all the data that  
7 we've seen, each of them have significant problems  
8 with them that have been identified and pointed out to  
9 us. And the question is, do you make use of those  
10 existing systems because they exist and we have prior  
11 information so we can track things? Do you do that in  
12 addition to or instead of trying to develop some new  
13 outcome measures, as Dr. Farrar was talking about? I  
14 think that's a decision that has to be made.

15           At a minimum, I think, at least in my  
16 opinion, we should take the existing metrics we have  
17 and make use of them at the same time while thinking  
18 of alternatives to those, and then begin to look at  
19 what would be the variables that would predict changes  
20 in those types of outcomes, physician prescribing,  
21 types of prescriptions they're engaging in, and the  
22 amount of education that's provided, the numbers that

1 opt in and opt out. Those would be the independent  
2 variables to predict the outcomes that we're  
3 interested in.

4 DR. KIRSCH: Dr. Kerns.

5 [No response.]

6 DR. KIRSCH: I'm going to try to summarize  
7 this as best I can, and just to warn you, we have  
8 several members of the committee who got together and  
9 put together a statement that we're going to project  
10 and ask for your thoughts about the statement to send  
11 maybe a clearer message to the FDA.

12 So with regard to discussing the assessment,  
13 how to assess the impact of the REMS, I think that the  
14 consensus of the committee is that we would want to  
15 make use of all the existing outcome measures that  
16 we've seen presented over the last two days now. But  
17 in addition to that, develop new outcomes, as Dr.  
18 Farrar had mentioned, but not lose track of the  
19 existing outcomes in order to be able to truly  
20 determine whether or not there's a positive or not a  
21 positive effect of the interventions that we've  
22 suggested.

1           The specific metrics that should be used in  
2 sources for data on those metrics, again, like I just  
3 said, we want to use existing databases, although some  
4 of those are delayed in their reporting. I think the  
5 committee agrees it would be a mistake to throw that  
6 data out, but at the same time, determine new  
7 variables that would more specifically address the  
8 outcomes we're trying to look at in the way of more  
9 than just mortality, but the morbidity as well.

10           I think the committee as a whole would  
11 prefer not to have specific registries. The changes  
12 in those metrics that would suggest a need to make  
13 changes in the REMS, I think, if morbidity and  
14 mortality improve, that would be a good thing. The  
15 appropriate period of follow-up for initial evaluation  
16 to determine if the REMS is working, although I think  
17 if the new metrics that may be developed could be  
18 followed on a very frequent basis, certainly the  
19 existing metrics would take months and maybe even  
20 years to determine whether or not there was a positive  
21 effect of the REMS.

22           I personally -- I shouldn't give my personal



1 opinion, but because of the type of data we're talking  
2 about, I think the sense of the committee is that we  
3 would want to look at the data over a period of at  
4 least quarters to years to see whether or not the  
5 impact of the intervention is effective or not.

6           Anyone want to add to that?

7           [No response.]

8           DR. KIRSCH: Amazing.

9           Yes, Dr. Krantz?

10           DR. KRANTZ: Just a small comment. I think  
11 what was most disturbing to me was that we really  
12 can't look at mortality, which is the elephant in the  
13 kitchen, until four years. As you recall, the last  
14 data we have of the 14,000 deaths was 2006. It's  
15 2010, as I looked today.

16           So one question I had is can we use the  
17 surrogate marker of emergency room visits, that we can  
18 get from RADARS, as you mentioned, or other sources,  
19 as a way to give us an inclination of where we're  
20 going towards, if we believe that most of these are  
21 poisonings and not, indeed, cardiac deaths. So I  
22 think that would be a useful tool to use.

1           The other thing I wanted to bring up to the  
2   Office of Epidemiology and Surveillance, is there any  
3   way we can look at state-level data and not have to  
4   wait for the CDC to do their amalgamation over a four-  
5   year period? That could give us a quicker signal.

6           DR. KIRSCH: Dr. Dormitzer.

7           DR. DORMITZER: The emergency room data is  
8   collected by SAMHSA, and that usually is about like a  
9   nine-month lag after the year has ended. So 2009 will  
10   be released in September of this year. I can ask for  
11   state -- we can get state-level data. And SAMHSA also  
12   collects mortality data. But I think they collect  
13   six, six or seven states, and so I can get data for  
14   those states. It's on substance. So it's going to be  
15   oxycodone, hydrocodone, methadone. It's not going to  
16   be extended release or immediate release. That's what  
17   mortality will not give us.

18          DR. KRANTZ: Just as a clarification, is the  
19   SAMHSA data limited to the OTP environment, which is a  
20   separate, regulatory issue, if you will?

21          DR. DORMITZER: SAMHSA? No. SAMHSA  
22   provides emergency room visits.

1 DR. KRANTZ: Okay. So it's not just the  
2 OTPs? Okay.

3 DR. DORMITZER: For methadone, it's both OTP  
4 and analgesic methadone.

5 MS. WILLY: I had a comment. This is Mary  
6 Willy from DRisk. We've also talked with vital  
7 statistics, Dr. Anderson, who was speaking yesterday  
8 about the possibility of getting access to earlier  
9 data from the states. Some states, as you've heard,  
10 have the data sooner than others. So we're exploring  
11 that as another possibility.

12 DR. KIRSCH: Dr. Vaida.

13 DR. VAIDA: I just wanted to mention to add  
14 to it something that I'd mentioned before, too, is  
15 that we really didn't see any error data, preventable  
16 error data in the FDA error system. And that is  
17 something else that I think you should also track.  
18 And on a dynamic basis, too, you may be able to look  
19 for different outcome metrics that you want from the  
20 data that's in there. But I should at least mention  
21 to put that into the database to look at it. It may  
22 not be quantitative, but it should be good data.

1           MS. WILLY: To your point, we have been  
2 working with the folks at CDC, and they do collect  
3 information, the nice CAIDS, specifically about  
4 medication error. So we're exploring that, as I  
5 mentioned yesterday.

6           DR. KIRSCH: Dr. Morrato.

7           DR. MORRATO: I just wanted to add to what  
8 you had summarized in the sense that we've spent a lot  
9 of discussion around physician measures. And I just  
10 wanted to make sure that there's an equal amount of  
11 discussion around metrics that relate to the patient  
12 knowledge and behavior. So I actually wanted to  
13 endorse -- the FDA had a nice conceptual framework of  
14 how they laid out knowledge, behaviors, and outcomes  
15 that I think might be a useful way to map many of  
16 these measures. And to that, we should also be adding  
17 behavioral intent and attitude mapping, because those  
18 are things that are predictive of eventual behavior.

19           Then, in addition to the quick pharmacy  
20 audits that were mentioned by Dr. Farrar, there's also  
21 a technique where you can be doing home audits,  
22 medicine cabinet-kind of audits, either via survey or

1 telephone. For instance, the National Asthma Survey  
2 collects information about what kind of medicines that  
3 they're using. They allow patients to bring the  
4 medicines to the phone, and you can get information  
5 about, really, what is safe use, storage, and proper  
6 disposal, and get an audit of that. That I think  
7 would help complement knowledge, too.

8 DR. KIRSCH: Thank you.

9 Dr. Kosten.

10 DR. KOSTEN: Thank you. I wouldn't want to  
11 lose track of it. We do have a lot of surrogate  
12 measures that are, in fact, quite relevant to this,  
13 which is all the drug abuse data. I mean, we have  
14 monitoring the future. Those tend to be much earlier  
15 markers than deaths, of where you have a problem. And  
16 I think that you can look at how much the drug's being  
17 abused in all these various surveys. And if you have  
18 that by particular types of compounds, you can usually  
19 pick up trends over time, if nothing else, to identify  
20 which drug is problematic compared to others.

21 So we just don't seem to be mentioning that  
22 much, but yet, that is an outcome measure. It's

1 readily available, collected every year, tends to get  
2 a relatively small lag time compared to some of these  
3 other measures.

4 DR. KIRSCH: Thank you.

5 Dr. Boyer.

6 DR. BOYER: In regard to the question as to  
7 whether or not the emergency department data can be  
8 used, I think the answer to that is going to be no.  
9 DAWN is based on mentions, which functionally means  
10 that if a particular drug is mentioned in the chart,  
11 then it is a mention, whether or not the presentation  
12 was actually related to that drug use or not.

13 The Poison Control Center Data, we know that  
14 there are dramatic underreportings to poison control  
15 centers, particularly for drugs like opioids, which  
16 are relatively easy for emergency physicians to  
17 manage. So they don't call in either for reporting  
18 because they're so mundane or because they need  
19 assistance and treatment because the management for  
20 someone who can be resuscitated is relatively simple.

21 Even in poison control center data, where we  
22 were kind of surprised recently, looking at missing

1 data rates, even when specialists, the people who  
2 collect the data in poison control centers, were told  
3 to look for specific drug presentations, the missing  
4 data rate for those drugs, where they're looking for  
5 information specifically, was about 80 to 85 percent  
6 And then that data gets fed to RADARS, which  
7 functionally is a contract research organization. And  
8 how you manage the missing data on its way to  
9 analysis, I think, is a very, very real question,  
10 considering the sources of the funding.

11 DR. KIRSCH: Dr. Hatsukami.

12 DR. HATSUKAMI: I just want to reiterate  
13 what Dr. Morrato said, which was the importance of  
14 assessing attitudes, knowledge, and behavior of not  
15 only the prescribers, but also the patients. And on  
16 top of that, I think it's important to consider  
17 measuring those areas within members of the community  
18 as well, because it appears that education of the  
19 community was a significant part of the Safe Use  
20 Initiative. And unless we have campaigns that are  
21 effective, why use the money, in terms of continuing  
22 campaigns, which are not effective?

1           So I think a critical component is to assess  
2 community attitudes and behaviors.

3           DR. KIRSCH: Dr. Denisco.

4           DR. DENISCO: It was said already. But I  
5 also was going to add to what Dr. Kerns has said.  
6 NIDA does have -- to put in a little plug for my  
7 organization -- we do have some pretty extensive data  
8 network in addition to the excellent data networks  
9 that SAMHSA has, monitoring the future. It was  
10 mentioned, and it is considered a good measure for  
11 future use.

12           Also, we have a community epidemiology work  
13 group, which is sort of a community-based level of  
14 individuals who in treatment centers and other  
15 community areas, when they hear of an outbreak of  
16 fentanyl in Houston, it's put up and it's explored  
17 right in real time.

18           In addition to some very experienced  
19 researchers in the field like this, we do have ways to  
20 augment some of the data that was mentioned and to use  
21 all the federal partners, I think would be more than  
22 willing to assist in any way possible on this very



1 significant topic. Thank you.

2 DR. KIRSCH: Thank you.

3 So this is a statement that was developed by  
4 some members of the committee. And I thought it was  
5 worthwhile, with permission of the FDA, to potentially  
6 discuss and endorse, or not, the statement. I'll read  
7 it.

8 "It is the clear sense of the committee that  
9 the problem of opiate abuse and misuse are present  
10 public health concerns. The REMS process, as defined  
11 by FDAAA, has a limited effect, as it fails to address  
12 many of the root causes of the problem.

13 "The FDA REMS process lacks critical  
14 regulatory authority with regard to mandated training,  
15 enforcement, and coordination of data acquisition,  
16 that are key components of any process that is likely  
17 to impact this most important public health issue.

18 "The committee strongly recommends that  
19 legislation be developed that allows for a coordinated  
20 interagency approach that includes input from FDA,  
21 DEA, ONDCP, and other stakeholders inside and outside  
22 of government."

1           Comments? Dr. Terman.

2           DR. TERMAN: I just wanted to ask about the  
3 possibility that arose earlier about takeback programs  
4 or buyback programs.

5           Are there other stumbling blocks that aren't  
6 listed there in terms of coordination of such  
7 programs? I just don't have enough knowledge to know  
8 that.

9           DR. THROCKMORTON: Are you asking  
10 specifically --

11          DR. TERMAN: I'm asking if there are other  
12 agencies in the federal government that would be  
13 useful to list there if we were interested in  
14 suggesting such programs.

15          DR. THROCKMORTON: A couple things. First  
16 off, it'd be interesting to hear a little bit more  
17 about how the second paragraph relates to the first  
18 paragraph. As I read it, just for this first time,  
19 it's saying the REMS authority is limited, and then,  
20 that where necessary, you should seek legislative  
21 changes to enable cooperation with other federal  
22 partners.

1           Is that sort of roughly the message that  
2   you're intending to send with these two things? I'm  
3   not trying to put words into your mouth. I'm just  
4   trying to understand. Because there are many examples  
5   of coordinated work between FDA, DEA, and ONDCP,  
6   SAMHSA, NIDA, CDC right now that don't require  
7   legislative change, that are sort of happening day to  
8   day. There are specific things like takeback programs  
9   for controlled substances, where, at least I'm told --  
10   not being a lawyer nor wanting to try to be one --  
11   that legislative changes are required.

12           So the intent is to focus on that latter  
13   piece, as I'm understanding it, focus on the places  
14   where legislative changes are needed to accomplish  
15   those intergovernmental co-operations.

16           Is that fair?

17           DR. KIRSCH: Add in the statement "as  
18   required"?

19           DR. THROCKMORTON: "Where necessary," or  
20   something, because in the specific issues of drug  
21   takebacks -- as Dr. Jenkins has said, in the specific  
22   issue of using the DEA, the existing DEA registration

1 system as a part of the things we've discussed, those  
2 things would require legislative change. Many other  
3 activities I would say would not.

4 DR. KIRSCH: Dr. Wolfe.

5 DR. WOLFE: I think what Doug is saying,  
6 that you don't need legislation to coordinate with  
7 other agencies. We already have that. And what  
8 you've added now -- and it could be maybe even a  
9 little clearer -- is that to augment the REMS program,  
10 additional legislative authority has to be granted, A,  
11 to FDA, and to other agencies, such as DEA, to be able  
12 to carry on those pieces that can't be carried on now.

13 DR. KIRSCH: Dr. Covington.

14 DR. COVINGTON: Well, I agree with what you  
15 just said. And if it's likely that somebody is going  
16 to be listening to this, it might be more useful if we  
17 had a unanimous vote on it when we get it reworded.

18 DR. KIRSCH: Yes. The intent is to vote.

19 Dr. Denisco? Please use your microphone.

20 DR. DENISCO: I'm sorry. Thank you.

21 I think that we could get bogged down, or a  
22 future group could get bogged down, where we say

1 recommends that legislation be developed that allows  
2 for coordinated approach. That exists already;  
3 rather, that the committee strongly recommends that a  
4 coordinated interagency approach be continued, and not  
5 mention any specific organizations, like the DEA and  
6 ONDCP, because the variety of federal agencies that  
7 are involved, there's environmental protection that  
8 had to be involved with flushing drugs down the  
9 toilets.

10           So it becomes really limiting. So say that  
11 this should be continued, and that, where specific  
12 legislation be required, this should be -- whatever --  
13 this should be sought by the specific agency involved.

14           DR. KIRSCH: Do you believe that the  
15 comment, "And other stakeholders inside and outside of  
16 government," captures those groups?

17           DR. DENISCO: I think the emphasis on DEA  
18 and ONDCP is excessive.

19           DR. KIRSCH: Dr. Kerns?

20           DR. KERNS: It seemed to me that we're  
21 converging on the idea that it's not about coordinated  
22 legislation to allow coordinated interagency approach;

1 it's about it addresses limitations in the current  
2 legislation to address some of the concerns that we've  
3 raised in this group. So it's to address current  
4 limitations in the law.

5 I guess I'm recommending for, "The committee  
6 strongly recommends that legislation be developed that  
7 addresses current limitations in the law," maybe,  
8 "especially involving interagency collaboration" or  
9 something like that. But I don't even think that's  
10 necessary.

11 DR. KIRSCH: Okay. Any other suggestions?

12 Dr. Peairs?

13 DR. PEAIRS: I'm just wondering if the  
14 second paragraph is accurate. I think the FDA REMS  
15 process does have authority for mandated training.  
16 It's that this particular proposal lacks those items,  
17 unless I'm reading that wrong.

18 DR. KIRSCH: I think the emphasis is the  
19 process as defined currently.

20 DR. PEAIRS: For this particular proposal?

21 DR. KIRSCH: Yes.

22 DR. PEAIRS: Okay.

1 DR. KIRSCH: That's what we're asked to  
2 comment on.

3 Dr. Kosten?

4 DR. KOSTEN: Just, I hope we can get some  
5 input from the FDA and other places, because there is  
6 a law on the books already -- this may simply reflect  
7 my age -- that not only allows but asked for  
8 interagency agreement, that interagency agreement has  
9 not been in effect for -- it may be even 15 to 20  
10 years now. It was dissolved. But the law is still on  
11 the books, as far as I know. And now, there may be  
12 enforcement authorities that I'm hearing about, that  
13 the DEA has, that the FDA doesn't have, with  
14 providers. But when it says, "current limitations in  
15 the law," it would be sure nice to say what are those  
16 limitations.

17 I don't think there's any specific  
18 limitations across these agencies getting together,  
19 and in fact, I think there's a law that encouraged  
20 that. Now, why they stopped doing it is another  
21 question, but there are enforcement restrictions in  
22 here that only the DEA can do. So I would like to

1 actually have -- if we're going to say something like  
2 this, to have a lawyer who knows the laws and prove  
3 this for us. And that's an FDA request that I would  
4 make.

5 DR. KIRSCH: Now, remember, our committee is  
6 advisory, not prescriptive. And what we write here, I  
7 trust, if the FDA takes to heart, or the public takes  
8 to heart, will not be the final language that's used  
9 in any sort of legislation. So I think the purpose of  
10 this is to send a clear message to the public, and to  
11 the FDA that we urge interagency interaction to solve  
12 this problem.

13 DR. KOSTEN: I think it's always nice to  
14 look like you knew what happened in history, is all  
15 I'm saying.

16 DR. KIRSCH: Thank you.

17 Dr. Krantz?

18 DR. KRANTZ: I just had one small worry  
19 about the premise of the first paragraph. I mean, in  
20 essence, what I thought I heard this committee say is  
21 that they want to use the existing REMS system,  
22 tighten it up, strengthen it, create a more



1 restrictive REMS, if you will. And by sort of  
2 claiming that it's unhelpful is that sort of sending a  
3 message that we don't want to use that vehicle. That  
4 was one unintended consequence I'd be concerned about.

5 Then, I guess if it's something we want with  
6 the DEA for registration, I would simply suggest we be  
7 as declarative, as Dr. Kosten said, as possible.

8 DR. KIRSCH: Dr. Bickel?

9 I'm sorry. Dr. Denisco?

10 DR. DENISCO: When I read it now, "The REMS  
11 process as defined by the FDA will have a limited  
12 effect," the REMS process, it's not clear.

13 Is it the REMS process in general or is it  
14 as presented today? It's getting unclear to me. And  
15 that "The FDA REMS process lacks critical regulatory  
16 authority," we're not sure that it does. We're just  
17 saying that the REMS that was proposed had some  
18 limitations that we wanted to address.

19 DR. KIRSCH: Dr. Deshpande?

20 DR. DESHPANDE: So wordsmithing any  
21 document, even five or ten sentences in a large group,  
22 is difficult. My sense of this is that we've heard

1 for two days that this committee sees this as a bigger  
2 problem than the authority that the FDA has to  
3 regulate. And there are certain comments made by  
4 every one of us that address the hope that we could do  
5 something about the problem.

6 At various times, we've heard both  
7 representatives of the FDA and us say that there needs  
8 to be authority that either needs to be granted to the  
9 FDA or to the DEA or to any other alphabet soup in the  
10 government.

11 What I heard from the committee members, all  
12 of us sitting here, was that we thought this was an  
13 important enough problem that we needed to make a  
14 statement that said the committee really recommends  
15 further action than just the REMS issue that we're  
16 discussing today.

17 I think we can make a simple statement. And  
18 I'm hoping that, as we're wordsmithing this, that it  
19 becomes simpler rather than more complicated, to give  
20 the appropriate impetus and a public statement that we  
21 take this seriously, and that we expect our federal  
22 government to respond in an appropriate manner. And

1 if the FDA has taken this on -- and I applaud them for  
2 bringing this to our attention and to the public again  
3 -- then we need to help them address the issues in a  
4 timely manner.

5 DR. KIRSCH: I believe that when we voted  
6 and went around the table, and each gave our opinions,  
7 we each, in our own way, emphasized many of these same  
8 issues. So because of the comments that you made  
9 about how difficult it is to wordsmith this with such  
10 a large group of people, and if we're going to present  
11 it to the FDA and to the public as the opinion by this  
12 committee, I think it would not do it justice to do it  
13 in that fashion.

14 So I think all of our comments were made as  
15 part of the public record, and we said in our own way  
16 our feelings about this. So I think it's best to be  
17 left alone. Unless there's otherwise strong opinion.  
18 I will adjourn the meeting.

19 (Whereupon, at 3:33 p.m., the meeting was  
20 adjourned.)

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