FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE DRUG AND RISK
MANAGEMENT ADVISORY COMMITTEE (DSaRM) AND THE
ANESTHETIC AND ANALGESIC DRUG PRODUCTS
ADVISORY COMMITTEE (AADPAC)

Wednesday, June 12, 2019
8:29 a.m. to 5:10 p.m.

Day 2

FDA White Oak Campus
Building 31, the Great Room
10903 New Hampshire Avenue
Silver Spring, Maryland
Meeting Roster

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PROCEEDINGS

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. HERNANDEZ-DIAZ: I would first like to remind everybody to please silence your cell phones, or smartphones, and any other devices if you have not already done so. I will also like to identify the FDA press contact, Lyndsay Meyer.

If you are present, please stand; in the back, over there. Thank you.

My name is Sonia Hernandez-Diaz, and I will be chairing today's meeting. I will now call the Joint Meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee to order. We'll start by going around the table and introducing ourselves. We will start with the FDA to my left and go around the table.

DR. STAFFA: Good morning. I'm Judy Staffa. I'm the associate director for public health initiatives in the Office of Surveillance and
Epidemiology.

DR. HERTZ: Sharon Hertz, director for the Division of Anesthesia, Analgesia, and Addiction Products, Office of New Drugs here at CDER.

DR. McANINCH: Hi. Jana McAninch, senior medical officer, prescription drug abuse teams in the Division of Epidemiology, Office of Surveillance and Epidemiology.

DR. HORN: Hi. Pamela Horn. I'm the clinical team leader in the Division of Anesthesia, Analgesia, and Addiction Products.

DR. EGGERS: Good morning. Sara, Eggers, the decision, support, and analysis Team in CDER's Office of Program and Strategic Analysis.

DR. NELSON: Good morning. I'm Lewis Nelson. I'm the professor of emergency medicine and a medical toxicologist from Rutgers, New Jersey Medical School in Newark, New Jersey, and I oversee the New Jersey Poison Control Center.

DR. KATZMAN: Hi there. I'm Joanna Katzman. I'm a senior associate director at Project ECHO and a professor at the University of New Mexico. Thank
you.

DR. MIKOSZ: Good morning. Christina Mikosz. I'm a medical officer at the CDC in the Division of Unintentional Injury Prevention.

DR. ZIVIN: Kara Zivin, professor of psychiatry at University of Michigan and research scientist at Department of Veterans Affairs.

DR. MARSHALL: Good morning. I'm Brandon Marshall. I'm an epidemiologist at the Brown School of Public Health.

DR. HOFFER: Lee Hoffer. I'm an associate professor of medical anthropology and psychiatry at Case Western Reserve University in Cleveland, Ohio.

DR. LESAR: Good morning. Timothy Lesar, patient care services director, director of clinical pharmacy services, Albany Medical Center in Albany, New York.

DR. MEISEL: Steve Meisel, director of medication safety, Fairview Health Services in Minneapolis.

DR. BOUDREAU: Good morning. Denise Boudreau, scientific investigator at Kaiser
Permanente Washington, where I do pharacoepidemiology research and also professor at the University of Washington.

DR. GRIFFIN: Hi. Marie Griffin, professor of medicine and health policy at Vanderbilt University in Nashville.

DR. CHOI: Moon Hee Choi, designated federal officer.

DR. HERNANDEZ-DIAZ: Sonia Hernandez-Diaz, professor of pharmacoepidemiology, Harvard Chan School of Public Health in Boston.

DR. LITMAN: Ron Litman, professor of anesthesiology in pediatrics, University of Pennsylvania, Children's Hospital Philadelphia, and I'm the medical director of the Institute for Safe Medication Practices.

DR. URMAN: Rich Urman, anesthesiologist, Brigham and Women's Hospital in Boston.

DR. JOWZA: Good morning. I'm Maryam Jowza. I'm an assistant professor in anesthesiology and pain management at University of North Carolina in Chapel Hill.
DR. ZACHAROFF: Good morning. I'm Kevin Zacharoff, faculty and clinical instructor and course director of pain and addiction at the Stony Brook School of Medicine.

DR. SPRINTZ: Hi. I'm Michael Sprintz. I'm an anesthesia pain medicine and addiction medicine. I've been in recovery for 18 years. I'm also assistant professor at University of Texas Health Science Center, and I have a clinical practice specializing -- private practice specializing in chronic pain and addiction patients.

DR. McAULIFFE: I'm Maura McAuliffe. I am a professor of nursing and the director of the Nurse Anesthesia Program at East Carolina University, Greenville, North Carolina.

DR. McCANN: Hi. I'm Mary Ellen McCann. I'm an associate professor at Harvard Medical School in anesthesia and a pediatric anesthesiologist at Boston Children's hospital.

DR. GOUDRA: Basavana Goudra, anesthesiologist at Penn Medicine, Philadelphia.

DR. GARCIA-BUNUEL: Good morning. Martin
Garcia-Bunuel. I'm a primary care physician and the deputy chief of staff of the VA Maryland Healthcare System in Baltimore, Maryland.

DR. MACKEY: Good morning. Sean Mackey, professor and division chief of pain medicine at Stanford University.

DR. BECKER: Good morning. Will Becker, associate professor at Yale School of Medicine and prime core investigator at the VA Connecticut.

DR. SHOBEN: Hi. I'm Abby Shoben. I'm an associate professor of biostatistics at the Ohio State University.

DR. HIGGINS: Jennifer Higgins. I'm the AADPAC consumer representative.


MR. O'BRIEN: Good morning. I'm Joe O'Brien. I'm president and CEO of the National Scoliosis Foundation in Boston. I am the patient representative, and I am a patient myself who was fused from T4 to L5 after 6 spinal fusions.
DR. SCARAZZINI: Good morning. Linda Scarazzini. I'm the head of pharmacovigilance and patient safety at Abbvie and the industry rep for drug safety and risk management.

DR. HUMMEL: Good morning. Michele Hummel, associate director of pharmacology at Otsuka Pharmaceuticals in Princeton, New Jersey and acting industry rep.

DR. HERNANDEZ-DIAZ: Thank you.

For topics such 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 chairperson. 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 place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now, I will pass it to Moon Hee Choi, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. CHOI: The Food and Drug Administration is convening today's joint meeting of the Drug Safety and Risk Management Advisory Committee and the Anesthetic and Analgesic Drug Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representatives, all members and temporary voting members of these committees are special government employees or regular federal employees from other agencies and are subject to
federal conflict of interest laws and regulations.

The following information on the status of these committees' compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

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

For today's agenda, the FDA is seeking
public input under clinical utility and safety
concerns associated with the higher range of opioid
analgesic dosing, both in terms of higher strength
products and higher daily doses, in the outpatient
setting. FDA is interested in better understanding
current clinical use in situations that may warrant
use of higher doses of opioid analgesics.

We are also interested in discussing the
magnitude and frequency of harms associated with
higher doses of opioid analgesics relative to lower
doses, as well as optimal strategies for managing
these risks while ensuring access to appropriate
pain management for patients.

FDA frequently hears from patients and
healthcare providers that higher dose opioid
analgesics continue to be a unique and necessary
part of effective pain management for some
patients. FDA is also cognizant of serious safety
concerns associated with both higher strength and
higher daily doses of opioid analgesics both in
patients and in others who may access these drugs.
Higher strength products may be more harmful in
cases of accidental exposure and overdose, and may
also be more sought out for misuse and abuse.
Along with a number of other factors, a higher
daily opioid dose is associated with greater risk
of overdose.

Concerns have also been raised that higher
dose opioid regimens may carry a higher risk of
addiction, although robust evidence for a casual
relationship is lacking. There is a strong
association between higher opioid dose and duration
or persistence of opioid analgesic therapy, and
assessing temporal relationships and independent
effects of opioid dose and duration on the risk of
both addiction and overdose is challenging.

In addition, FDA acknowledges the complex
and evolving landscape of the opioid epidemic, with
myriad federal, state, local, and payer efforts to
encourage more judicious prescribing of opioid
analgesics and the growing threat of highly lethal
illicit opioids.

To better understand both the clinical
utility and harms of higher dose opioid analgesics
in the current environment and to discuss the
advantages and disadvantages of various potential
risk management strategies, FDA brings these issues
to an advisory committee to seek input and advice
from the clinical, patient, public health, and
research communities.

In particular, FDA seeks to discuss:

1) The current clinical use and situations
that may warrant pain management with opioid
energies at higher product strengths and daily
doses, factors influencing prescribing practices,
and specific patient populations for whom there may be utility in prescribing these medications at higher doses;

2) The magnitude and frequency of harms associated with opioid analgesics at higher product strengths and daily doses relative to lower strength in daily doses, including the role of opioid dose in adverse health outcomes in both patients and in others who may access the drugs; for example, risk for developing addiction, fatal overdose, the relevance of therapy duration and physical opioid dependence, and risk in different subpopulations; for example, patients with chronic non-cancer pain, young children, adolescents; and

3) Possible FDA interventions and their expected impact on patients and public health more broadly, including, for example, potential effects on prescribing and pain management practices, patient experiences and behaviors, and adverse outcomes such as addiction and overdose.

This is a particular matters meeting during which general issues will be discussed. Based on
the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the topic at issue.

With respect to FDA's invited industry representatives, we would like to disclose that Drs. Linda Scarazzini and Michele Hummel are participating in this meeting as nonvoting industry representatives, acting on behalf of regulated industry. Their role at this meeting is to represent industry in general and not any particular company. Drs. Scarazzini and Hummel are employed by AbbVie and Otsuka Pharmaceutical Development and Commercialization, respectively.

We would like to remind members and temporary voting members that if the discussions involve any other topics not already on the agenda for which an FDA participant has a personal or
imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all participants to advise the committees of any financial relationships that they may have regarding the topic that could be affected by the committees' discussions. Thank you.

DR. HERNANDEZ-DIAZ: We will now proceed with the FDA's introductory remarks from Dr. Sharon Hertz.

**FDA Introductory Remarks - Sharon Hertz**

DR. HERTZ: Good morning, everyone. Thank you, again, to the AADPAC-DSaRM and invited guests for being here today. I have a brief introduction, and I'll be back for the charge before we get into the discussion. So I'm going to keep this, as I said, brief.

We've heard a lot of information about the clinical settings where higher dose strengths in daily doses of opioids are used for pain management and the safety concerns associated with them.
Higher dose strengths and higher daily doses are an element of palliative and hospitive care for some patients. They're often associated with the management of chronic pain as well.

A number of patients, given the opportunity and adequate support to work collaboratively with their healthcare providers, have been able to lower their daily doses without detriment, and often with benefit. There are greater risks for overdose with higher dosage strengths and higher daily doses. However, they are a small percentage of the total use of opioid analgesics.

While there may be a proportionately higher risk for overdose, death, and suicide, as we've seen in at least one population, the VA study, most of these actually occur with lower dosage strengths and daily doses. And of course, the number of opioid analgesic prescriptions has begun a steady decline since 2012, but overdose deaths continue to rise, so it's a complex problem.

This morning we're going to present some of the options available to this agency for managing
risks, followed by the open public hearing, where we will hear from individuals with important perspectives to share, and then we'll go into our discussion. And I'll be back then to present the charge. So thank you, and I'm looking forward to today.

DR. HERNANDEZ-DIAZ: Thank you.

Just briefly, I would like to ask Dr. Warholak to introduce herself. She's joining on the phone.

DR. WARHOLAK: Good morning. This is Terri Warholak, and I am professor and assistant dean at the University of Arizona College of Pharmacy.

DR. HERNANDEZ-DIAZ: Thank you.

We will now proceed with an FDA presentation from Dr. Pamela Horn.

FDA Presentation - Pamela Horn

DR. HORN: Good morning. I'm Pamela Horn. I'm a clinical team leader in the Division of Anesthesia, Analgesia, and Addiction Products. I'd like to talk to you about some examples of regulatory actions we have available to us this
morning and how they've been applied to opioid products over recent years, and then also expand a little bit on the framework that Dr. Eggers introduced to us and talked about yesterday.

This is the outline of my talk. First, I'm going to remind you of the framework for structuring regulatory actions and their potential impact, including the factors that come into play between a regulatory action and the ultimate outcomes we would be seeking to effect with the action. Then I'll illustrate three categories of regulatory actions with some recent examples, and then end with some considerations for anticipating potential impacts and evaluating the effectiveness of public health interventions.

Here, I'm just placing up the same slide that Dr. Eggers put up yesterday just to remind you of the three elements of the framework. Here is the outcomes slide again. The targets of the types of regulatory actions I'll talk about today are summarized here.

I want to point out that this slide only
addresses harmful outcomes associated with opioid analgesics. It's not covering the benefits that opioid analgesics provide, and that's because my talk will focus on potential regulatory actions that could have an effect on managing risks or reducing harms associated with opioid analgesics.

On this slide, the individuals who can be impacted by regulatory actions, targeting the harms associated with opioids, are separated into three groups. There's a risk for overdose and death in all these groups. There are additional risks for developing opioid-use disorder and associated conditions and harms in the group that is misusing or abusing opioids. And in the group that are being treated with opioid analgesics for pain, there are additional risks and harms in that group that can result from inadequate pain management that could be an unintended consequence of some of the regulatory actions that we have available to us.

Before talking about the regulatory actions, this slide is meant to talk about a few of the
contributing factors that could affect the outcomes that I just discussed and some information that we have, based on recent data. This only is a little tiny snapshot of all of the contributing factors, and I only was able to use the information that we had in our background document and from our FDA presentations. I wasn't able to benefit from all the wonderful information we heard yesterday from our other speakers.

So just as an example, there's information in the background document and in Ms. Wood's presentation yesterday, that when a sample of experts were asked about the primary need for high-dose strength opioids, they identified cancer pain, the palliative care setting, and some unique and complex conditions that are associated with severe pain as the most frequently cited reasons for needing high-dose strength opioids.

Although diagnoses data are not available on prescriptions, the drug-use analyses that we saw yesterday showed that the bulk of the pain-related diagnoses in the FDA presentations of drug-use
data, in patients on higher dose strength products, were for more common chronic painful conditions such as arthritis and other musculoskeletal conditions; so there's a disconnect there. Also, we have data that show a clear trend of a decrease in high-dose strength opioid prescribing over the past several years.

So while these results are based on different data sources, the decline in prescribing likely reflects a reduction in use for the more common chronic pain conditions, and some open questions include what existing interventions are influencing this decrease in prescribing and who this decrease in prescribing is impacting.

For example, this reduction may represent a positive outcome if it's associated with a reduction in serious adverse effects. However, if it's resulting in reduced access for patients who benefit from the higher doses, it could reflect bad outcomes, including abrupt or rapid decreases in opioid doses or undertreatment of pain.

This is a reminder of the range of potential
regulatory actions that could be implemented to address FDA's previously articulated public health goals. Before moving on to some more detailed examples, I want to note that at the top of the arrow bar, communications and education are noted. They can take many forms and include drug safety communications, press releases, initiatives such as the FDA Safe Use Initiative, which has completed projects on important public health issues related to, for example, epidural, steroid use, and compounded medications, and that initiative also has ongoing projects for multiple opioid related issues.

There are many instances of overlap between these actions. For example, labeling changes are frequently accompanied by public communications. Many REMS have an educational component, and changes to REMS are frequently accompanied by labeling changes.

The first regulatory action that I'll talk about is labeling changes. FDA can require companies to make labeling changes in response to
new safety information. Labeling changes are
usually made to the sections I've listed in this
slide of the label, but they can be made to any
section of labeling, as you'll see in some of the
following examples for opioid analgesic products.

The first example goes for several slides.
It's an extensive labeling change that was made to
immediate-release opioids and it was required in
2016. These changes were made to update the labels
with similar information to that found in
extended-release opioid analgesics from previous
labeling changes. Here on this side, I have the
example language for the box warning that was
added.

This next slide shows the changes that were
made to the indication section. This is the
current indication for IR opioid analgesic products
that Dr. Hu talked about yesterday in her
presentation. This indication emphasizes that
opioid analgesics are indicated only when
alternative treatments either cannot be used, or
have not provided, or would not be expected to
provide adequate analgesia.

The labeling change that we're talking about here from 2016 also includes changes to the dosage and administration section. The first statement in the dosage and administration section recommends using the lowest dose and shortest duration that is consistent with individual treatment goals.

The information in this section is intended to be ordered by importance, so this statement is currently the most prominent part of the dosage amended administration section of the labels, and it's also the first statement in the dosage and administration highlights in the label. After this statement, there's information on individualizing initial dosing based on patient characteristics.

This is also from the dosage and administration section, and it provides recommendations for titrating the dose that emphasizes assessing the risk-benefit for the individual patient and to evaluate the patient clinically when there is an increase in pain prior to increasing the dose.
Now, I will move on to the second example, which was also from 2016. It was a labeling change that was required for all opioid analgesics in 2016, and it was prompted by safety information that showed that there was a greater risk of overdose and death with concomitant use of more than one central nervous system depressant medication; so opioid combined with another central nervous system depressant, which we heard about yesterday in the talks as well.

The third example that I'll have on labeling changes, before I move on, is a recent safety labeling change that we also heard about briefly in one of the talks yesterday. This is for the entire opioid analgesic class, and it involves the dosage and administration section again.

This change was prompted by reports that patients were being rapidly tapered or abruptly discontinued from opioid analgesic medications, and that was resulting in severe opioid withdrawal symptoms or other serious outcomes. The requested labeling change here has been submitted by the
various companies that were required to make it for their products, and it's currently under review.

Next, I'm going to move on to risk evaluation and mitigation strategies. This slide summarizes key information about REM, and there are REMS currently for all of the opioid analgesic products that we've been talking about in the last two days. I'll give you more details about the REMS for two classes of opioid analgesics in subsequent slides.

Listed here are the possible components around a REMS. The first sub-bullet are examples of information written for patients that can be dispensed with the medication. The second sub-bullet is a plan that pharmaceutical companies use to disseminate risk information to healthcare providers. The third is a new regulatory authority under the substance-use disorder prevention that promotes opioid recovery in Treatment for Patients and Communities Act.

On May 30th, the FDA opened a public docket to solicit feedback on potential use of this new
authority to require certain immediate-release opioid analgesics, that they be made available in fixed quantity unit of use blister packaging.

This proposal is for hydrocodone, oxycodone, tramadol, and codeine-containing products, and all of these products that are in the proposal fall below the cutoff for high-dose strength products that we've been using, that 90 MME that we've been using in our presentations. The fourth bullets are ETASUs, and those are further delineated in the next slide, and then the final sub-bullet there is a system that may be required to monitor and track certain ETASU elements.

This slide lists the possible ETASUs that can be part of a REMS. ETASUs must align with the serious risks listed in the labeling and they cannot cause undue burden on patient access to the drug. The issue of undue burden should especially take into account patients with serious or life-threatening diseases or conditions and patients who have difficulty accessing health care.

The next slide covers features of the opioid...
analgesic REMS. Opioid analgesic REMS applies to all of the opioids, except for the TIRFs that we've been talking about in the last day of presentations. The goal of the opioid analgesic REMS is to educate prescribers and other healthcare providers on the treatment and monitoring of patients with pain. The central component of this REMS is an education program that's based on what's called the FDA blueprint for healthcare providers, who are involved in the treatment and monitoring of patients with pain.

Under the REMS, application holders are required to make education programs available to healthcare providers, and they're meeting this requirement by providing unrestricted educational grants to accredited continuing education providers, who then offer the training to the healthcare providers.

The FDA blueprint describes the principles of pain management, including patient assessment, screening for risk factors of substance-use disorder, and non-pharmacologic and pharmacologic
therapies, including non-opioids and opioid medications. There's also extensive information about the risks of opioids, including how to recognize aberrant behaviors associated with the abuse of opioid analgesics, basic information on managing opioid-use disorders, and guidance on when to seek specialty consultation for addiction medicine, as well as for patients with difficult to manage pain.

In contrast, there's the TIRF REMS. The TIRF medicines are approved under a shared system REMS, and this is known as the TIRF REMS Access program. It's intended to mitigate the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors.

In contrast to the opioid analgesic REMS, this TIRF REMS is a closed-system program, and it has requirements for education and enrollment of patients, prescribers, and pharmacies. This is because the products covered here have been determined to only have a favorable risk-benefit profile in patients who are opioid tolerant, so the
features are intended to ensure that the patients receiving these products are indeed opioid tolerant.

Following an advisory committee meeting, which some of you were present for, the agency notified all application holders of TIRF medicines in March that the TIRF REMS must be modified to ensure that patients are opioid tolerant prior to receiving a TIRF medicine and to better capture adverse events of interest. This action is intended to reduce prescribing of TIRF products for opioid non-tolerant patients. The agency is also requiring the addition of a patient registry for patients that are prescribed the TIRF medicine in an outpatient setting.

The last regulatory action I will talk about is requesting market withdrawal, and this is the most restrictive example of a potential regulatory action. FDA can request market withdrawal of a product if the agency determines that the benefits of the product no longer outweigh the risks of the product.
In June of 2017, after an advisory committee meeting where the public health risks of Opana ER were discussed, FDA requested that Opana ER be voluntarily withdrawn from the market. This was the reformulated version of Opana ER. The risks that led to this request were related to a shift in the route of abuse from intranasal to intravenous abuse of the reformulated product, and that was associated with several outcomes, including an outbreak of HIV and an illness similar to a blood disorder called TTP.

In this example, there was a broad risk-benefit evaluation, where the risks that warranted the market withdrawal were in the context of abuse of the product that's outside of the intended and approved route of administration.

This is another slide that we saw Dr. Eggers present yesterday, and I just wanted to touch on the current activities, in that row, the first row in this slide, and the table. The kinds of ongoing FDA efforts to improve the safety of opioid analgesic use include some of the examples I've
shown you.

The labeling for opioid analgesics may be affecting prescribing of higher strengths and higher daily doses of opioids through the described target population in the indication section: the recommendations for dosage and administration, where the most prominent information is focused on using the lowest dose possible that can meet the individual patient's treatment goals; the educational components of the opioid analgesic REMS; and there may be additional effects on prescribing with the increasing restrictions that are in progress for the TIRF REMS.

Ideally, the changes in prescribing behavior that we're hoping to drive would be associated only with reduction of misuse, abuse, overdose, and deaths related to opioid analgesics, and not in the harms associated with untreated pain.

There are additional actions that can be taken in the three categories that I have shown you examples of this morning that could further affect the behaviors and outcomes that are listed on the
slide, with the same considerations of what the outcomes we want to reduce and avoid are.

The final piece that I want to just briefly touch on is about evaluating the actions taken. There's a great interest in understanding the impact of various interventions intended to mitigate harms related to the opioid crisis. While the data and methods have been improving this area, there are still many limitations, and it's proven extremely difficult to isolate the effect of a single regulatory action or other intervention.

You can see the myriad -- this is just a small sampling of all of the interventions that have been going on, and that these are difficult to isolate the effect of against this backdrop of many concurrent efforts in the evolving landscape of the opioid crisis.

That will conclude my presentation. I would like to thank my FDA colleagues for their contributions. Thank you.

DR. HERNANDEZ-DIAZ: Thank you very much, Dr. Horn.
I believe the FDA has some additional slides to answer questions that we had yesterday.

DR. McANINCH: Hi. Jana McAninch. There was a question yesterday from Dr. McCann about the age distribution of decedents of opioid involved overdoses, and we just wanted to share some publicly available information that might be helpful to the committee, so we're just going to pull up a slide.

The table that we're showing here is part of some data that were published by Puja Seth and others at CDC last year, using a national vital statistics data. These show the number and the age adjusted rate of drug overdose deaths involving any opioid on the left, and then involving any prescription opioid on the right.

There are two columns, one for 2015 and one for 2016. I just highlighted the age distribution showing the rates per 100,000 population, and this is for 2016. The one on the left, again, is for deaths involving any opioids. You can see that the highest rates are in those middle age groups, so
the 25 to 54 with the rates dropping off as you get to the more extremes, the younger and older age groups. Then if you look at the prescription opioids, I think you can see that the age distribution skews a little bit older, although you still see the highest rates in those middle age groups.

If you could go to the next slide. We're showing the same statistics, but now looking at heroin-involved overdose deaths on the left and overdose deaths involving synthetic opioids other than methadone, which is used basically to look at deaths involving fentanyl and fentanyl analogs, which are believed primarily to be from illicit sources.

Here, the deaths tend to skew a little bit younger than when you're looking at the prescription opioids, with the highest rates in the 25 to 34-year age group, with very small numbers in the younger and 0 to 14. The numbers were not high enough to be able to calculate reliable rates. Again, with the synthetics, you're seeing the age
distribution skewing a little bit younger, again.

Anyway, we just thought that might be helpful to address your question.

**Clarifying Questions**

DR. HERNANDEZ-DIAZ: Thank you very much. Are there any clarifying questions for the FDA for the presentation from Dr. Pamela Horn? Any clarifying questions? Thank you. Please remember to state your name for the --

DR. SPRINTZ: I had one question.

DR. HERNANDEZ-DIAZ: Yes.

DR. SPRINTZ: Hi. Michael Sprintz.

DR. HERNANDEZ-DIAZ: One second. I was going to remind you to state your name before, but yes, go ahead.

DR. SPRINTZ: Hi. Michael Sprintz.

Dr. Horn, I had a question. You'd mentioned that you have increased education or requiring for educational providers relating to identification management of abuse in at risk, with patients at risk or with substance-use disorders. Do you have any data whatsoever that actually shows, really,
the steps that have been taken and what those outcomes are of those steps? Has that impacted outcomes? Has it impacted prescriber behavior, and really, ultimately, patient outcome?

DR. STAFFA: this is Judy Staffa. I'm going to ask Dr. Ready back here to address that. All of the REMS, we have assessments required, so we can at least talk about the outcomes that are looked at and what we know about that at this point.

DR. READY: Through the REMS program, we have education programs available. With the REMS, we assess them periodically. We have assessment reports that come in. We've analyzed that data, and I think at this point, we have seen some data to show that increased knowledge changes prescriber behavior.

Is that what your question is?

DR. SPRINTZ: No.

DR. READY: Okay.

DR. SPRINTZ: It was more really about -- I guess you brought up another question of the REMS programs that are available but they're not
required.

DR. READY: That's correct. At this time, they're not required.

DR. SPRINTZ: Okay. Then I was asking not necessarily on prescriber behavior but rather more on patient outcomes. Has it made a difference?

DR. READY: I don't think we have that information, no.

DR. STAFFA: This is Judy Staffa again. I just want to clarify that was Dr. Selena Ready, for the record.

Over the years, as was mentioned, the REMS programs require the sponsors to make education available, so that education, it's not required for physicians to take it. What we've done most recently, and I think this committee was involved in discussing this a couple of years ago, was we now make that education available or require the sponsors to make it available to prescribers, but also to pharmacists and nurses; so anyone on the healthcare team that is working with patients with pain who might be prescribed these products
There are many other education programs available, and there are some states that actually require that. So it's been a real challenge to try to tease out the impact of these particular voluntary programs, but the assessment plans do have surveys to be asking both prescribers and patients about what they know and what they've learned, so they try.

DR. SPRINTZ: Do you have data on how many prescribers actually do the programs?

DR. STAFFA: Yes, we do. Dr. Claudia Manzo, from our Office of Medication Error and Risk Management, will address that.

DR. MANZO: We have data from the extended-release, long-acting REMS. The new educational program under the opioid analgesic REMS, which incorporates the immediate release, was only just released or started in March of this year. So we don't actually have data on how many people have taken the training.

Under the previous program, it's about a half a million individuals. Not all of them were
what we were targeting initially. That program
initially targeted prescribers of those products.
Under the new program, we target all healthcare
providers that are involved in the management of
those patients.

DR. SPRINTZ: Half a million -- we have
about, what, a million prescribers in the
countries?

MALE VOICE: 1.4.

DR. SPRINTZ: Oh, 1.4, so almost a third.

DR. MANZO: We were actually targeting,
initially, at least for that previous program,
prescribers of the ER/LA products, which we
estimated at that time to be around 320,000,
something like that.

DR. SPRINTZ: But 500,000, half a million,
you said that --

DR. MANZO: Half a million healthcare
professionals. They were not necessarily
prescribers of those products. So we think that a
fair number of them were, but not necessarily.
They weren't all prescribers of ER/LA products.
DR. SPRINTZ: Okay, but do you have that number? Do you know? Out of all the people who prescribed it, did 10 percent take these courses, or did 80 percent take these courses?

DR. MANZO: Well, it's actually what they reported. Whether they actually prescribed the product within the previous year of taking it, I'd have to go back and look at what those latest numbers were. I don't have them off the top of my head.

DR. SPRINTZ: Okay. Thanks.

DR. HERNANDEZ-DIAZ: Thank you.

Dr. Griffin?

DR. GRIFFIN: Yes, Dr. Horn, again. I understand that the labeling and the black box warning are the weakest tool, but I'm wondering is there evidence for effectiveness of that tool; not for opioids, but even for other things?

DR. HORN: You are wondering if there's any data on the impact of the black box warnings or other safety labeling changes? Not to my knowledge. It's not like a REMS where there's an...
assessment required of the impact of the REMS. So when those labeling changes are made, they're made, and then there are not data collected directly on the impact of that change.

DR. HERTZ: This is Sharon Hertz. What we try to do at the time of labeling change is to provide sufficient notice so that people will be aware. It's a really big challenge. I don't think many prescribers understand what the genesis of the current labeling for any given product represents. It's a common misperception, I think. Well, I think there are many common misperceptions, but one is that it's just promotional, and they don't really need to look at it, which of course is not the case.

So we try to make announcements, press release. We have different types of ways to try and communicate information. But it is a challenge, and I think meetings like this are one way we can further emphasize the importance of prescribers actually looking at the labeling.

If they have questions about elements of it,
where it comes from, who's vetted the information in the label, we have a huge staff here at FDA that interfaces with the public. And if there are any questions after the meeting by folks who are listening in, I encourage them to contact our drug information staff, and they will be able to provide a lot of information, and they also contact us in the divisions for additional information for some particular questions.

DR. McANINCH: I'd like to just speak to that question as well; Jana McAninch, Office of Surveillance and Epidemiology. I think, as Dr. Horn mentioned, assessing the impact of a single intervention is often very difficult. For example, the boxed warning about co-prescribing of opioid analgesics and benzodiazepines, it's theoretically possible to look at rates or trends in co-prescribing before and after the intervention, and there are statistical methods to assess changes.

But the CDC prescribing guidelines, which also have recommendations against co-prescribing,
were issued in very close proximity in time. So when you have these concurrent interventions, and also a myriad of other efforts going on at the same time, it's a very difficult study to design. And I think that applies to the assessment of the REMS as well.

So those are some of the challenges that we face in trying to answer those very important questions as well.

DR. HERNANDEZ-DIAZ: Thank you. Dr Hoffer.

DR. HOFER: Yes. This is Lee Hoffer. I have a couple of questions. The first one was actually on the age that was presented about the overdose. I was wondering if there is any way to look at that population of the United States and how the age of the population in the U.S. is changing relative to who is actually overdosing from prescription drug use, and if there is any correlation between that age getting a little bit older and the fact that we have baby boomers now that are entering this phase of life where they're getting older and they're having potentially more
pain.

So I was wondering if there is any way to look at those connections between how the population's aging and how the prescription -- just the prescription side, not the illicit side -- might be changing.

DR. McANINCH:  Jana McAninch. It's a really good question. You're speaking to is there a cohort effect as opposed to more of an age effect in terms of that distribution. I think that is a study that could be done. That's not the study that was done here. This was just looking cross-sectionally at two age periods, so I don't have the answer to that.

DR. HOFFER:  Yes. No, I just think it's an interesting way to think about it if we're talking about increasing the potency of opiate medications for an older population, potentially, that might be having more pain.

DR. McANINCH:  Right. These rates are age adjusted, so they are applied to a standard age distribution. So you can do that, to look over
time to try to adjust for those changes in the age
distribution of the population. But it's hard to
say just looking at a single year or those two
years of data.

DR. HOFFER: Actually, I had a second
question, too, to Dr. Horn and maybe Eggers as
well, about the framework. It's on slide 4, and I
noticed this yesterday. When we're talking about
potential harmful outcomes associated with opiates,
we have the individuals who are misusing and
abusing opiate analgesics in the middle, and we
talk about overdose and development of OUD.

My concern, because I work in the area
primarily where people are not in treatment and
they're using these drugs illegally, is what about
diversion? Is there anything that the FDA can
do -- and I know it might be challenging
intervention to consider within the context of box
warnings and things like this, buy what can be
done, I think, about misuse in relation to
basically diversion?

Diversion here, I'm not talking about
necessarily selling drugs, but just giving drugs to your friends or your family. I don't know. I think it's sort of a complicated educational message.

DR. STAFFA: This is Judy Staffa. I think that's a huge issue, and Dr. Horn mentioned the Federal Register notice we recently put out, a proposal, around packaging, and actually knowing from some of the surveys, from the National Survey on Drug Use and Health, that many people who misuse opioids or abuse opioids get them from a medicine cabinet or from excess tablets being around.

This packaging effort is designed to try to make it easier to dispense smaller quantities but also to be able to easily see if drugs are taken from that packaging. That's kind of the way we might be able to impact that kind of phenomenon, but it's important.

DR. HERTZ: This is Sharon Hertz. There's also a number of other FDA programs that are looking to reduce excess opioids in the community. We have initiated a study with the National
Academies of Science, Engineering, and Medicine to create a framework for possibly developing indication-specific dosing guidance, particularly for acute pain.

We have been working in a number of other settings. We've been participating in the best practices for the Pain Management Task Force, which recently released a really important report on managing pain in the U.S., which I encourage everyone to review.

That also discusses the key importance of focusing on the individual and providing the appropriate information that any individual being managed for pain needs to have; one element of which is, if prescribed opioids, how to store them safely and the importance of getting them out of their home when no longer needed. This is a really big cultural issue, getting unused, no-longer-needed medications, in general, out of the medicine cabinet, but it's critically important for opioids.

We've been also working in conjunction with
some other, federal committees and other
stakeholders to try and help facilitate policy that
would also reduce some of this excess. For
instance, third molar extraction, returning to the
use of NSAIDs over opioids.

This is all really important. I think we're
straying a bit, so let's perhaps get back to some
more specific clarifying questions for today, or
other clarifying questions, before we move on in
the meeting.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Nelson?

DR. NELSON: Thank you. Lewis Nelson. I
guess for Dr. Horn, but perhaps the others as well.
The Opana example is really interesting about some
of the public health vision that FDA has used to
balance the risks of drugs, or of opioids. And I
realize that that had to do with a root-specific
issue and not by the labeled oral route.

But I also understand that the FDA has even
new authorities and new perspectives on how to
better manage public health, and how to balance
public health issues. And I wonder as it relates
to the issues here, and the balance between the
drug overdose side and the pain, chronic or
even acute pain side, how you see some of these new
authorities or perspectives changing how FDA's
going to approach this.

DR. HERTZ: That's a great element to
contribute to the later discussion of the
discussion points. But right now, I think we
should stick with clarifications from what we've
already heard because that's a completely new area
of discussion; important.

DR. NELSON: [Inaudible - off mic]. I was
just following up --

DR. HERTZ: Yes, but I think it's big and
works well with the discussion.

DR. HERNANDEZ-DIAZ: Thank you. As a
reminder, only clarification questions. If you
have points, we'll have time for discussion later.

Dr. Nelson, any specific question or that
was a point?

DR. NELSON: [Inaudible - off mic].

DR. HERNANDEZ-DIAZ: That was it. Keep it
for later, then. Thank you.

Dr. Garcia-Bunuel?

DR. GARCIA-BUNUEL: Martin Garcia-Bunuel.

Dr. McAninch, just clarifying about the vital statistics. Your thoughts or even just the look you did last night, since we utilize that data to understand risk and implications of prescribing patterns, and many other issues we've tried to address, is there any possibility or any insight of how we gather vital statistics?

Is it changing? Is mortality data and the way we're gathering that data, or does MMWR comment on -- are we picking up more prescribed opioids? Are we testing for more? Should we consider the vital statistics in any different lens given our sensitivity towards the potential for opioids in overdose and suicides?

DR. McANINCH: Jana McAninch. Yes, that's a good question, and certainly when you're looking at trends over time, you want to know if the sensitivity of detection or ascertainment is changing over time. There is some evidence that it
has been, that we're doing a better job of testing for and documenting specific drugs that are involved in overdoses.

I don't have the numbers off the top of my head, but I think we're looking at a reduction of a few percentage points in the proportion of overdose deaths where no specific drug is identified, to say that it may be affecting those trends, but it doesn't explain them. We may be able to pull some more information on that with specific numbers.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Becker?

DR. BECKER: Will Becker with a clarifying question for Dr. Horn. Slide 15, you mentioned that the products that were under consideration for certain packaging and safe disposal technologies were -- I believe you said that none met the threshold for 90 MME. Can you clarify, did that mean per unit, and is that because they're not considering ER/LA products? Thank you.

DR. HORN: Sure. Thanks for that question. Yes. If you look at the Federal Register notice, all of the strengths are below the high-dose
strength definition that we used. I didn't calculate all of the minimum daily doses that are in the recommended labeling for all those products, but all of the strengths were on the low end.

DR. STAFFA: This is Judy Staffa. I can also clarify, those products were selected, as it explains in the FR notice, because together they constitute about 90 percent of opioids that are prescribed to opioid-naive patients. So that was just a starting place. It's more of a phased approach, but doesn't mean that packaging won't be then further applied to other products in the future.

DR. BECKER: Thanks.

DR. HERNANDEZ-DIAZ: Thank you. Mr. O'Brien?

MR. O'BRIEN: Yes. Joe O'Brien. This is a clarifying question for Dr. Horn. On slide 5, you had addressed that there appears be a conflict between what was identified as the need areas versus what we heard in the presentations yesterday by Dr. Markman and others in the clinical
perspective with the musculoskeletal areas.

I was just wondering what the process was and to assure there wasn't bias in terms of eliciting needs. I know within the musculoskeletal area, for example, complex adult spinal deformity is a very large community that requires lots of opioids and their management, and in the providers that were listed, some of them did not represent that in the area that they are. That population just is not serviced there.

So I was wondering what was the process you used to make sure you did include all of the particular potential communities that may be identified in the need.

DR. HORN: Hi. Yes. The information that I was talking about eliciting the needs came from Corinne Wood's presentation yesterday and those surveys.

I don't know -- Dr. McAninch, can you say a little bit, or Dr. Staffa, about the methods for the service?

DR. STAFFA: This is Judy Staffa. The two
areas that we tried to collect information from, one was just reaching out to some of the folks we have under contract, to their data, and just asking them. So yes, it's very likely that populations were missed. That's just a hit or miss kind of what do you think?

Then the clinical characteristics, that was more of a systematic look in insurance claims data. Again, insurance claims are coded, so they tend to not be as specific. Those kinds of patients may be captured in there, but just in a general way, not their specific issue being pulled out. So there were limitations to both of the methods we did.

DR. HERNANDEZ-DIAZ: Dr. Litman?

DR. LITMAN: Thanks. This is Ron Litman. Dr. Horn, forgive my ignorance questions, but I just would like some clarifications on enforcement. You'd mentioned that the FDA previously asked the maker of Opana to take the drug off the market when we identified some health hazards there, but does the FDA actually have the legal authority to take a drug off the market? Is
it just voluntary?

DR. HORN: I can say a little bit. I'll try a little bit. The first step in the process is to request a voluntary withdrawal from the company, and then there are ways of enforcing and requiring if they do not voluntarily comply.

I will let you take it from there. There are other things that you can do if they refuse to withdraw it.

DR. HERTZ: Filing a request for voluntary enforcement, there is a procedure that we can enlist. It's a legal proceeding where we then follow legal efforts to move toward product withdrawal, but it's not something that we can do unilaterally. It's a legal process that involves the courts.

DR. LITMAN: So technically, that's different from a recall.

DR. HERTZ: A recall is also very different, yes.

DR. LITMAN: Again, please clarify this for me about the REMS program. I've been coming to
these meetings for a couple of years now and I hear a lot about REMS. The sponsor of a drug, are they required to present their REMS before the drug is officially approved?

DR. HORN: Yes. If a REMS is required for approval, then it's required that they submit their REMS as part of their marketing application that's approved.

DR. LITMAN: Once it's submitted and once the drug's approved, there's nothing further that's required, correct?

DR. HERTZ: I'm going to ask Dr. Manzo to respond.

DR. MANZO: A REMS can be submitted premarket or postmarketing. In the case of the opioid analgesics, most of those products were already on the market. We still require companies to submit a proposed REMS. We review it, and approve it if it's acceptable.

Once it's approved, then they have an obligation to report on the effectiveness or the assessment. Whatever we've outlined in the
approval letter, they have to submit that according to a timetable. Then any modifications they make actually have to be submitted for approval as well.

DR. LITMAN: What kind of enforcement is around that, though? Once it's approved and they're supposed to report back, how do you monitor that or how do you enforce them if they don't?

DR. MANZO: Well, we haven't had any issues with individuals not reporting in assessments. We track that. We have our Office of Compliance that tracks it.

DR. LITMAN: I see.

DR. MANZO: Sometimes the information that we get, we might need to ask for more information or clarifying questions. But as far as enforcement, that hasn't been an issue because companies have complied with the requirement to submit it.

DR. LITMAN: I see. Then one last question about enforcement. What about postmarketing studies? Can you comment on that, Dr. Horn, about when the FDA waits for postmarketing results from a
sponsor?

DR. HORN: We have the authority for postmarketing required studies. We can require a sponsor to do a study if we discover new safety information, and that that cannot be adequately studied in the systems we have; predominantly our Sentinel system. We require the studies. We set milestone dates, and we require the sponsors to submit protocols and reports, some interim, some final reports, by those milestones. If they do not meet those milestones, we have a process whereby we send them letters. We post that information publicly.

But many times, studies are delayed because there are often challenges with the science, and the FDA will guide the sponsor and work with them to try to do the best protocol, the best study possible, to answer and address the question. So many times, my experience has been the delays are often related to the scientific difficulty of actually doing the study we need them to do.

DR. LITMAN: Thanks very much. That was
informative.

DR. HERNANDEZ-DIAZ: Thank you.

Dr. Zacharoff?

DR. ZACHAROFF: Hi. Kevin Zacharoff, and I have some clarifying questions for Dr. Horn. And I think based on something Dr. McAninch mentioned about conflicting educational programs, maybe Dr. McAninch as well.

As someone who has received a grant from the REMS program committee to develop an educational REMS program for the ER/LA REMS, I'm intimately familiar with the blueprint and the process, and so on and so forth. I also in my work am intimately involved in educating people in training: undergraduate medical education, graduate medical education, et cetera.

Dr. McAninch, I think you talked about conflicting educational initiatives with respect to the CDC guidelines coming out in 2016, et cetera, et cetera. Being licensed in three states, I'm wondering if there a mechanism for the REMS education to satisfy some of the state requirements
for education on pain or related subjects.

When I got notified by the states -- I'm licensed -- and about the educational requirements, I immediately thought of the REMS being one of those educational initiatives that could satisfy that requirement, but it didn't pop into anybody else's mind. And I'm wondering, is there a mechanism by which the REMS education can help satisfy some of the state and medical licensing requirements? That's my first question.

DR. HERTZ: So the shorter answer is, it's up to the states. It's their purview to determine what educational efforts will be suitable for their own requirements. We think that education under the current REMS blueprint -- when the full extent of training to complete the blueprint is developed, when it's developed, when it's accessible -- could fulfill a number of the requirements we're aware of in different states, but it's up to the states.

DR. ZACHAROFF: Okay. So the presumption is that there is an awareness at the state licensing level that the REMS education program exists and is
available?

DR. HERTZ: I am not speaking for the states. As a matter of fact, I recently spoke at the Federation of State Medical Boards annual meeting, so there are a lot of efforts going on. But I can't say what individual states are aware of and how they perceive REMS training and its intersection with their specific requirements.

DR. ZACHAROFF: Okay. Just lastly, with respect to the REMS slide that you showed, Dr. Horn, and the components of the REMS, the patient counseling document was there on this slide. It's an extremely valuable tool, and it's very well designed. And I'm wondering is there a mechanism for distribution of that particular piece of the REMS initiative, or element to ensure safe use, outside of the scope of a REMS education program.

I would personally love to see that patient counseling document be available to every prescriber in the country, and not only if they get exposed to the REMS education.
DR. MANZO: Claudia Manzo, Office of Medication and Error Prevention Risk Management. The patient counseling document is available on the FDA website. We do mention it. I think it's also mentioned within the product labeling. So there's access to it if prescribers have an interest in using it. They could even call the REMS, the program committee probably to get copies of it if they wished. But I don't know of any other mechanism to ensure that they get it.

DR. ZACHAROFF: Then just lastly, one question for Dr. Hertz, and this is really regarding the -- well, I'll leave it for this afternoon's discussion. Thank you.

DR. HERNANDEZ-DIAZ: Great. Thank you. Dr. Katzman?

DR. KATZMAN: Thank you. Joanna Katzman here. I have a quick question for Dr. Horn. It's really related to the labeling and packaging of the short- and long-acting opioids. I really so appreciate the re-labeling of the opioids and so happy you added the August 31st relabeling of the
risk of concomitant benzos.

I'm wondering if there might be -- have you thought about -- is there an ability to add -- a consideration to add an adamant consideration; for instance, with long-acting opioids or with very high-dose opioids, please consider naloxone use, in your packaging or something like in addition, Sharon, or Dr. Horn?

DR. HERTZ: We had an advisory committee this past fall discussing what co-prescribing might look like, what the pros and cons are, and we are still working on implementing what we are planning to do from that advisory committee.

The opioid blueprint discusses naloxone. For those of you who were there, you may recall, and for those of you who were not there, may not yet no, but many in the committee thought one of the most important conversations associated with naloxone, or many of the most important points associated with naloxone was the discussion with the patient, where it's necessary, and what having the conversation alone could do to improve opioid
safety.

So I encourage folks to take a look at the minutes or the transcript from that meeting. It was December 16 and 17 of 2018, and that should all be available online right now.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Urman?

DR. URMAN: Thank you. Rich Urman. A question for Dr. Horn, and I guess a follow-up to slide 16 talking about REMS and elements to assure safe use. We talked a lot about provider education, providing tools for providers. Can you comment on any specific, maybe tools under development that would target patients directly? So patient-centric tools, especially those who are on higher dose of opioids. Is there anything under development or currently exists? That would be helpful.

DR. HORN: I'm going to let, um, Claudia Manzo answer, but can you be a little more specific about what type of tool you're thinking of, so she can answer?

DR. URMAN: Any sort of educational
materials that obviously would be accessible to patients at all levels of education and so on, that would be readily available to them, whatever medium you want to use, electronic paper and whatnot.

DR. MANZO: Most of the information that is developed as part of a REMS is designed for the prescriber to provide to the patient when he or she is prescribing the product. For the TIRF REMS, for example, we have a patient prescriber agreement form that both the patient AND the prescriber sign.

The patient counseling document is a patient -- it's written specifically for patients, and it allows the prescriber to provide additional notes to the patient. Most of these are, again, designed more for that interaction between the prescriber and patient, although all of these materials are publicly available. But we don't have a mechanism really to get that information out to patients other than through the healthcare providers.

DR. URMAN: Thank you.

DR. HERNANDEZ-DIAZ: Thank you. Dr. McCann?
DR. McCANN: Thank you. Mary Ellen McCann. This question is for Dr. McAninch. The other part of my question yesterday was did we have a breakdown of these middle aged to late middle-aged high death rates, were they accidental or suicides. And I imagine you probably looked for that data and couldn't find it. Is that right?

DR. McANINCH: I didn't look at that breakdown specifically. Again, those data would be available. The numbers I showed you would include both intentional and unintentional overdoses. Again, I'll see if I can do some more digging and find some more information on that for you.

DR. McCANN: And the other part of the question was duration of analgesic use? It's hard for me to believe that a 50 year old is completely analgesic naive, whether they had narcotics when they got their wisdom teeth out at 18 or whatever. Do we have any data? Were these people on analgesics for 5 or 7 years, or was it they got their dose, and they loved it so much that they quickly spiraled into massive overuse.
DR. McANINCH: You're speaking of the
decedents, of people who died from overdose. I'm
not aware of that information --

DR. McCANN: being out there.

DR. McANINCH: -- being out there. Again, it's not something that I have looked at in
preparing for the advisory committee. I think it's a good question, and there are linkages that would
allow one to look at that, but that's not something we would have --

(Crosstalk.)

DR. McCANN: I guess the third part of that
would be any data as to how many of these people
had alcohol problems beforehand, because that might affect how you would -- possibly another black box warning to prescribers.

This is for Sharon. Do you know who in the
government is responsible for public service announcements? Because it strikes me that that
might be helpful. Can the FDA influence whoever
does the public service announcements about warning of the dangers of polypharmacy, or taking more
medications than you need, et cetera?

DR. HERTZ: I can only say I'm crushed at the question because we actively produce a number of these communications, and clearly, it's very hard to get wide uptake of our communication efforts.

I can speak specifically to what is a public service announcement, but we do have public directed messaging on a number of issues, but definitely on issues around opioid safety. What I can only do is -- I'm sure our comm staff is already listening to the meeting, but go back and see what we can do to further enhance awareness of these efforts.

DR. McCANN: I didn't mean to be crushing, but Facebook --

DR. HERTZ: Yes, we have a Facebook page. We have a Twitter account. I don't know if we're on Instagram, but, yes, there are a lot of efforts about that, and I will quickly email and see if I can provide some links in follow-up.

DR. McCANN: It's interesting because I'm
probably of the demographic of the prescription pill users that have died. I don't see it. So whatever sites I hit --

DR. HERTZ: You have to follow us to see it.

(Laughter.)

DR. McCANN: But it should be -- okay.

DR. HERTZ: No, I know. I understand. I'm sorry. I don't mean to be glib at all about this. There are a number of efforts. We're using social media. We're using press. I don't think that it gets the kind of coverage that -- be safe is not the same appeal as other things that capture national headlines, but we are consistently trying to improve the messaging.

Frankly, not necessarily right now, if you have some ideas for how we can -- what outlets we can use to try and reach different demographics, I'd love to hear them. We will definitely share with our comm staff and see what we can do to better improve getting more of this information out to the public's awareness.

DR. HERNANDEZ-DIAZ: Thank you. We will
bring it back at the discussion.

DR. STAFFA: This is Judy Staffa. I just want to go back to one of your earlier questions about the death data. One of the real challenges here is we have death data from across the country that doesn't have a lot of granularity. It's just very high level. So through a new effort between NCHS and FDA, we now have what we call Drug Mention -- DIM?

DR. McANINCH: Drug involved mortality.

DR. STAFFA: Drug involved mortality. Sorry. I got my acronyms wrong -- that is in the research data warehouse with NCHS, where if a specific drug is mentioned on the death certificate, that we can actually pull that off and be able to see that, and that's been very helpful. However, as you've heard from some of the speakers, particularly Dr. Goldberger yesterday, many of these deaths have many drugs on board.

There's also not a national way for us to link people who die from an opioid overdose with their prescription records. This can be done and
is being done in pockets at certain state levels or health plan levels. And when we do that, what we see is that, routinely, not everyone who dies from a prescription drug overdose has a prescription from opioids.

So that tells us, number one, they could be getting it from someone else's prescription, which we know happens, but they can also be getting prescription drugs illegally. There are black markets for these things.

So we have no mechanism to understand where these are coming from, so we can't make the assumption that everyone who dies from a prescription drug opioid overdose is a patient that's actively being treated with prescription opioids. Clearly, there are some in there, but we just don't know the circumstances behind all of them.

DR. HERNANDEZ-DIAZ: Thank you.

DR. McANINCH: May I follow up quickly?

It's just a related comment and a follow-up response to Dr. Garcia-Bunuel's question about
specific drugs being documented in death certificates.

This is from a paper published by Holly Hedegaard at the National Center for Health Statistics in December of 2018. Again, this is based on the additional data that Dr. Staffa was mentioning. Based on analysis of the literal text of the death certificates, the percentage of drug overdose deaths, mentioning at least one specific drug or substance, increased from 73 percent of the deaths in 2011 to 85 percent of deaths in 2016. The percentage of drug overdose deaths that mentioned only a drug class, so opioids or stimulants, but not a specific drug or substance, declined from 5.1 percent of deaths in 2011 to 2.5 percent in 2016.

So we are getting better, but there's also a huge amount of variability across jurisdictions and state to state in the specificity of drugs mentioned on the death certificates.

DR. HERNANDEZ-DIAZ: Thank you. Last question from Dr. Mikosz.
DR. MIKOSZ: Yes, thank you. Christina Mikosz. I actually wanted to build on Dr. McAninch's points to clarify a little bit about the CDC data sources. Is that something that I can do right now or should that better be saved for discussion?

DR. HERNANDEZ-DIAZ: If it is a clarifying question for the presentations, now. If not, we'll hold it for the discussion.

DR. MIKOSZ: It's more expansion of answers, so I guess it helps address some of the clarifying questions, but I myself am not actually asking a question. But what would be your preference; to save this for later?

DR. HERNANDEZ-DIAZ: I think, yes, that would be great.

DR. MIKOSZ: Sure.

DR. HERNANDEZ-DIAZ: Thank you. And with that -- one last question from Dr. Meisel.

DR. MEISEL: Steve Meisel. What tools are available from other agencies, such as the DEA, that FDA can work in or has worked in partnership
with for any of these types of efforts, if any?

DR. STAFFA: This is Judy Staffa. We do actually talk to other agencies, I can assure you of that. The DEA specifically, I know we have talked with them about educational programs.

Claudia, do you want to talk about that?

DR. MANZO: Sure. Claudia Manzo, Office of Medication Error Prevention and Risk Management. More recently, we actually worked with them to disseminate information about the new education under opioid analgesics. They sent that out. Hopefully everybody who has registered with the DEA got that announcement. But they send out information on the availability of the opioid analgesics REMS education to all of their DEA registrants.

DR. HERNANDEZ-DIAZ: Okay. Thank you.

With that, let's take a 10-minute break and be back at 10:05. Panel members, please remember that there shall be no discussion of the meeting topic during the break among ourselves or with any member of the audience. We will resume at 10:05,
please.

(Whereupon, at 9:54 a.m., a recess was taken.)

DR. HERNANDEZ-DIAZ: It took us a little bit longer because the FDA prepared information to answer clarifying questions, and somehow they were able to put everything together and upload it in five minutes, so thank you so much. Now, we have some slides to answer our questions.

DR. HERTZ: Hi. This is Sharon Hertz. I just put together some resource slides where you can find some of the information that we've been discussing. This is a website for the opioid analgesic REMS. It's dot-com. It's separate from our website, but you can also access it through fda.gov.

This is the landing page, and you can see at the top there's a menu for medication guides as well as the packaging information. It describes what is the REMS, and it gives you links for REMS accredited CE programs, and there are many opportunities throughout this website to find them.
If you look for patient counseling guides, this is the page that describes that. You can see, if I were to scroll down -- which I can't; this is a screenshot -- that there are links where you can download patient counseling guides, and I believe it's in more than one language that's available on this site.

This is the top of the patient counseling guide. It gives you an idea of what some of the information is and how it's been worded. There's a lot of different messaging there. It's a little bit going to be out of order because of the columns being broken up by the screenshots.

As you scroll down on it, you can see some more information about how you can take it safely. The prior one, obviously, is emphasizing storage, not sharing it; some of the concerns about interactions with other CNS depressants; other options for pain management. There's a whole section on naloxone and some additional information. You can see at the bottom of the patient counseling document, there is an
opportunity for
prescribers, or other healthcare team members, to
put in additional specific information they want to
share with patients.

Here is the landing page where you can find
direct links for any of the medication guides.
It's another way of accessing it. You can look up
by product on the Drugs at FDA's website. They
will be available as part of the labeling at
DailyMed if you use that to access labeling.

So that will be part of the record. But I
just wanted to show you that going to the opioid
REMS website, opioid analgesic REMS website, is an
opportunity to gain access to all of this
information.

Open Public Hearing

DR. HERNANDEZ-DIAZ: Thank you. We
appreciate it.

We are going to start with the new session.
Both the Food and Drug Administration, FDA,
and the public believe in a transparent process for
information-gathering and decision-making. To
ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with any sponsor, its product, and if known, its direct competitors.

For example, this financial information may include a sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency
and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 please step up to the podium and introduce yourself? Please state your name and any organization you're representing, for the record.

DR. FUGH-BERMAN: Good morning. My name is Adriane Fugh-Berman. I'm a physician who directs PharmedOut, which is a Georgetown University Medical Center project that fosters rational prescribing and exposes unethical pharmaceutical marketing practices.

My disclosure is that I'm a paid expert witness at the request of plaintiffs in litigation.
brought by state and local governments regarding pharmaceutical -- I'm a paid expert witness at the request of plaintiffs in litigation regarding pharmaceutical marketing practices, including litigation brought by state and local governments against opioid manufacturers.

PharmedOut supports the removal of ultra high-dose opioid preparations from the market. Problems with ultra high-dose opioids include the fact that the margin of error is so small. The consequences for taking a second dose after forgetting that one dose was already taken or deciding that the first dose was ineffective could be death. I can't think of another self-administered class of medications where doubling a dose has potentially lethal consequences. A single pill can kill an opioid-naive adult or child.

When a range of doses is available, patients assume that all doses in that range are safe. They may also believe wrongly that pills or preparations at the lower dose and end of the range are
completely safe. Patients whose pain is not well managed on lower dose opioids may aspire to higher dose pills even though evidence shows that when opioids don't work at lower doses, they are unlikely to work at higher doses. Adverse effects affect not only the patients but any children, family, or house guests who have access to these pills. The more opioids that are around, the more opioids that will be available, and the more opioids that will be diverted.

Opioids are considered intrinsically valuable. People just don't throw them away. I remember hearing from one addict who talked about going to open houses, and then asking to use the bathroom so he could steal opioids out of the bathroom cabinet, and sort of imagined, "Hi. Here for the house and garden tour. I'm sorry. Do you mind if I use your bathroom?"

You will hear from others that convenience is really important, but taking a higher dose of opioids shouldn't be convenient. A handful of pills is a visual reminder that you're taking a lot
of medicine, and that's a good thing. The only events made convenient by ultra-high opioid pills are accidental overdose and suicide. When one pill can kill the dose is too high.

You may also hear that higher doses are needed for people with swallowing problems. In fact, opioids can worsen dysphagia. Patients on high-dose opioids with dysphagia may be helped by lowering their opioid dose. It can cause esophageal dysmotility and other problems. And obviously, there are liquids, patches, and parenteral preparations for people with swallowing problems.

A patient on a chronic high dose of opioids is a lucrative patient for opioid manufacturers. Addicted customers are loyal customers. Richard Sackler at Purdue pushed sales reps to sell more 80-milligram pills in sales reps for Insys, which makes the highly addictive fentanyl sublingual spray, Subsys, have a slogan. "Start them high and hope they don't die."

Flexibility to drug makers means increasing
doses, but flexibility in dosing should be used to lower doses, not raise them. Individualizing opioids is industry code for increasing opioids. The higher the dose, the more money opioid manufacturers make because, incrementally, increasing doses doesn't cost them very much money. That's good business but bad for the public.

Promotional tactics have changed over time, but opioid promotion continues today, including an area that we're the only group in the world working on, is marketing messages and continuing medical education. And I can tell you that the REMS for long-acting opioids is chock full of marketing messages. We're going to be presenting some of that research at our opioids conference tomorrow and the next day. You're all invited.

There's no specific clinical utility of higher dose opioid analgesic products. These increase adverse events, and a conveniently lethal dose is not an advantage. Ultra high-dose pills make death convenient; it's that simple. Please remove them from the market to ensure that the
public's health, rather than opioid manufacturers' bottom line, is protected. Thank you.

DR. HERNANDEZ-DIAZ: Thank you. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you're representing.

MS. McGARITY: My name is Kristin McGarity. I represent myself, no disclosures. I'm not here to talk about pain. I'm here to talk about invisible disability. This is not something anyone should ever have to disclose or discuss, but I'm going to try to raise some awareness.

I'd like to ask everyone in this room to take a moment and imagine you're just out of college, everything going for you. You wake up one day, and it's unbearably painful to hold pee. It's not an infection. It's a flesh-destroying autoimmune disease.

Now, let's say you're lucky. You can afford the best care, over 40 treatments, medicine through a catheter 5 times a day; diets and psychosocial and neuroplasticity therapy, and nerve stimulation,
and a multidisciplinary pain program, and it only gets worse. You're in the bathroom every few minutes around the clock. Doctors start talking disability. You're 24. He said, "There's one other thing we could try called high-dose opioid therapy. Essentially, it's a palliative protocol, very risky, controversial. Barring a research miracle, you'll be dependent on medication the rest of your life," and a pill every few hours beats a bathroom every minute.

So you try it. Instantly, you can go an hour without peeing. You can sleep 2 hours for decades. You can do anything anyone else can do. You finish grad school, teach, manage employees, climb mountains, and play in symphonies. You fall in love. You try a slow, patient-centered taper, but at lower dosage, you're right back where you started, in the bathroom every few minutes.

You taper back up, live normally again, and that's where the story should end; except now, FDA might re-label or outlaw that dosage that spared you decades of confinement because studies don't
show benefit. That's because the people who
benefit aren't signing up for studies; they're out
living.

But how? How do you put on a facade of
normalcy for your kid every day, knowing the people
in this room could take away your ability to go
hiking, or fly in a plane, or watch a soccer game,
all because you have autoimmune disease and not
cancer? And what do you say to a room full of
people deciding whether you exist? What do you say
to a conference dedicated to the premise that you
don't?

Well, I know what I'd say. Lower dose does
not necessarily equal healthier life, and there's a
24-year-old somewhere who just failed the 39th
alternative therapy, and she deserves an education,
and a career, and a family, too. Thank you for
your time today.

DR. HERNANDEZ-DIAZ: Thank you. Will
speaker number 3 step up to the podium and
introduce yourself? Please state your name and any
organization you're representing, for the record.
MS. OGDEN: Good morning. My name is Kristen Ogden, and I'm the co-founder of a small advocacy group called Families for Intractable Pain Relief. I'm not a medical professional or a scientist. I am, however, the caregiver of my beloved husband of 46 years. I have been advocating for him for at least the past 20, and more fully engaged in advocacy since I retired from federal service in 2014 with 36 years of service. I'm a 1975 graduate of the College of William and Mary, and at the time of my retirement, I was serving as director of strategic planning and performance management for the Defense Commissary Agency.

Families for Intractable Pain Relief, as I said, is a small group. Our goals, specifically, are to raise awareness of what we are calling severe, constant, intractable pain and the challenges faced by those who suffer it, and we advocate for access to whatever therapies are needed to properly care for these individuals. We support the appropriate prescribing of opioids at
any dose by qualified physicians as the last resort
treatment to relieve the severe intractable pain of
any patient for whom such dose is deemed necessary
to stabilize function and bring quality of life.

I put this slide up here because we have
over the years been somewhat frustrated that none
of the definitions adopted by the federal
government really quite seemed to capture the type
of pain experienced by the folks who are the
members of our group. The pain does not relapse as
indicated in the recent definition adopted by the
task force. We're talking about excruciating,
constant pain without remissions; not curable, and
causes a lot of very adverse effects if not
adequately treated.

I've asked people often to think about what
would your life be like if you had a constant
experience of the worst pain that you can imagine,
every minute, every day, every hour, every week,
with no remissions. That is what life for my
husband and many other people has been like without
adequate pain care.
These are the characteristics of severe intractable pain as we describe it. Causes are twofold. It generally requires one of the few diseases up here on this slide to the best of our knowledge at this point in time: adhesive arachnoiditis, RSD or CRPS; various postviral and other neuropathies and encephalopathies; brain injury; and now also genetic connective tissue disorders such as Ehlers-Danlos and others.

Why am I here personally today? To share the experiences and outcomes of many of our patient members who have been successfully treated with high doses, and in some cases ultra high doses of opioids for many years. Many lives have been saved. These patients have achieved good pain control, improved function, and far better quality of life, and there is a wide range of therapeutic doses.

Many got good relief in the 100 to 200 milligram range. Some have fared very well on dosages in the 2000 to 3000, and that's where my husband falls, and it's very important that he
continues to have access to his medications. At the moment he doesn't, and I'll talk about that in a few minutes.

Most of our members, although not all, were members of Dr. Forest Tennant. In over 40 years of practice as an intractable pain specialist, he had no instances of overdoses, no patients became addicted after starting their regimen, and no instances of patients harmed.

So in terms of the question for which this meeting was called, the clinical utility of high-dose opioids, from our point of view, medical management of intractable pain can enable a patient's overall condition to be stabilized, while underlying causes are identified and treatments are attempted that can be accomplished without undue risk of adverse outcomes such as overdose, addiction, or death. Failure to treat it may lead to these adverse outcomes and early death.

Compassionate relief of this kind of constant severe pain is certainly the right thing to do.

I'm going to take a couple of moments and
quickly walk you through my husband's own personal history, his pain journey. He would be here with me today if he were doing a little better, but he's at the hotel. His pain journey started at about age 6; he is 69. He had a respite during his teenage years, worked through the pain as a construction electrician from age 22. Over time, all of his pain grew worse. At age 43, he could no longer do the work required of an electrician.

He got a diagnosis of fibromyalgia at age 40, and when he asked the doctor, "What can you do? How can you help me with this horrible, constant headache I have?" the doctor said, "Well, I could give you something, but you'd be a junkie in a week, so I'm sorry. There's nothing I can do for you."

He went back to college in 1993 to make a career change at age 46. His intent was to teach. He was awarded an academic scholarship to Syracuse. He began that program in the fall of '96, but for whatever not clear reason, in the spring of '97, all of his symptoms worsened. They mushroomed, to
the extent that he could no longer concentrate on
his studies and ended up having to withdraw from
graduate school.

In 1997 at that time, we began a nonstop
search for treatment. We had sought treatment over
the years. Most doctors would tell him, "Wow,
you've got great labs. You look healthy. I wish
my labs were as good as yours. If you hurt, I
can't disprove that. I don't know what to do."

Between '97 and 2010, he saw 9 pain
specialists, psychiatrists, psychologists,
chiropractors, therapists, and tried many kinds of
treatments. None of them helped very much at all.
Many, many medications, tried and failed. Quite a
few of these, he had very strong and sometimes
unusual side effects, hypersensitive to many
medications.

Finally, in 2010, we had success. In the
spring, he told me, "I can no longer stand this. I
know there are some doctors who will treat some
patients with high doses of opioid pain
medications, and I don't know what to do other than
to try that." We went and saw Joel Hochman and Houston.

The reason I mentioned him is we didn't have him very long because he passed away shortly thereafter. But he titrated my husband up to an effective dose of OxyContin, which was 720 milligrams per day. Prior to that, he had never had more than 100 milligrams, roughly, of oxycodone or other opioids that were attempted and failed.

I want to point out that he was titrated to this effective dose before the abuse-deterrent formulation was added to OxyContin. Dr. Hochman passed away. We contacted Dr. Forest Tennant, and he accepted my husband for an initial appointment. We saw him, signed the documents, medication prescribed, but OxyContin at 720 milligrams a day was no longer effective.

We saw Dr. Tennant again in 2010. At that point, he titrated my husband up, again, to the now effective dose, which was 1440 milligrams a day. And let me just say that I know these are high-dose
unit pills, but he did have a handful. His dose was six 80-milligram tablets 3 times a day. He also had oxycodone 30 milligram for breakthrough pain, and this resulted in what he calls the best years of his adult life.

From December 2010 to October of 2018, there was no dose escalation whatsoever, no impairment, and no significant side effects. The first time he ever said these are the best of years of my adult life was in this room at a patient-focused public meeting on fibromyalgia in 2014. He still says these have been the best years of his adult life.

Here are the components of that successful regimen: OxyContin, oxycodone, methylphenidate, Prozac, and oh my goodness, clonazepam. I would submit to the FDA, just for your consideration, that like the misinterpretation of the CDC guideline, some have interpreted the black box warning on clonazepam to mean under no circumstances should they be co-prescribed.

My husband, however, was first put on clonazepam and Prozac in 1992. He was already
taking it for management of anxiety, panic, and depression before he ever had any opioid prescribed on a continuing basis, and he had never had any adverse effects whatsoever. All of his physicians have known exactly what all he was taking and we keep them all informed, and we would strongly resist having to discontinue that medication because it works for him.

As I have said, he had greatly improved quality of life, excellent pain control, functional capability, greatly improved quality of life in every respect, but in 2018, we lost access to pharmacy support in Virginia. And since November, we have not been able to fill pain medications in Virginia, and that's a real wrinkle in our life. He does have a new regimen prescribed by his current doctor. Unfortunately, it's not working. It's not working well.

How did we get here? I didn't want to leave him at home alone because he's not doing well. He's not feeling well. So I considered cancelling and not coming to this meeting. He thought it was
important for me to come. He didn't want me to cancel. So I hauled a twin-bed mattress out of one of our bedrooms and put it in the back of my Expedition so he could lay down in the back to ride up here because his severe head and neck pain is now such that he can't sit up for more than about an hour at a time without his pain just laying him out.

Recently, Families for Intractable Pain Relief provided input on several occasions to the task force. We recommended or we commented that they failed to address what we've called the overlooked condition of constant severe, intractable pain. These folks, many of them are the high-dose patients. We call them outliers. In any set of data, you're going to have outliers. Well, our family members are outliers in terms of symptoms and often their doses, constant excruciating pain.

We think that the federal government could serve our population very well by educating physicians, pharmacists, law enforcement,
regulatory agencies, at state levels, particularly, that pain of this nature really does exist. My husband is a real human being, and the pain that I've described is real. It's debilitating and may lead to early death if not adequately treated.

My last bullet doesn't really pertain too much to the other content of the slide, but it occurred to me in looking through that people have also in the past seemed to doubt him, often physicians or other healthcare providers, "Well, you don't look like you feel that bad." We had a nurse tell him in a hospital, "You don't look like you're hurting that bad, so I'm not going to give you the medication." People with severe pain can smile, and they do smile.

Best practices to us would include recommending that for patients like my husband, who have been on a successful regimen for over 8 years, the best practice is to leave them alone and let them continue. Please avoid mandating changes to successful protocols. Changes are very destabilizing and difficult, not only to the
patient, but to the entire family.

I would say that one can best measure success by three outcome metrics: pain control, function and capability, and quality of life. As reported by the patient with confirmation by a family member, frankly, from my point of view as a family member, MME is irrelevant. Outlier patients often have limited ability to metabolize medications, and it's not what the number is; it's how my husband's doing.

High-dose therapy can be a legitimate practice for patients for whom all else has failed. It's been practiced for many years by some practitioners as a last resort. It's not new. It's helped many. There are criteria that have been written about in terms of what patients might be eligible. They've been published in Practical Pain Management, and I would think it might be helpful to take a look at those.

In the current environment, we fear that doctors will not come back to pain practice until the federal government provides some sort of
protection in the form of criteria, so use what's out there as a starting point. Too much delay is really a significant problem because people are dying by suicide and by impacts of undertreated pain, people who have lost their care,.

We still have care. We just don't have access to the best medication and we're fighting that. We're talking frequently with the Commonwealth of Virginia government to try to get them to backtrack on some policies they have adopted that caused the harm. I think we face an ever-growing crisis with too few doctors, too few pharmacies, and too many Americans suffering needlessly.

What can cause a requirement for unusually high doses? Here are a few things, cytochrome P450 abnormalities. Some people have malabsorption due to disorders of the digestive system or extensive gut surgeries, and it's now believed there's damage to pain control receptors due to tissue degeneration, particularly if you're talking about people with genetic connective tissue disorders,
adhesive arachnoiditis, et cetera, which now are my husband's recent and new diagnoses.

Pros and cons for extended release, I'm a big fan of extended release because they get my husband a consistent level of relief where he's not up and down all day long. There are many myths about intractable pain patients. Who are these people? They are in any number of walks of life. All of the people up here, these occupations represent friends of mine and people that I know.

What's at stake? Really, the right to life, liberty, and the pursuit of happiness, because you can't live your life when you're chained to the couch.

What can FDA do? Thank you for holding this meeting. Please continue to talk to patients, help change the public narrative, and educate to combat the stigma. We would very much support a special REMS or a training program so that people can sign up to help these folks.

My husband in his own words wrote to FDA that he now feels like there's some social
experiment that has failed, and he's no longer important. It's not important to treat him. Does he deserve to be thrown out like yesterday's garbage? I would say remember that smiling face, and certainly he deserves compassionate care like anyone else. Thank you very much.

DR. HERNANDEZ-DIAZ: Thank you. Will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

MS. WALDEN: I have no conflict of interest. I'm Emily Walden, a mother from Kentucky and the chair of the national FED UP! coalition that is made up of individuals and organizations across the country, working to end the opioid epidemic.

Many FED UP! members over the years have stood before the FDA begging for reasonable, appropriate, and much needed action from the FDA to do the job that they are obligated to do: protect public health and ensure the safety of drugs. Many members of the FED UP! coalition, including myself, have lost our children, and want nothing more than
to ensure that this does not happen to anyone else.

I'm here today asking you to do the right thing by the removal of ultra high-dose opioids from the market, a step in the right direction in protecting the public from accidental overdose deaths. This country continues to be ravaged by addiction and death due to the risky and overprescribing practices of opioids. Millions of Americans innocently taking pain medication have become victims of this heartbreaking epidemic.

Those of us that have made it our life's mission to prevent the overwhelming and tragic loss continue to see the devastating effects. We are still attending funerals. We are trying to convert those that are just beginning their path of a lifetime of pain, grief, and sorrow without their loved ones. Prescribing the highest dosage of an opioid can cause immediate respiratory depression and death in a patient who is regularly taking opioids and taken as prescribed.

In the case of diversion, a higher dose opioid is even more dangerous. The most common
motivation for misuse, 63 percent, is to relieve physical pain. Someone who takes a single dose could suffer a fatal overdose from just one pill.

The American Academy of Pain Medicine did a study in 2010, which stated, "The higher dose in extended-release oxycodone prescriptions had higher rates of prescriptions to overdose decedents than lower dose oxycodone products, and the highest dose, oxymorphone, had the highest proportion of prescriptions prescribed to overdose decedents for all other opioids."

Another study by Rand Corporation, researchers who analyzed prescribing data in Massachusetts from 2011 to 2015, found that half of adults received at least one opioid prescription during that time. They found the strongest risk of death from any cause was after receiving a high-dose prescription opioid.

Since the loss of my 21-year-old son, TJ, a Kentucky national guardsman with a bright future and a loving heart, I have researched some of the past FDA decisions concerning opioids, and there
been many disturbing actions that have led to this horrible epidemic.

The FDA allowed for clinical trial designs to be altered in 2006 called enriched enrollment. It ignores safety and science for easy opioid approvals. They have allowed label changes without proven efficacy. They have ignored inappropriate marketing practices and risky prescribing, thus failing to do their job. Hundreds of thousands of people have lost their lives.

In July 2017, the FDA announced it would utilize a new benefit-risk framework, proposed by the National Academy of Sciences, that would consider the public health effects of opioid misuse and removal decisions. The fact is, high dosages of opioids have a direct link to overdose deaths, and removing these from the market will save lives.

The FDA must start taking real action to prevent addiction and death. I don't understand how the FDA recently removed blood pressure medicine from the market due to a potential cancer risk; yet hundreds of thousands of people have died
from opioids, and they are still considered safe
and effective in all dosages and pretty much the
same indications from the very beginning.

How many people need to die before
corrective action is taken and safety becomes a
real concern of the FDA? Please do the right thing
today. We are still seeing cases of new addiction.
We are still seeing deaths. And most of these
deaths started out with a prescription. What was
on the slide of fentanyl and heroin, I work the
needle exchange programs. Those people started
with a prescription and an injury. The harms in
prescribing high dosage opioids outweigh the
benefit. Please do the right thing.

DR. HERNANDEZ-DIAZ: Thank you. Will
speaker number 5 step up to the podium and
introduce yourself? Please state your name.

MS. HOLTUM: Thank you. My name is Lexi
Reed Holtum. I am the executive director of The
Steve Rummler HOPE Network, and I have no financial
relationships to disclose. As I'm listening to
other speakers this morning, a couple of things
popped into my head. So before I get into my prepared speech, I would like to just state those things.

One, thank you for your attention. I realize that this is a really long process, and that many of you have been working really hard before you got here and after you leave. So thank you for being so acutely attemptful [ph] because we're watching how you're listening, and it's really just heartening to see so much attention. I appreciate it.

Secondly, we are not the only country in the world with chronic pain, with irretractable pain, but yet we're still consuming the vast amount of opioids that are produced on the planet. There is room for improvement. We're not doing it right, and we need to do a better job. And that's why you are all here, and thank you again.

Now I'll get into my prepared speech, and I'm assuming I'll cut it short. The Steve Rummler HOPE Network's mission is to heighten the awareness of the disease of addiction as it relates to the
physical and emotional burdens of chronic pain, and
to improve the associated care process.

We have several goals. I'm not going to
read them for you today. But ultimately we achieve
our goals, and most of it is to uplift and educate
and help prescribers have solutions, and then to
have people not die from this public health crisis
that's been going on for two decades, and we all
know it started with Porter and Jick. Right? We
have that tail end of don't die, which we do
overdose prevention, our front end of supporting
our good prescribers and having what they need, and
in the middle, we've got advocacy.

I'm really proud of the work that we do. We
know in Minnesota, in the last 2 weeks, that we had
174 overdoses in our state, in 2 weeks. The vast
majority of people that are using the illicit
street drugs started -- 80 percent of the people
that are using illegal street drugs today in our
countries started with prescription opioids.

It doesn't really matter were they
prescribed them directly or did they take them out
of a medicine cabinet because the culture that we live then is that we trust our prescribers. We trust that medication that our doctors prescribe. It's safe to have in our households. And the reality is, whomever has been duped into this falsehood, we're here. So if people started because they borrowed their relatives' prescription opioids, and that's how they ended up on this pathway to the disease of addiction, it doesn't really matter at that point; we are where we are.

When my fiance, Steve Rummler, who's the namesake of The Steve Rummler HOPE Foundation, overdosed and died because he was prescribed opioids to treat his chronic pain, he never should have been prescribed them in the first place, it did not work. It created a state of euphoria and a bit of a state of -- he felt heard and believed -- because so many chronic pain patients, because things aren't measurable, are treated like maybe are making it up or maybe you're a little bit crazy.

So Steve experienced that. When he was
finally prescribed his opioids, what happened for him was that he had euphoria, and he felt heard, and he felt believed, but the ultimate loss was that we, and our community, and our country in 2011, when he died, lost 15,000 lives.

It's projected now that we are as a nation going to lose over 70,000 opioid overdose death-related lives. That's more than died in all of Vietnam. So I want to just state here that we need the FDA to immediately remove from market the high-dose opioids, the ultra high-dose opioids, and figure out how to remove the remaining high-dose opioids as well.

There are other solutions. We can create those together, but the first thing is this shouldn't be a public health crisis where the solutions are driven by nonprofits, where the solutions are driven by people who lost loved ones. It is time for the FDA and for the higher up tiers to engage in a way in which we create public health and safety. It's time. So please work with us and achieve that. Thank you so much for your time and
consideration.

DR. HERNANDEZ-DIAZ: Thank you. Will speaker number 6 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. LaGRECA: Yes. My name is Tony LaGreca, and I represent myself, and I also represent Team Sharing. Team Sharing is a group of parents who have all lost a child due to the overdose epidemic that is plaguing our country.

Five years ago, my son Matthew died of an acute overdose of methadone. Two years later, his partner died of an acute overdose of methadone also. My son had been addicted many years back after a football injury in college. He was sent to a local hospital, where his first prescription was 110 milligrams of oxycodone, 3 to 4 a day as needed. At that time, I didn't even know what an opioid was.

For the other race [ph], he was in and out of rehab for the rest of his life. Once after a 30-day rehab, he left the facility and got into a
bad car accident. Many broken bones occurred. By the time I saw him in the hospital, he was prescribed on 80 milligrams a day of OxyContin and a filler of oxycodone if needed.

My son was prescribed extremely high doses of opioids by doctors who did not realize they were harming him. This is why high-dose opioids should come off the market. The existence of high dosage pills suggest to prescribers that the FDA considers the dose to be safe and effective.

The first problem here is there are no programs in place to wean patients off once these high doses are no longer needed. He was on these doses for months with no recession plan. The medical world does not want to hear about the addiction side. We all know with these high doses, one would be dope sick if they are shut off. Trying to find a plan for weaning patients off is near impossible. This is one reason high doses are very dangerous. The medical establishment hasn't put any plan in place for these patients.

A year after my son died, I became a
bereavement facilitator for parents who have lost children with substance-use disorder, starting with prescription opioids. Unfortunately, I've spoke to hundreds of these parents over the four years. Two patterns were quite prevalent. First, and accident, injury, or dental work introduced opioids to the child. This drug, even at low levels, when in the body of certain people takes control of their brain. Nothing matters anymore, but feeding this evil drug to the brain. The patient doesn't abuse the drug; the drug abuses the patient.

The important thing also was opioids are just a mask for pain. They have no use in recovery of injuries or ailments. When patients are shut off abruptly to prevent dope sick, they go out and go on heroin, and die when they get too much of a batch with fentanyl. Others go and buy counterfeit pills, and some of these are laced with fentanyl, and death occurs. But this is not the majority, and that is why I'm here.

Many of the parents I have been with, their child went to sleep and didn't wake up; no needle,
no drama, just going to sleep. Their breathing
stopped and their heart also stopped, and they were
found cold dead in their bed. This is the silent
killer.

Adults between the ages of 45 and 60, or
older, don't get shut off from the doctors as a
rule. They keep getting prescriptions from their
doctor for opioids. The build up in their system
shuts down the brain and death occurs. The higher
the dosage, the faster this will happen. The
number of deaths recorded in the actual number is
way higher. Most of our country, the coroners and
medical examiners are not doctors, and autopsies
are not even performed.

My son and his girlfriend both died in their
sleep with a buildup of methadone in their bodies
shutting down their brain. Tens of thousands of
Americans have died the same way. The number of
opioid deaths is way higher than what is recorded
by the government. I believe you cannot increase
doses under any circumstances unless the patient is
terminal. Long-term use will bring an unhappy
Our country is suffering from an opioid epidemic. The word "epidemic" means a fast-spreading disease. I believe the FDA and the pharmaceutical industry has caused this epidemic, a disease that comes in a plastic bottle from your local pharmacy. Last year, it was reported there were 244 million prescriptions in the U.S. of various forms of opioids. You want to stop the epidemic; stop the unnecessary prescribing.

My son, who I love very much, has been taken from me. Thousands of other parents in America are in the same club without their child that they loved. My two grandchildren, Adam and Madeline, will never know their grandparents. And even worse, their grandparents, their grandparents will never know them.

I came here on my own expense. My goal is to explain the dangers of high-dose opioids. Let's stop the madness. Thank you for your time.

DR. HERNANDEZ-DIAZ: Thank you. Will speaker number 7 step up to the podium and
introduce yourself? Please state your name and any
organization you are representing, for the record.

MS. ROVERO: Hello. My name is April Rovero, and I am the founder of the National
Coalition Against Prescription Drugs. I have no
financial ties to disclose. My organization is a
nonprofit organization founded in 2010, and we are
in San Ramon, California. That's where I traveled
from to be with you today. We are focused on
saving lives, basically, by education, community
education, policy change, and legislative advocacy,
and that's at the state, the local, and the federal
levels.

When we put this organization together, we
really realized that all prescription drugs were a
potential danger, but certainly over the last few
years, we've been highly focused on the opioid
issue, given all the loss of lives we've seen.

How did I come here and why am I so
involved -- and I have been for the last 9 years,
basically, every day of my life out there talking
to individuals and groups of people, whatever I can
do -- is because I did lose my son also, Joseph
John, also fondly known as Joey Rovero, III, to an
accidental overdose.

Joey was a senior at Arizona State
University, about ready to graduate when we got the
devastating news that he had been found in his
off-campus apartment. And after being out with his
friends the prior evening, he went home, went to
bed, and he did not wake up.

As the story unfolded, 4 and a half months
later, of course we got the toxicology report and
the coroner's report back, we came to understand
that he died from a prescription drug overdose. We
also came to understand that he had seen a doctor
just 9 days before he passed away, and that doctor
had prescribed outrageous amounts of medication to
my son: 90 pills of 30-milligram strength
Roxicodone; 30 mL of 2-milligram strength Xanax;
and 30 pills of Soma, basically a lethal
combination as far as I was concerned.

The doctor's coroner's report indicated that
he died from a concentration of medications and a
little bit of alcohol. None of the individual ingredients would have taken his life, but together they did.

What I've learned is a whole lot. I didn't even know that prescription drugs were abused. I didn't realize that they were recreationally used in college settings, now down to the high school setting. I learned, and certainly see it to be true today, that there is a very low perception of harm. K through 12 in the classrooms, kids are not getting the education they need. The colleges, the universities, they're not educating these kids. So any youth in college today I believe is in a very high danger zone. If they decide to party on the weekends, these medications are in the mix. And of course now we've got fentanyl that we have to be worried about as well.

Bystander intervention and harm reduction is what our organization is now really focused on. We know these young people are going to get involved in party situations, and they don't have the education to really make sound decisions. So we're
now educating a lot on naloxone awareness. If they're over 18, we not only educate them; we give them a kit, a rescue kit. We teach them about the good Samaritan laws and what to do if you have a friend in trouble. What does an overdose look like? They don't know. They haven't been taught that.

The bottom line is we see accidents happen all the time. Young kids are getting these medications from parents or other adults that don't lock them up. They think they're candy, and they take them down, and they get poisoned by them. We have teens that want to experiment, and it's easy to get those pills in their medicine cabinet.

Young adults like my son can go to a doctor, and they can get whatever they want to try to party with and have fun with. Elderly people can forget that they just took their medication and double up, and they can be in deep trouble very quickly.

The horrible toll opioids are taking on American families today is absolutely indescribable. I know every single day that I'm
going to get word that somebody in my world has
passed away, someone in the country. It's
horrifying, and it's a dagger to the heart every
time it happens.

Literally, no family is safe as far as I'm
concerned, because if you don't have a child or
someone in your family that's recreationally using
this stuff, they're getting prescribed this because
our doctors are still prescribing these medications
and high dosages of them often without real need.

I challenge you to watch a video. There's a
YouTube video that we have put together. It just
has 650 of our Americans showing the lives that
should be here still. That video is just the tip
of the iceberg.

I hope you'll take all of this into account
as you make sound decisions about what you're going
to do about these high-opioid dosages. I
personally hope you take them off the market. I
think there's good reason to do that. But we've
got to be bold. We've got to make really good
decisions and do something. This problem is out of
control, and it's not getting better anytime soon.
Thank you.

DR. HERNANDEZ-DIAZ: Thank you. Will speaker number 8 step up to the podium and introduce yourself?
(No response.)

DR. HERNANDEZ-DIAZ: Speaker number 8?
(No response.)

DR. HERNANDEZ-DIAZ: If not, we'll move on to speaker number 9. Step up to the podium and introduce yourself, and please state your name and any organization you are representing, for the record.

DR. BUSCH: You have me down for five minutes, right?

I'm Dr. Daniel Busch. I'm a psychiatrist in general practice and a clinical assistant professor of psychiatry at Northwestern University Medical School. The opioid insanity wound up impacting my practice. I had a new group of iatrogenically ill patients.

Mr. A was a 35-year-old truck driver who was
on opioids and valium for back pain. His wife called me one morning to tell me that he had died during the night of an accidental overdose.

Ms. B was a 30-year-old woman with severe headaches, which would get better with each increase in her opioids, but then become even more severe. She was ultimately diagnosed as having opioid-induced hyperalgesia.

Mr. C was a formerly successful attorney in his 50s, who presented with compromised mental status due to high-dose opioids prescribed for back pain. After a car accident, he was found to be accidentally wearing 2 fentanyl patches.

Ms. D was a woman in her early 60s with a history of depression and head and neck pain. Her internist opposed her plan to go to a highly reputable pain clinic, and told her 2 years from now, you'll be in the same amount of pain, but you'll be hooked on opioids. Since then, Ms. D has gone to a series of well-trained, well-respected pain doctors. Opioids were gradually increased to over 250 MME daily. She was placed on fentanyl
lollipops for breakthrough pain.

Ms. D is now an 81-year-old woman. Her pain is no better. In line with changing practices, her pain doctor recently decreased her pain medicine. She was furious, and asked me, "What am I supposed to do about my pain?" "Fortunately," she told me she had stored up enough Norco from previous prescriptions that she could get around his treatment plan.

My patients fit in well with Sullivan's 2010 observation about who actually gets high-dose opioids. Rather than the careful selection of low-risk patients, we see a pervasive pattern of adverse selection, where the patients at the highest risk for poor outcomes are selected for high-dose and high-risk therapy.

Since 2010, there's been a dramatic decline in high dosage prescription of opioids. MMEs of high-dose opioids have declined by 61 percent, and the FDA briefing document informed us that the number of patients receiving the high-dose strength products has declined by two-thirds over the past
This change has involved a progressive decline that began in 2010 and since then, and I would point out that this is before the FDA upscheduled hydrocodone acetaminophen products to Schedule 2, and long before the CDC guideline. My sense of all this is that what began to happen is that doctors began to realize that these medicines were not working that well, and that there was a lot of morbidity associated with these higher doses.

The FDA frequently hears from patients and healthcare providers that higher dose opioid analgesics continue to be a unique and necessary part of effective pain management. Ultimately though, these advisory committees evaluate scientific evidence, and there is no scientific evidence that there's any defined subgroup of chronic pain patients who benefit from high-dose opioids.

On the other hand, there's plenty of evidence of the greater risks that's associated
with higher dose opioids. There's more addiction, more overdoses, and unfortunately, more deaths associated with higher dose opioids.

I think the advisory committee should be recommending to the FDA that indications for dosing and duration of opioid pain treatment must be based on clear scientific evidence that benefits outweigh risks. Specifically, that the high-dose strength products should be removed from the market. They're unnecessary and dangerous. Second, the FDA should support the CDC guideline of cautious prescribing, with second looks before going above 50 MME and again before going above 90 MME, to reassess benefits and risks of opioid treatment.

Thank you.

DR. HERNANDEZ-DIAZ: Thank you. Will speaker number 10 step up to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

DR. BALLANTYNE: I am Jane Ballantyne. I'm an anesthesiologist and pain medicine specialist, and have been for 30 years. I'm a professor of
anesthesiology and pain medicine at the University of Washington in Seattle. I'm also president of PROP, or Physicians for Responsible Opioid Prescribing, who I'm representing today. This is a group of physicians who've advocated, for a long time, for more rational and responsible opioid prescribing. I'm a paid consultant on opioid litigation.

Since the focus of my whole career has been on pain management, I care very much that people receive the best we can offer in terms of reducing the burden of pain. I'm going to focus for a moment on cancer pain because the argument that high-dose pills are needed often focuses on cancer or end-of-life pain.

In 1986, we used to say that 90 percent of cancer or end-of-life pain could be well-managed with opioids, with no need to resort to fancy treatments such as injections or invasive procedures. And that was my experience. It was true. Most patients that we were treating in those days, we could treat well as they neared the end of
their lives.

By 1999, it was no longer true. So what happened between 1986 and 1999? What happened was that the doses gradually got higher and higher, so that when we were treating people at the end of life, it became very difficult to overcome their tolerance. There are two reasons that happened.

One is that the disease of cancer changed, which meant that it became a chronic disease, and opioids had been prescribed for longer. But another reason was that the teaching of the 1980s and early '90s was that the dose could be titrated upwards in a limitless way in order to overcome the pain, which meant that patients that got to the end of their lives were already on very high doses.

Then we realized that it wasn't just cancer pain. It was happening with chronic pain as well. I haven't got time to go into what we now know about the mechanisms of deteriorating pain control over time. Suffice it to say that when higher and higher doses are needed, pain relief gets less and less good. What we aim for these days is to keep
doses as low as possible in order to preserve analgesic efficacy. I have spoken to efficacy. High doses, ultimately, even if not immediately, don't work very well.

I will now turn to safety. One of the most serious adverse events associated with high dosages is the development of an opioid-use disorder. A person taking a relatively low dose of prescribed opiates is 15 times more likely to develop an opioid-use disorder than a person who's not been prescribed opiates. That risk continues to rise as the dose is increased, as you've just seen. At high doses, greater than 120, the person's risk of developing a disorder is 122 times that of a person who's not been prescribed.

Dose-related serious harms are not limited to risk of overdose. High doses of opiates are associated with increased risk for motor vehicle accidents; fractures from falls; immune suppression; opioid-associated androgen deficiency, which in turn causes reduced libido; erectile dysfunction; fatigue; depression; decreased muscle
mass; weight gain, osteoporosis; and infertility. Thus, high-dose usage should be avoided not just because it ultimately does not provide good pain relief, but in addition, it is not safe.

You have heard, and maybe we'll hear more, of many instances where single-tablet, high-dose opioids can harm people inadvertently, such as borrowing someone else's medication; taking an extra dose in the fog of sleep and pain; being a young person experimenting; or accidental ingestion by an infant or toddler. In each case, that person has no way of knowing or imagining that a single tablet could be lethal.

My focus, however, has been on the role of high-dose opioids in the treatment of pain. Do we really need high doses or high-dose tablets in order to treat pain well? The vast majority of people suffering pain, whether it be end of life during acute painful crises or chronically, do not need high doses of opioids, and in fact get much better pain control if lower doses are used.

There are a few outliers, nevertheless, who,
for whatever reason, maybe genetic, maybe to do
with the underlying painful condition, or maybe
because they're reaching the end of life, who do
seem to need and to benefit from high-dose opioids.

Removing high-dose pills from the market may
result in a few patients having to swallow more
tablets or capsules, but this is unlikely to result
in a significant inconvenience or hardship for many
patients. For example, if immediate-release
oxycodone 30-milligram tablets are removed, a
patient who currently takes 1 tablet every 6 hours
would instead take to IR oxycodone 15-milligram
tablets every 6 hours. At the same time, opioid
analgesics are available in any dose, liquid form,
compounding production of capsules, sublingual
form, patches, and suppositories, and these
preparations are particularly suited for
end-of-life pain care.

In conclusion, the harms of high-dose opioid
pills outweigh the modest benefit of allowing
patients to swallow fewer tablets or capsules. The
vast majority of patients do not need or benefit
from high-dose opioid therapy or high-dose pills.
If one considers that our most up-to-date,
benefit-risk framework takes into account public
health factors, as well as individual health
factors, the need for removal of high-dose opioid
tablets becomes even clearer. High-dose opioid
pills should be immediately removed from the market
to prevent further harm to thousands of adults,
adolescents, children, and toddlers. Thank you.

DR. HERNANDEZ-DIAZ: Thank you. Will
speaker number 11 step up to the podium and
introduce yourself? Please state your name and any
organization you are representing, for the record.

MS. KAUFMAN: Good morning. Thank you for
the opportunity to be here today. My name is Leah
Kaufman, and I'm the manager of national treatment
quality initiatives at Shatterproof. Shatterproof
is a national, nonprofit organization dedicated to
ending the devastation the disease of addiction
causes family.

In 2012, Gary Mendell founded Shatterproof
after his son Brian's death that followed a 10-year
struggle with substance-use disorder. As a parent and accomplished businessmen, Gary was determined to create one well-funded national organization dedicated to the addiction cause, like those that exist for other diseases.

Today, Shatterproof advocates for changes to federal and state policy, engages in payer reform, and is piloting a provider rating system in 5 states. We also provide public education through family and workplace programs. Shatterproof has been one of the leading advocates for the successful issuance and implementation of CDC recommendations for safer prescribing practices of opioids.

To that end. I'm here today to urge the joint committee and the U.S. Food and Drug Administration to approve the request made by Shatterproof, the Association of State and Territorial Health Officials, Physicians for Responsible Opioid Prescribing, and other prescribing and other public health stakeholders in our August 2017 citizen petition, submitted under
Section 355(e) of the Federal Food, Drug, and Cosmetic Act.

The petition requests that the FDA immediately remove ultra high dosage unit oral and transmucosal analgesics from the market, given their outsized risks. To be clear, there are appropriate and medically necessary uses for prescription opioids. They're effective in treating certain types of pain or helping people recover from complex medical procedures. However, ultra high-dose opioids present a distinct public health risk that must be addressed.

Ultra high-dose opioids are those that when taken as directed exceed the CDC threshold for dangerously high daily opioid intake of 90 morphine milligram equivalents; for example, the OxyContin 80-milligram tablet, which is as powerful as 24 tablets of Vicodin and can be fatal even when taken by a person with high opioid tolerance.

Because only a single pill is taken at a time, the patient and prescriber may not appreciate that this is a dangerously high dose. Even when
taken as prescribed, ultra high-dose opioids are associated with increased risk of overdose, motor vehicle crashes, neuroendocrine dysfunction, and other negative effects.

A particular concern with ultra high-dose opioids is accidental ingestion, borrowed medication, and recreational use. Recent studies have shown that 11.5 million Americans misuse prescription opioids annually. Sixty-three percent of all misuse originates with a prescription opioid from a friend or relative. Someone who borrows even a single dose of an ultra high dosage opioid to use for pain relief could experience life-threatening respiratory depression.

An overdose could also occur in an opioid-tolerant patient who accidentally just takes one extra dose or who intentionally takes an extra dose for unrelieved pain. These high-dose opioids are equally dangerous when misused for recreational purposes. For example, an opioid-naive teenager who makes the mistake of experimenting with an ultra high-dose opioid could suffer a fatal
overdose from just one pill.

    The perceived advantage of ultra high-dose opioids is that they enable patients to take fewer pills. But given that individuals, such as palliative and cancer-related pain patients who do require high-dose opioids, could still receive adequate treatment with multiple pills, patches, or other formulations, we believe these ultra high dose opioids can be removed from the market without imposing unnecessary hardship on those with legitimate pain needs.

    In 2017, the National Academy of Sciences issued a report outlining a new framework for the FDA's opioid approval and removable decisions. We commend the FDA's endorsement of this new approach, which takes misuse potential into account when weighing the risks and benefits of opioid formulations.

    Addressing the particular threats from ultra high dosage opioids is an important part of what the FDA can do to use the new paradigm for evaluating drug safety, which includes not only
patient safety issues but also risks to the community. Therefore, we urge the FDA to approve their request set forth in the petition. Thank you for your time.

DR. HERNANDEZ-DIAZ: Thank you. Will speaker number 12 step up to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

DR. FUQUA: My name is Anne Fuqua. I don't have any financial relationships of interest. First, I want to thank the FDA speakers and committee members for the effort and thoughtful deliberation you have given to this issue of higher dose opioids. I was impressed and relieved by the emphasis speakers placed on weighing risk and benefit for each individual.

High-dose patients like me exist in a precarious state. We want to live our lives to the fullest, yet many of us say we feel we live in a holding pattern due to uncertainty about whether we will be able to continue treatment that is effective for us as individuals.
I would love to go back to school. I don't want to be on SSD the rest of my days. I realize it wouldn't be smart to start school only to find out a few months later I'm unable to finish because my doctor is no longer able to continue to prescribe the medication that allows me to be a functional human being.

I'm approximately only 1000 MME. I have been stable for over 10 years with no side effects. I don't have endocrinopathy or sleep apnea. I have a life I'm incredibly grateful for. I live independently, and I'm able to do things I never dreamed would be possible when my body was ruled by spasms that made it nearly impossible to sit in a standard manual wheelchair like this.

I know the likelihood of finding someone who will be willing to take me on as a patient, if I had to change doctors, would be almost nonexistent. I'm not willing to become a prisoner of my own body again. I don't want to die, but that's not living. We need a safe-harbor provision that would allow physicians to take over the care of a patient like
myself or titrate a new patient who's failed other measures without fearing for their license or freedom.

Having a chronic illness is difficult as it is. Patients shouldn't have to wonder if each month is the last they'll be able to continue a successful regimen. Even when medications are prescribed by a respected physician, this does not guarantee that the patient will be able to fill their medication.

In some instances, wholesalers are usurping the prescriber's judgment and restricting the number of dosage units a pharmacist can dispense to any patient in a single month. This would create a big problem with the smaller dosage units taking more pills. This arbitrary figure is not based on patient-specific factors; rather it applies to all patients at a given pharmacy. So far, this seems to occur mainly in California.

The recent clarification of the CDC guidelines, the pain management best practices as approved by HHS, and the statements at this meeting
are incredibly important. Prescribers are wary. Many patients say their doctors stated they want assurances they will not be prosecuted or sanctioned by their licensing board if they prescribe in accordance with these measures.

We desperately need to translate this to patient care. Change is coming, but for patients who are exhausted from three years or more of tapering, uncontrolled pain, inability to sleep, change can't come soon enough. Five years ago, I would found out about a suicide every couple of months. Now, names get added on a near daily basis. Many times, several are added in a single day.

The 280 suicides Dr. Darnall cited yesterday is now close to 300. Some of those deaths are recent. Others are older but reported by friends or family only recently. No one should suffer from pain that's so severe, ending their life becomes a viable choice, especially if medication has already proven effective for improving their symptoms.

Thank you.
DR. HERNANDEZ-DIAZ: Thank you. Will speaker number 13 step up to the podium and introduce yourself? Please state your name and any organization you are representing, for the record.

DR. EGILMAN: The reason I moved this is because, like many of the other things you're doing, you're not considerate of the public. The webcast is shooting from there. All the speakers have had their backs turned to the webcast. That will be the first recommendation.

This is who I am. Ironically enough, you asked the speakers to give a disclosure, the community speakers, but you forgot the biggest conflict, which is the FDA itself, which is, of course, funded by big pharma through PDUFA. So all the FDA people, you should speak up and say, "Hey. My agency gets paid by the companies we regulate."

That's something that should be kind of important for people to know in the public.

Now, here's my disclosure. And by the way, the speakers yesterday, I missed it. I didn't hear them talk about their conflicts. And of course,
many of those speakers were part of IMMPACT and ACTTION Rx, which is a joint, as Senator Manchin called it, pay-to-play operation of the FDA, and consultants to the pharmaceutical industry, and the pharmaceutical industry. They spoke yesterday, and they didn't say a word about that.

I serve as an expert witness. I'm at Brown University, and trust me, this doesn't represent anything Brown wants to say because Brown gets some money from all the pharmaceutical companies. But at least one Brown University trustee that currently serves as a CEO of an opioid manufacturer, that was Teva in the past, the same guy now is the head of Cardinal. He's a Brown trustee. That's a conflict.

Also, through the litigation, I get to read many secret studies, marketing documents, and depositions of corporate FDA employees, none of which I can talk about today, or mention, or reference, all of which are available to the FDA if they ask for them. But of course, they don't want to know what the companies really know, so they
don't ask for them.

Let me start by talking about my -- let's start with where I'm going to end, maybe before I get cut off. You're talking about PSAs. Let's talk about McDonald's and Coke. Why? Because the pharmaceutical companies spend 5 or 6 times more than they do pushing these drugs one at a time. PSAs. Come on. That's spitting in the ocean, and it's the Pacific and Atlantic combined.

You want to do something serious? When you send a warning letter, make them do a remedial program by funding hundreds of millions of dollars of marketing to nonprofits, who you can get to set up to do that work. Make them fund them to do that.

You know. Califf said -- he was at the FDA -- only 1 percent of physicians read the PDR every year, any part of it. So you think you're dispensing your duty, pharmaceutical companies and FDA, by slipping something into the PDR or a warning label that you know nobody's reading? That's pro forma. That's a joke, except there are
150 people dying, and they can't laugh at that joke. That's just this drug. This one you made a big mistake on. Most drugs, you kill a few thousand people, a couple hundred thousand people; here, you're going to be setting world records.

Jerry Avorn set up a program where he had detailers marketing generics in Massachusetts. You can set that same program up and make the pharmaceutical companies pay for it when you catch them lying, cheating, and stealing, which you've done. Every large manufacturing company has been convicted of misdemeanors for which they've paid billions of dollars.

Misdemeanors. When you're a large company and you do $1.6 billion in penalty, that's a misdemeanor. When you're a normal person, or let's say not a normal person, a regular average American poor person, you steal a third hubcap, you go to jail for life. You need to talk to McDonald's and Coke, recommendation number one, about how to get information out to the public about these hazards and physicians, and I'll show you a slide later on
about how the companies do it.

By the way, where you start is more important than where you end up. All these people who are dying on street fentanyl, they started on prescriptions.

Oh, by the way, there are -- we just did a little bit of a survey -- 78 PDR years of opioids that are not in the PDR. The companies didn't even have their labels in the PDR over the last 10 years. So how is a physician going to read the label? They don't get the drug. You don't check that either.

By the way, REMS doesn't work. There's a study on that. They said the FDA didn't pay attention to this study. Nice to see you're continuing that practice, not paying attention to that study, not mentioning the fact that this in the study to see if REMS work, and it doesn't.

So let's go back to the talk. Why are we here? We are here because the CDC did something and the FDA and their funders, big pharma, want to block it, so they can make more money. Here's
where we're going to be going. This is my roadmap. Higher doses, more addiction, not less pain, and it's because of corruption and incompetence -- I can't tell you which, and Marketing.

First stop, addiction. Higher doses, more pain and more addiction; another one. Second stop, opioid-induced hyperalgesia. Contrary to what Dr. Rowbotham said yesterday, there are lots of good data on OIH, including randomized-controlled trials, including animal studies; lots of good data. So what happens? Patient is prescribed drugs. They have more pain. You stop the opioids, they get less pain. Look at that. There's a mechanism. It's well understood. I'm not going to go into it in my 5 minutes.

This is ice bucket. It's the second recommendation, and I want to talk about it here. Dr. Rowbotham mentioned it yesterday. You put a patient's hand in ice. You give them placebo; 20 seconds to pain. Give them an opioid, lots of pain at the same time or less time.

So what do you do? When patients have more
pain when you treat them, stop the opioids or give
them higher doses? I suggest you do a clinical
study. Every doctor's office has ice and every
doctor has a stopwatch. So before you put somebody
on opioids, you put their hand in ice, and you
check their pain.

I know you're going to cut me off soon. So
let's go to chicken and eggs. This is where the
FDA is coming from.

DR. HERNANDEZ-DIAZ: Last one.

DR. EGILMAN: This is Rappaport's slide.
This is FDA slide. This is an FDA slide.
Analgesic trials are more difficult than other
trials. It's also subjective. There's too much
placebo effect. We know the drugs work. That's
how I learned science. So what do you do with the
FDA? You know the drugs work, so you create a
study that make them work. That's an EERW [ph].

Let's go to marketing. This is your
marketing model. This is your description of what
you need to do to get information out to doctors.
This is Lucentis' marketing plan -- [mic off].
DR. HERNANDEZ-DIAZ: Thank you.

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

Since we are close to lunch time, we are going to start lunch time earlier and come back earlier later. So we will now break for lunch. We will be in here again, in this room, one hour from now, 12:40. Please take any personal belongings you may want with you at this time, and committee members, please remember that there should be no discussion of the meeting during lunch among yourselves, with the press, or with any member of the audience. Thank you. Back here at 12:40, please.

(Whereupon, at 11:36 a.m., a lunch recess was taken.)
DR. HERNANDEZ-DIAZ: Welcome back.

Dr. Sharon Hertz will now provide us with a charge to the committee.

**Charge to the Committee - Sharon Hertz**

DR. HERTZ: Good afternoon. I'm just going to go over a little bit of background before we get into the discussion. We're holding this meeting because we understand that there are many aspects to dealing with the current opioid crisis that have to be considered in a thoughtful and scientific way, taking into account many factors, including access to drugs, safety of patients, safety of non-patients, and the overall public health aspect of the drug or the drug group.

We also understand there's often an urge to do something when faced with a crisis, especially one as serious as the current opioid crisis, but easy answers are only useful for easy problems, and addressing safety concerns associated with opioids in 2019 is far from an easy problem.
It's critical for us to try and identify all of the potential consequences of any actions we take, both favorable and unfavorable. We've seen tragic unintended consequences that have occurred as a result of well-meaning efforts to manage pain and well-meaning efforts to reduce the burden of the opioid crisis.

For a period of time, there's been a failure to recognize important distinctions between patients conscientiously working with their prescribers to find a way to manage their pain, regain their ability to function in a meaningful way in their lives, and individuals who are not using opioids to manage pain but are seeking opioids for abuse.

There's also been a failure to recognize the importance of carefully managing the use of opioids for patients getting into trouble with positive reinforcing effects early after opioids, or at any point after opioids are started, so that these problems can be identified early and given the support and appropriate management to avoid further
A critical aspect of our mission is to protect the public health by ensuring the safety, efficacy, and security of human drugs, but we have to remember that no drug is safe in an absolute sense. All drugs have adverse effects. And to answer the question of whether the benefits of any given product outweigh the risks is one that must consider specific data for that product, the clinical context in which it's used, and the extent to which risks can be mitigated.

So we look forward to hearing your discussion of our questions on the topic at hand, and we plan to listen very closely to your opinions and thoughts, and we'll discuss this extensively after the meeting within our agency to do our best to meet our mission on behalf of the American public. Thanks.

**Questions to the Committee and Discussion**

DR. HERNANDEZ-DIAZ: Thank you. We will now proceed with the questions to the committee and panel discussions. I'd like to remind the public
observers that while this meeting is open for
public observation, public attendees may not
participate except at the specific request of the
panel.

We're going to read each question. I'm
going to ask if there is any problem or
clarification needed for the wording, and then
we're going to focus on one sub-bullet at a time.

The first question we have in front of us
for discussion is discuss the role of higher daily
doses and high dosage strength products of opioids
analgesics in the management of pain.

A) Discuss the settings or patient
populations where there may be a clinical need for
higher daily doses of opioid analgesics.

B) Discuss the specific clinical utility of
higher dosage strength opioid analgesic products
relative to lower dosage strength products.

Is there any need for clarifying the
question?

DR. SPRINTZ: [Inaudible - off mic].

DR. HERNANDEZ-DIAZ: Yes.
DR. SPRINTZ: Do we have a specific definition for higher daily dose and high dosage strength? Is there a specific number or definition for that on which to base our answers?

DR. HERNANDEZ-DIAZ: I guess that can be part of our discussion, but -- that can be part of our discussion.

Thank you. Please be aware that we will have time to discuss adverse effects. We are focusing on efficacy, effectiveness, for this first question, and A relates to daily doses; B relates to higher dosage strength opioid analgesic Isaac products.

Let's take the discussion for A, discuss the settings or patient populations where there may be a clinical need for higher daily doses of opioid analgesics. Now, we are open for discussion.

Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. Based on what I heard in the last two days, I would say there seems to be a greater need for end-of-life care use, the palliative care population. Perhaps
older adults, again, that has problems associated
with it. But it was clear that disorders of the
nervous system and joint conditions also appear to
be populations in need.

DR. HERNANDEZ-DIAZ: Dr. Sprintz?

DR. SPRINTZ: Hi. Michael Sprintz. My
first question is what are we defining as high
daily dose? I've also heard the term "ultra
high-dose opioids." I don't know how that is being
defined and how are we defining high dosage
strength, because I know that in our initial
discussions, high dosage strength was arbitrarily
used at a single tablet or pill and had an MME of
90 morphine equivalents or greater. That was the
defining thing. And then at other times, we heard
where we were talking about a high daily dose, and
it was based off of CDC guidelines of 90 morphine
equivalents per day. So I just wanted to get some
clarity on that.

As far as conditions, active cancer,
hospice, there are rare pain conditions that we've
seen where opioids are appropriate. In some of the
instances, I've seen it with some patients in trigeminal neuralgia. We see a lot of CRPS patients as well.

Also, the way that I looked at it is conditions where comprehensive pain management are in use, and ultimately inadequate, and these should always be done within the context of also adding behavioral health therapy in it as well. That's something that we do in our own practice in-house because chronic pain and opioid use -- pain's an experience. It's physical. It's psychological. It's emotional. It's synergetic. It's all of those things. So we can't just treat the physical without treating the emotional and psychological aspects of things.

DR. HERNANDEZ-DIAZ: Dr. Mackey?

DR. MACKEY: Addressing the question specifically, I think other members of the committee have mentioned the low-hanging fruit, which is cancer and end of life. I think that's an easy group to point to. But just to amplify what was said before, I think those people who have
failed comprehensive approaches, including behavioral, physical, other pharmacologic procedural self-management, there is a subset of people who, we've heard and in my own clinical experience, have benefited from long-term, even higher dose opioids who have remained highly functional, who behave themselves and don't experience adverse events.

I think that issue about not displaying adverse effects and not displaying maladaptive behavior also fits within the appropriate setting here that we're discussing.

DR. HERNANDEZ-DIAZ: I want to remind you to state your name before you speak. Mr. O'Brien?

MR. O'BRIEN: Joe O'Brien. I guess I'd answer the question first by way of disclosure. Personally, in December of 2017, after my sixth spinal surgery, I came home on approximately 450 MMEs, opioids. I am now, a year and a half later, tapered down to 105 MMEs.

I would say what we did learn at this meeting was that, yes, we had the cancer patients
and hospice patients, but clearly we saw evidence of the musculoskeletal patient community, which is the community that I am more familiar with. And clearly within that community, there is a large chronic pain community and obviously acute pain community as well. But in a chronic pain community as well, that does exceed the 90 MMEs per day, based on their anecdotal discussions with us.

So I would say that is a population that is managing and seem to be behaving well with that, and that would be included in that category.

As to the higher dosage unit, the pill itself, I think that can be a discussion, that it's not necessarily -- because most of the patients -- yes, it is usually forced upon them, in many cases where there's policy, because of the number of pills. So if you have a smaller dosage, the number of pills is too high, so you're guided to a higher pill because it's smaller number of pills, and it gets by.

So that's usually by that. I don't think it's necessarily patient desired to have a larger
pill on there, when you really get into the 80s and 
higher on that. I think the 20s or 30s are 
probably the common one, that they can do multiple 
pills on that.

DR. HERNANDEZ-DIAZ: Thank you. Ms. 
Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. First, 
a quick question for Dr. Hertz or Dr. Staffa. Does 
the FDA have the ability to tell pharmaceutical 
companies or distributors that they should not put 
a limit on how many pills? The issue that 
Mr. O'Brien was just talking about, is that a 
fixable problem through you?

DR. HERTZ: No.

MS. ROBOTTI: Okay.

DR. HERTZ: My understanding is the 
organizations that put limits on what can be 
dispensed for individual products, first of all, 
it's not us. And I think there are many different 
Sources of that. It could be many different 
authorities that are implementing policy. But no, 
we have no ability to impact that.
MS. ROBOTTI: Okay. Then as a comment, I have not seen clear studies, convincing studies, that high doses and low doses, that one is better, one is safer than another. But I also haven't seen clear and compelling evidence that opioids work better than alternative integrated comprehensive behavioral therapies when combined and used appropriately.

I'm not trying to say that they would or they wouldn't, I just think that that should be studied because we didn't see any efficacy studies here. We simply talked about abuse and all that. And we also didn't talk about the adverse events of long-time stable use of opioids. Is there a detrimental effect over the course of 10 years, 20 years, 30 years? So those are more the questions I have than a comment.

DR. HERNANDEZ-DIAZ: Thank you. Maybe for I think a very important question is, is there scientific evidence or formal studies looking at the efficacy of giving higher doses versus lower doses or versus alternative therapies, a
combination of things?

I think it was mentioned that there are some efficacy studies for opioids overall and there is data on adverse effects of higher doses versus lower. I don't think there are formal studies, even we have listened to specific patients.

Is anybody aware of formal studies showing for pain that higher doses are better? We saw some evidence presented by the speakers yesterday, where they were successfully -- like were able to lower the doses for a sample of patients and maintain the pain under very controlled circumstances. That's all I heard yesterday, but I might be missing.

DR. SPRINTZ: If we don't have a definition for what higher dosage means, how can we say whether we've heard of studies or not? That's part of the problem.

DR. HERNANDEZ-DIAZ: You say higher dose versus lower is a different -- [indiscernible] on the label. But yes, lower than higher --

DR. HERTZ: This is Sharon Hertz.

DR. HERNANDEZ-DIAZ: Yes, please?
DR. HERTZ: Why don't we focus on, when we're talking about higher dosage strengths -- I'm just going to put this out there to give people an anchor, and you can disagree with what I'm about to say and define what you think is appropriate and how it works for your statements.

For those who don't have a particular set of numbers in mind, perhaps one thing would be to consider 90 MMEs per day or individual dosage strengths that require opioid tolerance. So it's going to differ based on the product and the potency of the individual products. Some dosage strengths and some entire product lines are only indicated for people who are already tolerant to opioids, not people who are new to opioids.

Does that help? It's not a fixed number, but it's one way to look at it.

DR. HERNANDEZ-DIAZ: I think it is going to work. So it's going to be -- I'll retry, but 90 has been used. And unless there is a problem with 90, we can use as a reference 90, too, or doses after tolerance.
DR. MEISEL: This is Steve Meisel, a clarifying question. Are we including in this higher dosing strength product the concentrated liquids? Would that be considered part of a high dosage strength for our conversations?

DR. HERTZ: Yes. Some of them are quite highly concentrated and can deliver 90 MMEs per day without a great volume.

DR. HERNANDEZ-DIAZ: Let's focus on the daily doses, and then we'll discuss the formulations with high doses.

So the question for discussion was is there scientific evidence to support that higher doses, say over 90, are more efficacious than lower doses for pain, versus lower doses or versus alternative therapies?

DR. HERTZ: I would like to clarify, the question is more of a clinical need question as opposed to evidence from data, because what we didn't focus on was a complete review of efficacy studies because there is a lot out there.

I think that what we're trying to focus on
is if we're thinking about any kind of efforts that might have an opportunity for us to take action on these products, what would the potential impact be? And one consideration there is if there is a clinical need that you've heard expressed that you think is appropriate or not appropriate. That's sort of what we're trying to get at.

Is there a clinical basis? That's why we have asked clinicians to speak, and we have clinicians among others on the committee. So it's really more about that.

DR. HERNANDEZ-DIAZ: Okay. So based on the clinician perspective and on the patients that we have heard, can we identify a clinical need, based on what we have discussed? Dr. Zacharoff?

DR. ZACHAROFF: Hi. Kevin Zacharoff. I happen to be of the mindset that I'm not necessarily willing to define high daily dose as 90 because I think it was a fairly arbitrary decision. But I am willing to think about some dose that I would consider high.

So with respect to 1A, I define someone
who's already on an opioid as opioid experienced.
I worry when people use the phrase "opioid tolerant" because tolerance means that there's a
state of adaptation that has developed as a result of the liver or whatever means of metabolism
ramping up to deal with the load.

So from an opioid experienced patient population, I would definitely think there will be a clinical need for higher daily doses the longer the person is on the opioid analgesic. Not true for all opioid analgesics because not all opioid analgesics are metabolized the same way, and hepatic enzyme induction doesn't necessarily play a role. But in any patients who are opioid experienced, I would expect that there would be a likelihood for the need for higher daily doses the longer the person's on the medication.

Additionally, we heard data from the VA system yesterday about the fact that there could be patients who are initially opioid naive, then become opioid experienced, and then after being weaned and discontinued, they actually are
considered to be opioid naive again, which I would agree with.

So I would say that the opposite of a patient who's on chronic opioid therapy where there may be a need for higher daily doses is somebody who's been weaned or who is opioid naive. I would not consider that to be an appropriate person who is a candidate for higher daily doses.

In terms of the diagnoses, I don't know that there was a lot of data presented yesterday to give us an indication of what specific patient populations. I often hear cancer come up. I think about the CDC guidelines, which are intended to be directed towards people managing chronic non-cancer pain in a non-expert healthcare setting. That's my interpretation of the CDC guidelines, that they were not intended to be guidance for people who are in expert clinical settings.

So the way I interpret 1A is the clinical settings, where the expertise of the clinicians matches the risk profile for the use of higher daily doses is where I would consider those higher
daily doses to be appropriately used.

    CDC guidelines, people who aren't of a high
level of expertise, probably not a good idea,
regardless of what you define as a higher daily
dose. But certainly in an expert level setting, I
would consider there would be a host of a number of
medical conditions and patient populations where it
would be appropriate.

    I'll just close with respect to the cancer
issue, and that is having done work with a lot of
cancer centers who do consider risk stratification
to be an important part initially of treatment,
that more and more cancer patients are surviving
their cancer diagnosis, and they're going on to
suffer from chronic pain as a result of the
disease, the treatment, or both.

    I think it begs the question that we need to
consider when we think about patient populations is
when is a patient with cancer-related pain no
longer a cancer patient with chronic pain and vice
versa? So I think there's a whole host of
surviving cancer patients with enduring pain that
could also be considered to be appropriate patient populations. Thank you.

DR. HERNANDEZ-DIAZ: One follow-up or clarification question. I think one important point for our discussion is the differentiation between naive opioid users, initiators, and the opioid experienced or long-term patients that are tapering the dose, increasing, or maybe we can discuss later decreasing the dose, so that we discuss or highlight even better, or more, the clinical need for initiating opioids at high doses, if any, versus opioid experienced patients.

DR. ZACHAROFF: Yes. I think most importantly, I don't consider opioid experienced to be equal to opioid tolerant. I actually interpret opioid tolerant as somebody who's developed a tolerance to opioids and may need increasing doses. Just because just because you're experienced doesn't mean you're going to be tolerant.

DR. HERNANDEZ-DIAZ: The clinical indication of high doses for opioid-naive patients, could you say --
DR. ZACHAROFF: No. I don't think -- I thought I made that statement. But no, I do not consider high daily doses or high doses strengths appropriate for opioid-naive patients in any situation.

DR. HERNANDEZ-DIAZ: Dr. Jowza?

DR. JOWZA: Thank you. Maryam Jowza. I think for the sake of discussion, we could be talking about a couple of different things when it comes to point A. One is the clinical utility of the higher dose opioids. Then I think part of what is maybe a little bit of confusion in our minds is are we talking about any clinical utility, using it acutely, for example, for someone who has experience with opioids, has a degree of tolerance.

So in that setting, when a patient goes to have their gallbladder out or has a broken hip, of course there's going to be clinical utility to use something in the acute setting.

The second part of it is using it chronically and long term to bring the patient to the point where they become tolerant. I think that
that's a different discussion and that's a different issue. Based on some of the comments that I've heard, it seems like we're a little bit unclear about which part of it we should be focusing on. That's all.

DR. HERTZ: This is Sharon Hertz. Focus, really, we don't want to limit the focus. Like you've described a situation, that's what we want to hear. Do you think there's a clinical setting? Do you think there's a need? If you do, what does that look like to you? Perhaps if you think there's a specific of where it should be avoided, feel free to comment on that as well.

DR. HERNANDEZ-DIAZ: Dr. Nelson?

DR. NELSON: Lewis Nelson. I have a few thoughts. First, I think it's really hard to answer the efficacy question in a vacuum because it really does become a risk-benefit or a value question. I realize we're addressing simply efficacy here, but it's very unbalanced and unfair. I also think that it's a hard question to answer on an individual patient level simply, and it has to
be looked at, at an epidemiologic and public health level as well.

With that preface, I would take a fairly strong line and say that the only people in my mind who should be on high-dose opioids are people at the end of life who are really suffering. I think that anybody else, the decision to use becomes a very slippery slope.

I understand the difference between primary care doctors and pain specialists, and I understand that every patient who has chronic pain believes that they have a legitimate chronic pain and they deserve or need to be on high-dose opioids. But again, if you look at this from a public health perspective, it's really not an adequate answer.

We know that chronic pain is not just acute pain that lasts a long time. It's a different physiological process, and I think we have to treat them differently. I don't think anybody would disagree that opioids work well for tooth pain, and they're probably arguably the best drug that we have, although obviously not the first line for
almost anything. But for chronic pain, I think there are just far too many problems that we see with their use for whatever neuropathic or any other sort of indication that we've come up with.

It's both at an individual patient level when you look at the issues with addiction and overdose and other things, and the persistence of chronic pain, whether it's related to hyperalgesia, or tolerance, or other adaptations, it's not clear. But the slope is just far too slippery for me, and we just see too many problems on an individual patient and a public health level.

To that end, I think the pharmacology of the drug doesn't really make sense to be used chronically. Tolerance is a real issue. There's really no reason why if you start at 10, and go to 20, and then to 40, 40 should be enough. You should go to 80, and 120, and you should just go forever. Tolerance, you shouldn't just stop adapting, and that's just normal physiology.

So it was never clear to me, and I'm not going to ask why in this meeting, why some people
feel that they stabilize at a certain dose, and I wonder if it's more than simply the opioid at play. We need to explain these things to me in order for us to better understand how opioids could be used because when you balance it against the risk, which I know we're not talking about, it becomes an untenable position for me to take.

When it comes to the high dosage strength, I see absolutely no reason we should have them. If you feel the patient should be on them, that's a decision that's between a doctor and a patient. They can take multiple pills, take a liquid formulation, get it compounded, do something else, but the general availability, just again, it can't be simply an efficacy question. I think you have to look at it on a public health and an individual risk basis.

I just don't see any specific clinical utility for high doses because, again, high doses are just little doses added together, and there's no reason we just can't take little doses added together.
DR. HERNANDEZ-DIAZ: Thank you. Dr. Becker?

DR. BECKER: Will Becker. Addressing question A, I want to just echo end of life and want to underscore that having cancer doesn't mean you're at the end of your life. Also, there are many conditions that are painful at the end of life other than cancer, where high daily doses of opioids are very appropriate in my view.

The second setting where there's a clinical need is for patients who have already been put on high doses. I would agree through the lens of 2019, there were patients who were started on high-dose opioids for, let's say, chronic low back pain, even 10 years ago; folks, I started on high dose -- or eventually got up to high-dose opioids for chronic low back pain that I would not do now, knowing what I know now.

However, if there's a patient who has reached those doses, and I need to work with them to assess the risk and benefit, and to work with them to lower the dose if benefit is no longer outweighing harm, then I'm going to need to
prescribe them high-dose opioids in that process. That is a clinical need that we can't ignore. These have been referred to throughout the last couple of days as legacy patients. We do need the ability, in my view, to prescribe high-dose opioids to those folks so that we can start the process of working with them to get them to safer places.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Litman?

DR. LITMAN: Thanks. Ron Litman. We wouldn't be here if there was this dilemma of how to balance the people that need the high doses versus the public health. I want to throw my hat in the ring of the experts who think that there is a need in some people. The problem, though, besides the public health issues that Dr. Nelson mentioned, doing efficacy studies are really -- the kinds that the FDA requires like prospective are nearly impossible to perform. We have to take the word of people who require them.

I do believe that there's a subset of those patients, that there are hyperalgesia issues, and
it is very possible that if you did a randomized study where you randomized one arm to, say, other modalities like physical therapy, that it will result in success, but in the long term. The short term is really scary with a lot of pain and suffering.

So we'll just stick with A, and I will say that there are patients I'm convinced that need high daily doses, and the FDA really shouldn't and cannot put any kind of caps on that.

DR. HERNANDEZ-DIAZ: Thank you.

Dr. Katzman?

DR. KATZMAN: Thank you. I'd just like to say a couple things. I work in a large chronic pain center for the last 10 years. I think I'm in the same mindset of Dr. Mackey, and Dr. Sprintz, and Zacharoff, and Litman, that I do think there is a subset of patients that if they have severe chronic pain where they have not responded to smaller and medium dose opiates, -- and the higher doses of 90 is what we used to think of as actually fairly moderate doses, so I'll just put that out.
there -- have not responded to rehabilitation and behavioral health, and are actually still doing that rehabilitation, behavioral health, and self-care, and all the things they need to be doing, and are being effectively screened for addiction on an ongoing basis, and have adequate family support, in many situations they do need to be on higher doses.

These are patients with maybe CRPS, arachnoiditis, a gunshot wound to their head, and severe thalamic pain. We see these patients in the dozens on a weekly basis. You need to be in consideration that in many states, such as New Mexico, most of America live in rural towns and communities. Even patients getting into a pain center, they might be able to have a consultation once or twice, and then they revert back to their hometowns. But if they can into a consultation for a short time, that would be beneficial.

I agree with Dr. Becker wholeheartedly that there are these three groups right now that we have to be extremely mindful of. There are patients in
this country that are on high doses or what we are
now calling very high doses of opioids. What we've
seen is that the vast majority of them are taking
care of themselves and taking care of their
families very well. And unless the taper is coming
from them, as Dr. Darnall said eloquently
yesterday, it can be very tenuous how that
de-escalation, if it's successful or not, and the
risk can be as devastating as a suicide. So you
have that bucket of patients.

Then you have new chronic pain patients.
What we've seen from studies from the VA, from
Dr. Sandbrink's talk, is that the VA has done an
amazing job at not starting new chronic pain
patients on opioids; on dropping the morphine
milligrams equivalents up to 80 percent; and on
decreasing the co-prescribing of opioids and
benzodiazepines by up to 60 percent.

So we can do that through education, and
we've seen that with our Army and Navy ECHO pain
program, almost the exact same curves downward, not
quite as much, but through effectively educating
clinicians in pain management, and specifically
pain management by giving them tools.

Then the third category -- and this is where
the need for the high daily doses of opiates comes
in, the first and the third category -- is that
there is a subset of new chronic pain patients,
that you give them the behavioral health, and the
physical therapy, and the adjuvant medications, and
the nonsteroidals, and they still need to be on
opiates; and not just small doses and medium doses
of opiates, but they do need the high doses of
opiates because their pain is so severe that they
haven't been able to respond to even a coordinated,
interprofessional, interdisciplinary approach, and
they do need this for a quality of life. Thank
you.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Goudra?

DR. GOUDRA: Basavana Goudra from Penn
Medicine. I kind of agree with my colleagues,
which is that there shouldn't be an arbitrary limit
on the amount of opiate prescription, and the
reason is this. Those who are anesthesiologists
see what's called variability, which has been mentioned forever in the anesthesia literature, all the time, including patients who are opioid naive.

I had patients who required -- just an example, for example, I do endoscopy anesthesia all the time who require, just to give you an example, propofol, because that's what we use most, but pretty much the same thing applies to opiates as well.

I might have an 80 year old who requires 20 milligrams and stops breathing. There could be the same who requires 100 milligrams. The same thing applies to opiates. Some patients require massive doses for the same surgery, those who do not require much, and some nothing.

We don't know the brain chemistry and we don't know the metabolism. Cocaine is a classic example, which is affected by this kind of a hepatic metabolism. As a result, we really don't know. When some of the patients represented, you say their relatives require big doses, I believe them. It's possible.
So as a result, my opinion is the problem is far bigger than just putting a limit on the doses. It's much more than that. I guess that's what we're discussing here.

DR. HERNANDEZ-DIAZ: Dr. Garcia-Bunuel?

DR. GARCIA-BUNUEL: Good afternoon, Martin Garcia-Bunuel. With permission, is it possible when I make my comments, if you can put Dr. Eggers' slide number 9 up as a reference point? I do that as an opening to my comments; one, I appreciate that slide, given the complexity of the issues that we're trying to grapple with.

I also want to make sure I'm trying to make myself useful for the committee and for everybody, and try to speak as a primary care physician most of all, but also reference the fact that I do work in a system. I work in the VA system.

In some ways, what I like about this and to make comment on, is it's very important for us to appreciate that as we discuss this, the VA system, Kaiser, other integrated systems throughout the country, we do have the luxury of being able to
appreciate and potentially impact the influences on prescribing.

Having said that, for 1A, what I was looking at is the oval of prescribing practices. For primary care, what I think we've observed is when we introduce a pharmaceutical agent into the healthcare system, in many cases, especially if we're talking about outpatient care and if we're talking about the treatment of chronic pain that's occurred over the last 10 to 15 years and the changes in practice, that is where a lot of the supply went. It went into that oval, and it was distributed by primary care physicians, primarily.

If you look at prescribing patterns, still, a lot of these medications are still being prescribed by primary care, and appropriately so in that my colleagues who do this as a subspecialty, there isn't the capacity to be able to provide that level of care for every patient.

So having said that, I don't think that primary care is the appropriate setting, though, to be prescribing ultra high or high doses of opioids
in general. The reason I say that is I think, one, that's how we got here. We created a tremendous supply of this medication. We created an expectation of prescribing, and that rippled down right onto the level of primary care, where it was incumbent upon us to meet that expectation; and we responded accordingly, and now we ended up with thousands of patients who had tolerance and required escalating doses.

Where I'm getting back to that as in agreeing with Dr. Zacharoff and others, is we need to have access for patients to high doses of opioids who are being taken care of by people who have the expertise. For the non-experts, for the many of us who are non-experts, we have to be careful of what we supply for prescribing.

If we create new high-dose formulations, fancier high-dose formulations, those that are proprietary and expensive, they will make their way in. They will be used by some who have the expertise, and then they will end up rippling down into the primary care world, and we will then be
faced with an ongoing crisis.

From an FDA perspective, I don't know, when we look at that diagram and I look at your box there under regulatory action, how you can consider these things, and how it can then have that downstream effect, both positive or negative.

One comment I will add on your diagram, Dr. Eggers, which I kind of put in my mind, in my mind, there's another influencing factor, another oval, which is industry and the pharmaceutical companies. They are a big influencer, and I wouldn't put them as just a byline. But I think you really have to consider that because that's where you do have a lot of influence.

Once you engage industry and new product comes, and new product is developed, that's a huge influencer and that ripples through. So I think you have to include as its own influencer. Then the other thing is the payer system. Once again, the VA, we have the luxury of not having that influencing model, but that is, I would say, another influencer.
So long answer to 1A, but I'd say definitely got to have the access for patients who need those medications. I think, as others have talked about, legacy patients, patients in special situations, that can be overcome by good doctor-patient relationship and multidisciplinary care. But we have to be careful that we don't let that amplify out into the prescribing world of primary care because that is an amplifier that we already know has become way too dangerous. Thank you.

DR. HERNANDEZ-DIAZ: Thank you. I think we can come back to number 9 and putting the other two players at the end for recommendations. So we'll be back.

Dr. Hummel?

DR. HUMMEL: If I could just share my thoughts with regard to the question, A in particular. I think there are a number of instances where settings in both patient populations, where high dose of opioids are necessary. I'm not a clinician, but I've spent 25 years of my career working at a rehab hospital in
Philadelphia.

Typically, the patients that come in have suffered from traumatic brain injury or stroke. These patients are confined to wheelchairs. Their conditions do not get any better. They're pretty much confined to wheelchairs throughout their life. And because they're working there for so many years, patients come back and forth to the hospital.

The doses of opioids do increase with time. We know that because of issues of tolerance. There are also the practical issues of patients being confined to a wheelchair, so they have muscle loss, atrophy, and time. Basically, it's bone on bone, so you're not only addressing the traumatic brain injury being associated with that, or their stroke, but now you have other conditions that develop with time.

Patients obviously live longer. They're living longer in a wheelchair now. I can say this from personal experience with my mother, she too suffered a stroke. My brother and I took care of
her for 16 years. She was in a wheelchair with left-sided paralysis. She had phantom limb pain.

There is an issue with pill burden as well. My mother had psychiatric issues from the stroke. So not only did we have to get pain medication in her; we had to get blood pressure medication in her. We had to get anti-seizure medication in her. What are pills in her? For people that are caretakers, pill burden is a significant issue. To try to get someone to swallow 15-16 pills in a day is difficult. It's a practical issue that I think needs to be addressed.

So I for one believe, just based on my experience, my professional experience but also my personal experience taking care of my mother for 16 years, that, yes, certainly high doses of opioids are needed.

DR. HERNANDEZ-DIAZ: Thank you. Dr. McCann?

DR. McCANN: Just first, a clarification. Are we answering 1A and B or just 1A?

DR. HERNANDEZ-DIAZ: 1A.

DR. McCANN: Oh. I want to do 1B.
(Laughter.)

DR. HERNANDEZ-DIAZ: Okay. You will be first for 1B.

Please as a reminder, state your name when we call upon you. Dr. Zivin?

DR. ZIVIN: Kara Zivin. I am not a clinician. My expertise is in health policy and epidemiology, but I appreciate, from working in a health system for my career and being around, studying this, especially in behavioral health populations, that there is clearly some clinical need for a high dose use of opioids as we've discussed already.

I think one issue that I found interesting and useful from the briefing materials and discussion yesterday was the note that despite we are very concerned about these high doses, that it's actually a very small fraction of the opioid-using population that is on these high doses, with the understanding that the definition of high dose is still a bit in flux. But it seemed to be about 1 to 2 percent of opioid users who are
taking opioids at that dose.

I think when we try to consider potential policies or other actions that the FDA could take around addressing this issue, it's important to remember that there are both unintended and intended consequences for any decision that we might make, as we all know; and that both overuse and underuse can co-exist at a population level. Trying to figure out how best to make sure that those who need medication can get that while keeping it out of the hands of people that don't, I believe is our challenge.

Again, I go back to this issue of a relatively small amount of people who may actually need it are on high doses. Thanks.

DR. HERNANDEZ-DIAZ: Thank you.

Dr. Sprintz?

DR. SPRINTZ: Hi. Michael Sprintz. I have a couple thoughts as I was thinking about as everyone was talking. One of the first things, I appreciate Sharon's comments about this problem being a complex problem. It really, really is;
that doesn't have a simple answer; and ultimately requires a systems level solution, which ultimately will require commitments and alignment of interests of all stakeholders, which as we know is really challenging.

At the same time, I agree with my colleagues, Dr. Zacharoff, Litman, Katzman, and Mackey, that we need appropriate -- we want to -- these medications should be prescribed by appropriate physicians with appropriate expert level specialists. I also appreciate that we're not everywhere, and it's very hard sometimes to have an expert level person there. Those are challenges that we have to continue to work to solving.

That being said, I'm also an addict in recovery, and that included opioids. So I appreciate the issues of those, and I'm very respectful of people who've lost someone they love as a result of this disease. I have lost people myself. At the same time, I treat patients with chronic pain, and some of them have substance-use
disorders and some do not.

So for patients where we're talking about high dose, I don't think I said it the first time, but at my practice, we screen all of our patients for substance-use disorder, and our patients should be effectively screened for risks with substance-use disorder. If we find them, if possible, refer them to an addiction specialist, an expert level specialist in that area.

Finding someone who has both expertise in chronic pain and addiction, unfortunately, is really rare, and it's hard. I know Dr. Katzman worked on a telemedicine project, the ECHO project, that helped to train people at a distance. So there are solutions that are coming around to help solve those problems, but I agree there's a lack of expertise in both areas that cause part of the problem.

Then ultimately, we really have two goals. One is preventing exposure of new pain patients to the risk of developing a substance-use disorder, but at the same time effectively managing their
pain, and then identifying and helping patients who have substance-use disorders already with chronic pain. In those contexts, I think there are reasons for the high-dose strength, but how it is delivered is definitely something that we have to be much more cautious and careful about.

DR. HERNANDEZ-DIAZ: Dr. Mackey?

DR. MACKEY: Sean Mackey at Stanford. In the spirit of what Sharon said earlier about this being a complex issue and we need to take into account the consequences of it, I submit that if we're going to have this discussion, we need to run the counterfactual on this question, which is if we or if the FDA chose to limit these daily doses, these high-dose opioids, what are we going to do with the patients if we do limit that?

I appreciate that we can reduce these opioids. Dr. Sandbrink showed some nice data showing they can take patients down. And I think he said those were clinician-directed efforts at reducing patients. They can wean the doses down, and other groups have shown that. But at what
cost? At what cost? We don't have the data on their quality of life. There's some intriguing data coming out around the increases in suicide, but the data hasn't been published. So we really need to understand the implications of these actions to a much greater extent.

Then getting back to the point, if we reduce -- and again, I appreciate the public health consequences of this, I really do, and also the personal consequences of it that I've lived with through my family. But if we reduce, what are we going to do with these patients?

I oversee one of the largest interdisciplinary pain programs in the country. I've got every resource you can imagine; COG -- I'm not going to list it, every resource you can imagine. And I'll tell you that they're all very helpful tools, but if we take a number of the patients that we care for off the high-dose opioids, those tools are not going to address the problem.

So I implore us to consider the patients out
there and what we will do if it's reduced. We cannot abandon them. We have to have solutions in play to address this issue if it occurs.

DR. HERNANDEZ-DIAZ: Dr. Becker?

DR. BECKER: Will Becker. I think we're starting to mold in the issue of what is the right setting, which is part of the question, so I'm glad to hear that. I do want to make a strong statement of advocacy for real meaningful access to addiction treatment. So often, it's considered as part of, well, you know, if this were to develop, we'd refer someone somewhere.

This is a known complication of this drug. I would advocate that anyone who has a license to prescribe high-dose opioids, there'd be a mandate that they'd also be certified to prescribe buprenorphine; so something bold to really bring the access to addiction treatment to the front and center because that's been a missing piece for a long time. When we use medications that have high risk of addiction, as these are, and we don't have meaningful access to the treatment, it's really a
disservice to patients. Thanks.

DR. HERNANDEZ-DIAZ: Dr. Nelson?

DR. NELSON: Lewis Nelson. I just wanted to follow up on some of the comments that have been made. I really am a little concerned about a chicken and egg question. Are people on opioids because they have chronic pain or do people have chronic pain because they're on opioids?

Obviously, based on my comments, I think you know where I stand. I think hyperalgesia and tolerance and a lot of these other things, and the subjectivity of pain in general, are probably what's led to a lot of high-dose opioid use. Then it's a self-perpetuating problem, which is sort of where we get to where we are today.

So going back to the settings and patients, I know there's been a lot of comments about people who are on high-dose opioids already. In my earlier comments, I didn't mean to exclude those people. We can't just stop them from being on their opioids. I don't doubt that. I think my comments are focused on the new initiate, so to
There's sort of a lost generation here of people who we have to deal with in, whether we choose to keep them on opioids, or taper them down, or put them through some of, quote/unquote, "addiction treatment model" to get them on buprenorphine and off opioids. It's a totally separate issue.

The one thing I also can't get by is the fact -- I thought Dr. Garcia-Bunuel's comments were right on, which is that the vast majority of prescribers of opioids in the country, for chronic opiate therapy, are primary care providers. There are a tiny number of pain docs.

If we're going to say -- and I appreciate the idea that we shouldn't have the average doctor prescribing these medications to people and send them all to pain docs. There aren't enough pain docs who do this. You're going to have to add tenfold number of fellowships in order to do this. So the practical reality is that's not going to happen.
There is always also the specialty bias that you'll often hear about, which you hear about in a lot of these meetings, where everybody thinks that they can manage these things. And I don't doubt that you can, but my slippery slope comment matters, too, because, obviously, a pain doctor is going to do things that pain doctors do, which is what you're trained to do and what you're supposed to do. But I still think we need a critical look at whether or not it's the right thing to do, which is a much bigger question they're going to have to hear.

But the practical limitation is we can't get these people to pain docs. They're going to be managed by primary care docs for the foreseeable future. I don't even know if there's a way to limit the use of these medications only to pain docs in any real way, so it's not going to happen. It's a great concept, though.

DR. HERNANDEZ-DIAZ: Dr. Jowza?

DR. JOWZA: I am a pain doctor. I work in a state hospital. We see a lot of patients who have
chronic pain. And I've inherited a good number of them who are on high dose, ultra high dose from some of my colleagues who have retired. I'm just coming into that practice, and then I have my own new patients that started to come in.

The high-dose and ultra high-dose patients, I do have to say are not doing any better than my own patients that I've started on. I usually have a very frank conversation before starting a patient on an opioids. I tell them, despite what you see, the sky is not the limit in terms of opioid analgesic effect. Maybe it is in acute pain but not for chronic. I think that that's the problem that we've run into with having these patients on high-dose opioids and why they always will continue to hurt.

I do also think that, over time, probably related to some of the hormonal changes that happens or mechanisms that I'm not entirely clear on, despite the pain, there are some psychological changes that push the patient towards more of the depression part of the spectrum than anything else.
I think that that's -- I don't have data, but just from my clinical experience -- largely related to the opioid effect and not just the pain effect.

This is my long-winded way of saying for patients who I've inherited who are on high-dose opioids, I have a hard time weaning them. There's a lot of pushback. There's no voluntary weans. The data that was presented by the VA, I found incredibly amazing and also have a very hard time to reconcile with what I see in my clinical practice, which was an onslaught of patients, who previously got their care from the VA on high-dose opioids, now going through their other insurance in order to get care and to get someone to take over their medications. That's the one caveat. So when someone is up at a high dose, good luck trying to bring them down. It's not going to happen unless they want to do it.

The second part of it is, if someone hasn't been started on a high dose and I'm starting it, I put a limit on it. We do opioid rotations. We dose decrease. And I say I'll might do maybe one
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or two escalations. There's a limit to how high we will go, because if you're not better on 200 MMEs -- and I'm just making that number up -- what's to say you're going to be better on 400 MMEs, or 600?

I actually firmly believe that there is opioid-induced hyperalgesia. There's good clinical evidence in favor of it. I think there's anesthesia literature that it happens very quickly with remifentanil infusions, so after just an anesthetic. For that reason, I personally have a limit to how high I'll go up on somebody.

I tell them from the get-go, before I even write the first prescription, if we get to the point where we go up to the limit and you're still hurting, and you're still hurting and you're not able to do what you want to do, I'm going to start weaning you, and we're going to take it off for some period of time, just to set the stage.

I think it's a hard conversation to have, and I think in a primary care setting, it's also even more difficult. I don't know if there's a way
to make some sort of regulatory change or
recommendation to have something like that happen
more often, because I do think that pain treatment
across the board in someone who is on high doses
and is hyperalgesic it's nearly impossible.

The options, there are no good options.
Everyone talks about the multidisciplinary,
multi-modal treatments, which is great. But if the
co-pay for oxycodone is $3, but their co-pay for
physical therapy is 70 [dollars], what are people
going to want to do? That's it.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Hoffer?

DR. HOFFER: Just a quick comment. I think
also the environment we need to consider here, too,
because the patients that are -- and I'm not a
clinician. I work with people who are actively
using primarily opiates in a street-based setting
or in their homes.

Where they go when they're tapered or
they're cut off by their physician is to me, to my
studies. We see them all the time. People are
deadly afraid of coming off those high doses. Once
that starts happening, they wig out. Why I want to mention the environment is that it's very easy for people to make these switches. You think, well, how can they find heroin? They find heroin through the same people where they find fake pills from or pills off the street.

So I think that these transitions are very, very easy for people that are in this position where they feel like they have no options.

DR. HERNANDEZ-DIAZ: Thank you. I think I will try to summarize 1A.

(Laughter.)

DR. HERNANDEZ-DIAZ: In one sense, I think we agree on a couple of things, and in others, there are just different opinions, so I will just say a combination of things that you all said.

I think we will agree there is no indication for initiating patients, opioid-naive patients, at very high doses, but that there is a clinical need for high daily doses for very specific patients that represent below 1 or 2 percent of the opioid users. That is end of life, hospice patients, and
cancer treatment patients, with a discussion that now cancer patients have longer term survival, increasing doses due to their endurance of cancer. So it's not the same as end-of-life treatment.

Then there are other conditions that were discussed, like acute sickle cell crisis, some neurological conditions like trigeminal neuralgia, and some musculoskeletal conditions. There is some severe chronic pain that was discussed as well that is not responding to lower doses, to rehabilitation, to behavioral health, et cetera. With the appropriate screening for addiction, and if there is family support, these patients may also need higher doses.

There was also mentioned patients on wheelchairs that have been getting higher doses due to tolerance, but lowering their doses can really impair their quality of life and deteriorate their condition. It was emphasized that it might be indicated for people who had failed other approaches, so that we have to try first other things, including behavioral and psychological.
approaches.

The second group of patients that was discussed was the legacy patients, patients that are already on high doses, in part, because of the problem we have created, and we cannot abandon them now. Now we have to work with them, trying to lower the doses if they are on higher doses, if possible.

We discussed that unless the tapering is coming from them, it can be risky to raise the dose, and the risk can go all the way to suicidal ideation and suicide if there is anybody misinterpreting the guidelines and doing rapid forced opioid tapering that can destabilize patients with chronic pain, and precipitates opioid withdrawal and enforcing [indiscernible] pain and loss of function.

We discussed how doses can be reduced. We have seen some data, but it is really difficult and we have to wonder how at what cost for these patients and how their quality of life can be affected.
The third group of patients we talked are patients that do not respond to a coordinated approach and need to maintain their quality of life. We also said that in order to consider higher doses, we need to make sure that the patients are not displaying adverse effects or behavior. For example, patients that have been at already high doses and trying to identify high-risk patients for addiction or overdose.

Then we had a discussion about the setting, that, ideally, the high doses should be used only at an expert clinical setting where the expertise of the clinicians matches the risk profile of the high daily doses. That includes meaningful access to addiction therapy. Prescribers of high doses need to also be comfortable using buprenorphine, and we might want to stay away from the primary care setting because that took us to the current crisis of thousands of patients with tolerance and escalating doses. High doses might not be for experts and we need to be careful with the doses prescribed so that we do not end up feeding the
epidemic, and amplifying to primary care might
dangerous.

However, in this context, we also
acknowledge that many patients live in rural areas
that might get to consultation only for short
times. We'll talk later about maybe trying
telemedicine or other approaches. They might not
have access to the experts. Overall, in the
country, there is a limited number of pain
specialists, so there might not be enough in order
to follow these recommendations of using in only
expert clinical settings.

Finally, from a public health point of view,
we acknowledge that there is no answer. There is
no evidence of efficacy, and there are way too many
problems and evidence for them. If we use higher
doses, we can perpetuate the problems and go into a
slippery slope. Pharmacology tolerance is normal
and expected, and we cannot keep going higher and
higher doses if they are not working in particular
because the balance might be unattainable.

We have no clear compelling evidence to
support escalating doses forever, but we also acknowledge that it will be difficult to have efficacy studies in this context. So we do not expect to see data anytime soon.

From a clinical point of view, it's also acknowledged that there is evidence that high doses will lead to hyperalgesia and tolerance. Some high doses will still not help, so there is a need to have conversations with the patients to put a limit of how high you go when lower doses are not working. Sometimes there might be no good options because disciplinary approaches might be economically not plausible.

Lastly, we note that still high-dose patients represent 1 to 2 percent, so the implications of the policy might affect them but might also have an impact in a larger population for question number 2 in terms of adverse effects that we will discuss.

Anything to add or particularly anything to correct what I've said?

MALE VOICE: That was one sentence.
DR. HERNANDEZ-DIAZ: That was one long sentence.

(Laughter.)

DR. HERNANDEZ-DIAZ: Okay. I'm so glad. Maybe we can move on to question 1B. For question 1B, now we are going to focus on the clinical utility of higher dosage strength opioid analgesics. Dr. McCann wanted to talk about that, so we are going to let her be first.

DR. McCANN: Thank you. Mary Ellen McCann. There is a specific clinical utility of higher dose strength, and that would be convenience for the patient, lower pill burden, and perhaps less hassles with the insurance company. I know within my own family, within my children's dorm rooms, within friends, that everybody shares pills. They share antibiotics, and they share opioids.

Most of the young people in our country have insurances where there's a $5,000 deductible, so somebody that twists their ankle, they're not going to go to the emergency room. If they're in pain, they're going to ask their friend for a pill. And
the idea that a single higher dose strength pill could kill somebody in that setting I think is borderline criminal. So that's what I want to say.

DR. HERNANDEZ-DIAZ: Dr. Litman?

DR. LITMAN: Thank you. Ron Litman. I would like to come down on the public health side here, and I acknowledge Michele's points before and the problems with convenience to patients. I have two elderly parents who have lots of medical problems and deal with the same thing. But in my mind, when you weigh the two, the public health concerns in my mind take precedence.

I think there should be creative ways of making the drugs so that there aren't as many pills, maybe with liquid formulations or compounding. I mean, there's got to be some way that patients who require high doses can get them without a high-pill burden. I can't imagine the pharmacologists and pharmacists can't figure that one out.

DR. HERTZ: The compounding has been mentioned twice now. How does compounding fix the
problem of high-dose products, since it seems like
if we did do away with them, they would be
compounded instead?

DR. LITMAN: Honestly, I'm not an expert.
From my experience using compounded products -- I
work at a children's hospitals, and there are kids
with rare diseases that need to get a lot of the
products compounded by special labs. They're
individualized products that are made for certain
patients.
They're not widely available to the public. A
physician just can't prescribe for this; it's got
to be worked out for these particular patients.

No? Please correct me.

DR. MEISEL: Steve Meisel. Just to
elaborate on that, any physician can write a
prescription for anything. A patient can bring it
to any compounding pharmacy, and it's made, period.
There's no restrictions on that sort of thing
whatsoever.

To get to Sharon's point, if we stop making
it available commercially but by compounding
pharmacies make it available, that doesn't change
the community availability of a concentrated
product. It just shifts it from something that
comes from a commercial manufacturer to a
compounding pharmacy, which is more likely to have
compounding errors, mistakes in accuracy, and those
kinds of issues that go along with it that you
wouldn't see typically from a commercial
pharmaceutical vendor.

DR. LITMAN: Yes. Thanks. That does make
sense. In my mind, I was thinking more about if
you had a patient with a special consideration,
like Michele's mom, that would be a situation that
would be less likely to be diverted for a variety
of individual reasons. But I do understand.
Thanks.

Overall, I would side with the public health
concerns. I would go along with what
Dr. Ballantyne said before. And that is I don't
see a compelling medical reason to have certain
high concentrations of it routinely available.

DR. HERNANDEZ-DIAZ: Thank you. Dr Urman?
DR. URMAN: Some of the points have already been made by the panelists. Just like Dr. Litman said, I don't see a strong, compelling medical reason other than looking at it from a practicality point of view. Certainly, there are a subset of patients, patients who have difficulty swallowing as somebody said, or cognitively impaired individuals.

Certainly, from a cost economic implication in terms of -- as it was mentioned by one of the speakers the other day that, costs are similar, so the more pills you buy, the more you pay. So it's not so much strength as it is the number of pills that you pay for, so that's an important consideration.

One thing I would say is if you're looking at opioid-naive patients versus opioid-experienced patients, maybe we could consider making high-dose strength pills available to patients who are opioid experienced versus opioid naive. That would be one clinical aspect. That would be more of a practicality type of situation. But we shouldn't
ignore patients who are either cognitively impaired or have some medical issues why they can't consume lots of pills, a hundred other pills in addition to opioids. That's my thinking.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Becker?

DR. BECKER: My comment is -- Will Becker, first of all -- pretty much redundant to other folks, that the public health risk outweighs the potential benefit to patient convenience.

I will say the personal health risks are there, too. Dr. Ballantyne mentioned a scenario or a patient who's in the fog of sleep, not sure whether they took their dose or not. That's real, especially with aging patients and patients on multiple and other, centrally sedating medications. I just wanted to acknowledge the risk to the individual as well. Thanks.

DR. HERNANDEZ-DIAZ: Dr. Meisel?

DR. MEISEL: Steve Meisel. I'm going to take a bit of a contrary review. I think we've agreed that there are at least some situations where high doses of opioids are appropriate. We
can disagree about what falls into that bucket versus a different bucket. But I think we all agreed that there are some situations where high doses are the right things to do, whether it's cancer, end-of-life only, or something broader. So it's going to get used.

The argument that I hear about, well, let's take the higher dose forms off the market, it will send a message that higher doses are unusual, and you would decrease marketing, I suppose, from the vendors that are selling the high-dose formulations; that's true.

If somebody were to take a single dose, that could be fatal in that scenario. I get that, although I think the scenario in, say, a college dorm is different than a scenario in a chronic cancer patient, end-of-life sort of deal, like Mary Ellen was talking about, sharing pills and that sort of thing. But I get it's a possibility.

I also want to be aware of the unintended consequences. Every action has a reaction, has the opposite side of the story. And if we don't
address the opposite side of the story, we'll create situations that might be worse. You don't want to exchange a current set of problems for a worse set of problems.

The problems that I see, if we were to limit and take those off the market, are large. We've already heard stories about pill swallowing problems. That's a burden that I think should not be underestimated. We've heard stories about people taking a thousand MMEs at a given dose, or we ask people to take 50, 60, 70, 80 tablets at a time. What does that mean, if we're asking people to take 50 tablets at a time in terms of anything, in terms of practicality?

The liquid formulations, my organization, we dispense an awful lot of concentrated liquid, hydromorphone, and morphine, and whatever, to a lot of these high-dose, end-of-life kinds of situations. Well, if that's part of the high-dose formulation and that gets taken out, well, then what do we do? These people can't swallow large volumes of liquids, and that's the reason, in part,
that we're giving them the concentrated, so they can get by with half a mL under the tongue or that sort of thing. So you have that.

I think I mentioned just a moment ago the suggestion if you're getting a high dose at a central compounding pharmacy, well, that introduces new errors with accuracy, and purity, and those sorts of things. I think it increases the risk of medication errors. If now a patient has to take 10 tablets at a time or 20 tablets at a time, what if they only count out 18, or they count out 22? That's a much higher likelihood, if they only had to take 1 or 2 tablets, of making a mistake in that space.

It sends the message to the teenager in the house that if mom can take 20 tablets, if I only take 1 or 2, that's okay because it's just a tiny dose. Does that increase the risk of inappropriate misuse in that regard because of an incorrect perception that I'm only taking a small amount of what mom has to take? That might be there.

Because of all that inconvenience, does that
then drive some of these patients into the street to get their opioids? I think we heard yesterday that that's a real issue. Would we risk making that issue worse by artificially limiting the availability of dosage forms that people use on the marketplace?

I always tell nurses and other people that if you have to give more than two of anything, it's wrong. It's probably a medication error in waiting. If you set up a message that in this situation, 20 tablets is okay, what does that do to medication error, that mental model for everything else?

Say it's in a hospitalized setting, where you don't have the large doses of OxyContin. We just have to give multiple tablets of the low doses of OxyContin. Now the nurse is thinking, okay, I have to give 10 tablets of this. So if I'm going to give you 10 tablets of Lasix, I'm not going to question that. You begin to lose that possibility. So I think there's some increased risk in that space.
I think if we make it that much more difficult for patients -- we heard some of this, this morning in the public testimony. We heard some of this yesterday, and I think we heard it through some of the discussion here this afternoon, about quality of life. What are our risks of limiting these drugs in terms of quality of life, and what does that do in terms of suicide, driving people into the street, or other types of illicit drugs? I think that's an unanswered question.

Simply by taking the position that high dosage forms, either the high concentration or high-milligram dosing units, take those off the market as if that's going to solve the problem, it may indeed solve some problems, but it will create others, and those other problems may end up -- we don't know, but may end up being worse than the problems we're trying to solve.

So I think we can maybe get to where we want to get by other actions. Maybe we take those high dosage forums and we create some restrictions in a REMS or something; certain types of physicians who
are certified, whether they're pain doctors, or oncologists, or whatever. We can dream up what those kinds of disciplines or programs could be. That would limit the prescribing and therefore the dispensing in that space. But to say that there is no utility of them, and the reaction of that is to remove them from the market without considering the unintended consequences, I think would be a very dangerous mistake.

DR. HERNANDEZ-DIAZ: We will go back to the consequences of when A or B at the end, so hold your thoughts there as well.

Dr. Higgins?

DR. HIGGINS: Jennifer Higgins. It's been said before, but we've heard anecdotal evidence that there's a pill burden with the low doses, and there's some therapeutic benefit for addressing unique pain needs. But I'm not really seeing evidence of this, and I know people have said an efficacy study would be hard to conduct.

I'm just wondering -- and this may be a question for the FDA -- up until now, we've been
looking at it in kind of a binary fashion. Do we remove the medications from the market or not? I'm wondering if there's a mechanism by which -- I'm thinking about clinical trials and medications that are not yet FDA approved are sometimes able to be accessed for patients for compassionate use.

Could such a method be used -- so if we were to remove the product from the market, would there be a vehicle for access by physicians, prescribers, for compassionate use?

DR. HERTZ: No. If they're not being made, then they're not being made.

DR. HERNANDEZ-DIAZ: Dr. Zacharoff?

DR. ZACHAROFF: Hi. Kevin Zacharoff. I'll save my adverse effects comments for a following question. But with respect to item B, I think that many times I have been present in this room when we've talked about the negative consequences of having more pills in the medicine cabinet, because pills can disappear, and if there's more pills, it's harder to tell that some pills have disappeared, et cetera, et cetera.
So we've had this exact same discussion about minimizing the number of pills that are kept in the home, and when I think about some of the comments I've heard, it makes me track back to educational deficits and gaps related to either poor uptake of the REMS education -- I keep seeing the CDC guidelines going through my mind about the words "carefully justify" and I wouldn't want to sacrifice the sake of the clinical utility of high dosage strength opioid analgesics for the sake of putting more pills in someone's medicine cabinet.

I do get incredibly frustrated, but I realize that what Mary Ellen said is exactly right. We're doing such a bad job from the educational perspective, that people in 2019 still think the right thing to do is save opioids for a rainy day when they no longer need them, and they still do share them in college dorms and share them even within their own households.

To me, that is a much bigger public health problem than sharing a high dosage strength opioid with someone who sprains their ankle, because then
that means there's an educational deficit on the part of the person for whom those medications were prescribed. That means that the patient counseling guide didn't get distributed to that patient, and that means that the healthcare provider didn't have the CDC checklist that's intended to go along with the CDC guidelines, which specifically talks about informed consent and responsibility, and that's what the opioid agreement is about, et cetera.

So I would agree with Dr. Meisel's statements about pill burden. I certainly have had a number of patients who have problems swallowing. I think if we were talking about any other medical condition, we would be saying, if you're going to prescribe 50 milligrams for someone, why would you ever prescribe two 25s? I would flip it back to the burden is on us to make sure that we don't dispute the clinical utility as a responsibility of poor educational efforts about the responsibility of putting higher dosage strengths in people's homes. Thank you.

DR. HERNANDEZ-DIAZ: Dr. Lesar?
DR. LESAR: Timothy Lesar. I just want to make a few comments about the dose size. When you talk about larger dose size, we really are naturally talking about sustained-release products and not so much whether they should be capped. Certainly, there are risks with the higher sizes that have been discussed, but their inherent design I believe leads to rapid escalation of doses. You don't increase OxyContin daily doses by 5 milligrams; you increase it by 20 or 60 or 80 a day.

So the inherent design in terms of dose size increments have really led to some of our problem because you can't slowly increase doses of these large dosage sizes because they don't come that way or it results in having to purchase numerous sizes.

I think one of our problems with allowing large dose sizes, which are almost all going to be sustained release, is that they lead to the need to escalate by larger increments than we probably should, and of course that leads to higher doses, which leads to many of the problems.
I understand all the issues with pill burden, but I think we have to throw out perhaps the increment design in terms of what dose sizes they are, and it's faulty in and of itself and has led to some of our over-aggressive increases in doses and some of our problems.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Jowza?

DR. JOWZA? Maryam Jowza. I have to agree with Dr. Meisel. I do think if we're going to say that there are some clinical scenarios where higher daily doses are appropriate, and we're also worried about not the pill burden to the patient so much if we're talking about a public health perspective, but the number of pills that are potentially available for diversion, then it does make sense to continue to make the higher dose pills available.

If, for example, I was a patient who was taking high-dose, extended-release let's say oxycodone, I don't know if they make a 90 milligram, but it's a 90 milligram, I know about this point, that this is a high dose, and this is something that's going to be detrimental if I give
it to someone who's opioid naive, because presumably I've been on it not just for 2 months or something like that; you've escalated to that degree. But if I have now a pill bottle with 540 tabs and they're all 20 milligrams, I'm much more likely to say, "Oh, hey neighbor, you sprained your ankle. Here, take one," because a 20 is much more likely to be shared than a 90-milligram pill.

I think those things are important to take into account. It's just the number of pills I think that are going to be available for others to share is going to be higher, especially if we're going to say it's okay for patients who are on high dose to remain on high dose.

DR. HERNANDEZ-DIAZ: Dr. Mackey?

DR. MACKEY: Sean Mackey. Commentary about I get the idea about compounding and the perceived simplicity of it. It does scare me, though, that you lose all the abuse deterrence as soon as you compound these. If you take a medication and you put it into a compounded format, you no longer are abuse deterrent at all. I find that troubling.
With this particular issue, I don't feel nearly as strongly about 1B as I did 1A, and I really do get the public health issues of it. I'm scratching my head wondering just how much of an issue the high doses are playing in the overdose deaths, and whether the problem is, at some level, starting to take care of itself.

The data that Corinne Woods showed yesterday were that only 0.5 percent of all opioids are in these high-dose categories. That's a 63 percent drop in 5 years. The number of these meds being prescribed is just dropping precipitously. When we look at the overdose deaths, the vast majority are at the lower doses.

So I am wondering just how much of a problem these higher dose agents are really causing, but I do get the lethality of it. I really do. And that's why I said I don't feel as strongly about this issue because one of these pills in the wrong hands can cause real danger. So at the very least, I would strongly advocate and amplify what my colleagues have said about additional educational
and safety measures put in place for those people
being prescribed and those prescribing these
agents.

DR. HERNANDEZ-DIAZ: Dr. Shoben?

DR. SHOBEN: Sure. Abby Shoben. I mostly
agree with Dr. Meisel, Dr. Zacharoff, and others
who've advocated for if you believe that there are
specific settings in patient populations, where
there's a clinical need for the higher daily doses,
then there is a real clinical utility of higher
dosage strength products to reduce the pill burden,
to make it easier for the patient to comply and to
reduce the number of pills; although I do have
serious concerns about the high numbers of low-dose
drugs in the house. It would be harder to notice
if one went missing either from accidental dropping
or from people pilfering.

DR. HERNANDEZ-DIAZ: Dr. Kaufman [sic]?

Dr. Katzman?

DR. KATZMAN: Thank you. I'm in the mindset
of agreeing that there is a place for the high
dose, with my colleagues, Dr. Meisel and others,
because of the pill burden, but also because of the burden for the caregivers that's been talked about with the public comments, and the young lady across the room about caring for her mom, as well as the quality of life for patients not having to take so many pills and problems with dysphasia.

But there's a category of healthcare providers that we really haven't talked about today. They're really MAs, and nurses, and pharmacists that work all around our country. I'm exquisitely aware of the three pharmacists, and each of them work 40 hours a week in our pain clinic. That's 120 hours a week between the three of them. And 80 percent of the time, they're on the telephone trying to get prior authorizations from insurance companies to get medicines approved, many of them being opioid analgesics and before pregabalin went generic, pregabalin and other medications, and SNRIs and other medications.

If we increase the volume of medications to increasing the number, certain opioid analgesics, it's going to change their burden and workload.
again, We don't want to change what we think is right, based on insurance companies and stuff, but this is a huge workload for pharmacists, and MAs, and nurses, and in the hospitals, trying to have patients swallow sometimes 10, 15, 20 pills for each patient as they round on the hospital. So that's three groups of caregivers, patients, and health care providers that are having to help in terms of swallowing all these numbers of pills.

I just would say to consider things like the restricted REMS program that you have, like Accutane, I think, and other medications to restrict these medicines to certain categories of clinicians, or perhaps not allowing more than like a 2-week supply, or a blister pack, or maybe just some kind of novel approach to restricting these medications so it's a little harder to reach. And I definitely support the idea that we need more education for clinicians. Thank you.

DR. HERNANDEZ-DIAZ: Mr. O'Brien?

MR. O'BRIEN: Joe O'Brien. I would just say that I have an MBA, but it took me 2 hours on the
night I came home, after a 10 and a half hour spine procedure, to do an Excel spreadsheet to figure both the 12 pills that I'm taking and the different times that I had to take. So it is an incredible burden to try to figure that out.

That being said, specifically with utilization, I would just add to Dr. Meisel and the previous speaker right now, that it's not just pill burden or workload. As I said before, it's access to health care. It is a real issue that in areas, whether it be the insurance companies or the pharmacies, that they are restricting the number of pills. So if we increase the number of pills, it may be in fact that the patient can't get what they need for their prescription. So that to me is a real issue in terms of that access to healthcare.

That being said, we seem to be interchanging here, and that's part of the problem with this issue we're dealing with today, is that it is a very complex issue here, like a spider web. That being said, on a public health perspective, God forbid if my grandchild got ahold of my
80-milligram opioid. That trumps all for me. But
I think there's a clear utilization, and I would
have to go along with that.

DR. HERNANDEZ-DIAZ: Thank you. We have a
few more speakers who want to speak, and we are
going to go there. If what you are planning to say
is important but has been said already, just be
brief. Dr. Hoffer?

DR. HOFFER: Thank you. This is Lee Hoffer.
I'd like to just repeat what Mr. O'Brien said there
at the end. We have a situation where we might
have a person diverting one of mom's 20 low-dose
oxies, and they might use it to get high, and they
might develop OUD. If they take one of mom's
80-milligram oxies, they're going to die.

So I guess my issue is that people divert
pills all the time. They're going to divert low
ones, they're going to divert high ones, and
they're going to want high-milligram pills.
High-milligram pills are better products for
dealers to sell because they can have a fewer
supply and they can charge more money.
So I think it's a real challenge. We talk about the dynamics, and the complex issues, and where you don't want unintended consequences. Here is one I think where if you have a single pill that will definitely kill somebody if they're naive to opiates, I think that's a real danger, and I would never approve that considering the fact that we already have this very high burden of opioid overdose with low-milligram pills.

DR. HERNANDEZ-DIAZ: Dr. Nelson?

DR. NELSON: I already gave my answer in the first part. I inadvertently answered B during A. But I did want to make a comment. I think from an improvement perspective, we're trying to find a workaround to a problem we shouldn't be having in the first place. As you know, I'm not sure we agree that most people should be on these very high doses anyway, and we're sort of enabling bad decision-making by allowing these doses to be available. As it has already been suggested, if we can escalate more slowly, probably it would be better, rather than escalating in these large
I don't think we're going to educate our way out of this problem. As Einstein said, "The definition of insanity is doing the same thing over and over again, expecting different results."
We've been educating ourselves, or trying to educate doctors, and patients, and everybody else for decades, or at least for a decade on this issue, and we don't seem to be making a lot of progress.

So holding our hat out to think that we're going to be able to fix this problem by telling people they should do something different isn't going to work. I'm sure I'm not breaking news to you on this, but we need a policy fix, an administrative fix, a mechanical fix, something; not just the hope that educating people a little bit harder is going to make a difference.

My final comment is I think there are two sides here that both make very good points about adding risks to the public and adding risk to patients. Clearly, I fall on the side of
protecting the public on this. If we have to add
burden and risk to one of those two groups, we
should add it to the patients who are taking these
medications, not to the public health.

I think we should protect the public at all
costs from all of the consequences we've already
talked about. And if patients feel that they're
willing to take this risk and burden to get these
high-dose medications, they should be willing to
take smaller pills in large numbers.

DR. HERNANDEZ-DIAZ: Dr. McAuliffe?

DR. McAULIFFE: Hi. I work in the acute
care setting in the operating room. We use a lot
of high-dose opioids for the acute care setting,
and we see a lot of individuality among patients,
so there is individual responses to the opioids. I
too am concerned about the amount of opioids that
are in people's medicine cabinets and how they are
diverted. I was trying to think of the
similarities with what we do in the operating room
and what people do in their homes, and I really
don't think that people are doing what we asked
them to do, which is to destroy the opioids when there's no longer a need for them.

In the operating room, we are very heavily incentivized to do just that by the DEA, and I'm wondering if there might be some way -- with especially the high strength dose opioids, if there's some way to incentivize patients when they're no longer using these opioids to somehow get them turned back into the system because I don't think they're putting them down the toilet, and I don't think they're destroying them. So maybe that could enter our discussion in some way.

DR. HERNANDEZ-DIAZ: Dr. Griffin?

DR. GRIFFIN: Marie Griffin. I'm concerned about the public health aspect as well, but I'm not convinced that any of the data we saw showed that these high-dose pills were really contributing very heavily to the burden of overdose deaths. I worry about the unintended consequences, and I'm wondering if packaging or some other solution would make more sense.

On the other hand, I would hate to see new
products come along, which are even higher doses or additional high dose. I like the idea that there is decreasing use of the high-dose products.

DR. HERNANDEZ-DIAZ: Dr. Nelson, do you have another question?

DR. NELSON: No.

DR. HERNANDEZ-DIAZ: Okay.

Let me try to summarize 1B, which was a discussion about if there is any reason to have high dose formulations versus adding little doses together. We talked about benefits of having them and about risks. The benefits were mainly around the convenience for patients, caregivers, and healthcare providers and the number of pills, pill burden, and pill swallowing problems.

I think we all agree that these high-dose formulations will be only to opioid-experienced patients that had escalated to that degree and that need many pills that is very high doses. It was mentioned that that is not always the case, that sometimes they are forced upon patients because of the number of pills you can buy, not necessarily a
patient decision.

We discussed that not having them available could end up in worse scenarios, where the concentrated liquids might be worse or as bad, where compounding can introduce errors and they don't have the abuse-deterrent formulation. They can increase medication errors when taking many tablets. They can give the false impression of safety.

There are more pills at home that are harder to track and may be available for diversion, and a 20-milligram pill may be more likely to be shared with neighbors than 90. The inconvenience of taking many pills might make illegal opioids more attractive. And if they cannot be swallowed or taken appropriately, they can impact the quality of life of the patient.

Cost, because of how insurance companies might put a limit in the number of pills, has been raised several times, and that might affect access to care. I wish that would be the only problem because then that would be a problem of how we have
the payers paying for them, so that could have a solution.

That was the benefits. The risks that were mentioned is a single dose can kill. Patients can accidentally take a second dose and die. Pill sharing and teens taking pills from the medicine cabinet can die with a single dose. They are better products for dealers to sell, so it can have unintended consequences down the road in the illegal opioids market. Small dosages allow for smaller increments, while sustained release has led sometimes to escalation at higher steps than needed. Those were the risks.

Overall, we have discussed the public health concerns take precedence. For 1A, that was not so clearly the case, comparing deaths versus inconvenience. Here, the balance was a little bit more towards the public health in the discussion. But the consequences of deciding not to have them, we will be going back to that later.

We mentioned education or lack of education being a public health problem. The guidelines are
not followed. We mentioned we could have REMS or other approaches, and incentives to return bills, and packaging solutions. So we'll go back to that and what to do at the end of our discussion.

In terms of the clinical setting where high dosage strength opioid analgesics might be indicated is what I think we have discussed. If you want to add anything or specifically correct anything I said for the summary, please do so.

(No response.)

DR. HERNANDEZ-DIAZ: Okay. Thank you.

We'll go to question number 2 that only has one question in it. Discuss the risks attributable to higher daily doses and higher dosage strength opioid analgesic products relative to lower daily doses and lower dosage strength products. In particular, discuss the differences in risk of misuse and abuse, addiction and non-fatal or fatal overdose with high relative to lower daily doses or dose strengths.

Include in your discussion the influence of therapy duration, physical opioid dependence, and
other factors, as well as risks in different
patient populations and to others who may have
access to these drugs, like children or
adolescents.

First of all, any question about the wording
or any clarification that we need to have?

DR. HERTZ: Hi. Sharon Hertz here. I'm
noticing that a lot of our conversation, as can be
expected, has expanded beyond perhaps the strict
limits of 1A and 1B, and have overlapped into 2 and
possibly 3 and 4. With the interest of actually
having you all make your flights tonight, among
other things, it's okay to acknowledge if you've
already said something. You don't have to keep
reintroducing it if it fits the next question.

DR. HERNANDEZ-DIAZ: Thank you.

Any clarification or we understand the
question. We're talking about safety now.

DR. HOFFER: This is Lee Hoffer. I do have
a clarifying question. And that is, are we talking
about removing products or are we talking about
approving high-dose products? I think this has
confused me a little bit, and I just want to be clear on it.

DR. HERTZ: So we're talking about the impact of any possible action that you think we should or shouldn't do. Nothing's on or off the table. It's the range of possibilities.

For instance, if you think the risks associated with dose or daily dose is X, and therefore should support an action, let us know; or as with the comments previously, if you're concerned that a particular action will have unintended consequences that could be counterproductive, tell us that. It's really more free floating then when we typically have specific voting questions.

DR. HERNANDEZ-DIAZ: Okay. So let's start a discussion. Please keep in mind that if what you are going to say has been said already, we don't need to repeat in the interest of finishing on time. Dr. Sprintz?

DR. SPRINTZ: Hi. Michael Sprintz. I think that we need to make sure that we differentiate
between overdose risk and addiction risk. Those are separate things, and there can be separate patient populations involved in that, although it's overlapping.

The other thing I wanted to state is to be clear that eliminating opioids doesn't eliminate addiction. Addiction has an inelastic demand. The increase in overdoses of illicit opioids in the face of decreasing prescription opioids also helps show us that.

When we talk about risks attributed to higher daily dose, even if it's a polypharmacy overdose, a higher amount of opioid that you take is going to increase that risk, as well as a risk in young kids and in adolescents. But in terms of relativity from a public health standpoint, as I understand it, yesterday, they were discussing that most of the overdoses involved lower dosage products, but I think that's because the vast majority of products on the market are lower dosage. But I would make the assumption that, obviously, if you take a higher dose along with
Xanax, and Soma, and alcohol, and whatever else, you're going to have an increased risk versus a lower one.

DR. HERNANDEZ-DIAZ: Dr. Meisel?

DR. MEISEL: Steve Meisel. Just for clarity to your point there -- I'm trying to think back to the 8 million data slides we saw yesterday -- the risk of overdose was lower in the higher dose formulations than the lower ones. Wasn't that also normalized for utilization so that the overall risk rate was lower in that population as well? Can somebody remind us of that if I don't remember that correctly?

DR. HERNANDEZ-DIAZ: If I understood correctly, the relative risk is much higher at higher doses. Once you take it, you have a higher risk. But because there are more users than the lower dose, the absolute number in the population still comes from the lower doses. But the relative risk, like if you were reaching those [indiscernible], was clearly higher for higher doses.
DR. MEISEL: Okay.

DR. HERNANDEZ-DIAZ: Dr. Marshall?


Something I've been struggling with the past few days is this inconsistency between these reductions in high dose opioid prescriptions we've been seeing; like nationally, a 40 percent reduction since 2011, and then fairly stable or increasing prescription opioid deaths, actually an increase of 20 percent from 2011 to the highest rate in 2017.

So I'm trying to think through what's explaining that. It might be that we're getting better at ascertaining prescription opioid overdose deaths. We've heard about that. It might be confounding by indication. People on high-dose opioids are at high risk for opioid overdose for other factors. I'd be interested to know from clinicians if there might be replacement going on, that people on high doses who are coming down are initiating benzos, which then may keep overall overdose risks stable.

I think something that's been highlighted as
well by Dr. Zivin is that the proportion of these high-dose prescriptions is quite small, 1 to 2 percent. So when we talk about attributable risk, it seems to me like the relative risk for the individual is really quite large on high doses, but the population attributable fraction of all opioid overdoses in the population due to high dose is actually quite small.

So I just caution us, if we were to remove high doses entirely tomorrow, I fear that the overdose rate might not actually decrease that much. That doesn't say that we shouldn't think very strongly about what to do with this for those individual safety problems and all sorts of other harms, but I just caution. I don't think we're seeing that much evidence of significant population health benefit with the reductions in the high-dose opioid prescribing we've seen so far.

DR. HERNANDEZ-DIAZ: Thank you. I'm going to have to use my chair position here and try to continue a little bit that discussion, because it has been mentioned a few times, two things. We saw
the increased use in opioids, in prescription opioids in the '90s, followed by the increased overdose and deaths from prescription opioids, then we saw heroin and synthetic opioid deaths.

I don't think we can interpret that as, therefore, there was no problem with the prescription. We created a cohort, the generation of abusers. We gave them the clients that now are dying from heroin, so I don't think we can say, therefore, the prescription opioids are not responsible.

The second point about since opioid abuse deaths are coming from the lower dose, therefore it might not be important, I think still those patients on the higher have a very high risk. And saying that compared to the lower dose, there are more cases coming from the lower dose should not be a reason not to go after the high doses, but a reason to also go after the low doses and not initiate so many patients on them, and that's not part of the discussion.

Dr. Becker?
DR. BECKER: Will Becker. I just wanted to bring up a risk that was briefly alluded to by Dr. Ballantyne, the impact of higher dose opioids on the hypothalamic pituitary gonadal axis. This has been shown in a number of high-quality studies, observational studies, and some perspective, that as we increase the dose, as we're bathing the HPA-HPG axes with higher and higher dose opioids, we will suppress, and that can lead to decreased testosterone production and decreased bone mineralization.

The other term that was used yesterday by Dr. Nelson was neuroadaptation. If we're giving higher and higher doses to the reward center of the mid-brain, we are going to at some point probably compete with the normal pleasure factors that one experiences in their day-to-day life. It has been shown in some interesting studies that there's decreased attachment for people on higher dose opioids with loved ones and increased isolation.

I guess some of these lesser discussed harms really trouble me because I think we think a lot
about overdose as hugely an important problem. We think a lot about addiction as hugely an important problem. But then there's this other group of people who we may have started on 10 years ago, and now we're looking at them, in the present day, and they're just not doing well. They don't seem to be living the fulfilling life we were hoping for, and we have stuck them. They are stuck based on our actions.

When I talk to a patient now about starting opioids, I say, "I don't want to be having this conversation with you in 10 years about what we hoped we might benefit from this, we did not."

Thanks.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Boudreau?

DR. BOUDREAU: Denise Boudreau. With regards to question 2 and risks attributable to the daily dose and higher dose strengths, especially, misuse, abuse, and addiction, so overdose aside, I think it's a really difficult discussion, even with the data that's out there, because ascertainment of
misuse, abuse, and addiction has been relatively poor. For addiction opioid-use disorder, for example, you need diagnostic interviews, and that goes as well for risks within different patient populations.

I say this in that we have currently ongoing a postmarketing requirement study of FDA studying this. I hope we're not doing it all for nothing because the answers that have been out there haven't been quite adequate because of the ascertainment of the outcome, per one.

I didn't hear anything yesterday of the talks that leads me to believe different. So I think there's a real lack of evidence, partly because of the outcomes -- again, overdose aside -- being really difficult to ascertain. Hopefully, we have better answers to that in the future.

I can say anecdotally, me and others, and many of you that are studying this, also know that it's become more difficult to study because new use of these high-dose products and extended-release
products is becoming less and less, so the patients actually haven't been there for us to study, too, as of the last couple of years. Thank you.

DR. HERNANDEZ-DIAZ: Dr. Hoffer?

DR. HOFFER: Lee Hoffer here. I just want to return, I think, to Dr. Marshall's question about the epidemic itself and why we haven't seen reductions in overdose from prescription drug use, but we've seen reductions in prescribing. I think one of the challenges is we're talking about three different epidemics. We have the pain epidemic with opiate medication. We have a heroin epidemic and we have a fentanyl epidemic.

While we've worked for quite some time on reducing the number of prescriptions, those burdens are still very, very high. So it might just be that we haven't hit the threshold yet, where we now we'll see people coming, and we'll see fewer overdoses from prescription drug use because it's just simply so high; whereas now we have also these other two epidemics that are sort of clouding the picture because people are using multiple drugs as
well.

I think when I first got this invitation to come here, I was like, "Oh. Why would we want to start introducing high opioids when we still have this problem that's producing all of these overdoses just from prescription opioid?" Even though our rates have come down a fair amount from prescriptions, compared to other countries, if we look per capita, if we look at the total population in the United States, those are still fairly high rates.

The other point to make is that the opioid epidemic is very different in different states. The region of the country, they're on different histories when it comes to what wave of the epidemic that they're in. This also might be contributing to the fact that those numbers haven't come down as quickly as we might hope they will.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Nelson?

DR. NELSON: Dr. Marshall and I, we answered the same question yesterday, and you went first yesterday, too, and I'll go second again today. I
do want to address that issue because it is really important.

Why are we not seeing a falling prescription opioid death rate when we're seeing a pretty market decrease in opioid prescribing? My take on it, as I mentioned yesterday, was that I think we're taking opioids away from a low-risk population but not taking away from a high-risk population. The data to support that is pretty reasonable.

If you look at ED, emergency department prescribing has fallen a lot. In emergency departments, we typically prescribe small amounts to relatively opioid-naive people for minor problems. Dentists have dramatically reduced their opioid prescribing; primary care doctors typically have.

What we don't really know and what I don't think we will know easily is what impact are we having on the high-dose prescribees. A lot of those come from pain medicine docs, some from primary care doctors that do a pain medicine practice, but they're a tiny number of patients, and it's
probably a forest for the trees problem. It's going be very hard to figure it out.

I'll tell you, when it comes to the medical examiner work, Bruce Goldberger and I, as a poison center person and medical toxicologist, do a lot of work with medical examiners trying to figure out what opioid causes death. Clearly, differentiating the fentanyls and heroin are easy. Knowing which prescription opioid is the cause of the death is not hard either. It's oxycodone or hydrocodone because you can sort of tell based on the relative levels. But what you can't tell is what formulation it came in.

Oxycodone in the decedent is the same whether it comes from an 80-milligram oxycodone or a 5-milligram Percocet, and it's impossible to really know that, which is why Bruce or somebody talked about the prescription monitoring programs and trying to get those linked up. But even that's going to be imperfect because, as you know, 30 percent of people die of opioid overdose who's never had an opioid prescription. So it's such a
difficult thing to untangle and try to figure it out.

There are the correlations that are hard to ignore, though. I know you commented or somebody commented about the complicated medical procedures, and people living through cancer, and why all those people should be on high-dose opioids. In every developed country in the world, there are people getting prolonged life from cancer and getting complex medical procedures. They're not on high-dose opioids and they don't have an opioid epidemic like we do. So there's something a little bit unique here, and it's hard to ignore the correlation between those two, the high-dose opioid use that we see and the death rates.

So even though you can say it's improved causality, it certainly shows a pretty strong association that's kind of hard to ignore as being causal. All of those things to me go together with the idea that high dose chronic use, presumably for pain in most of these cases, is a big public health and individual patient risk, and it does lead to
addiction, and it leads to fatal overdoses.

I think that's the reason we're not seeing a fall, is because we're not really yet taking away those pills, and we've been trying. The graph of reduced opioid prescribing has gone on for 7 to 8 years, but the fatality really was flat during all those years.

A lot of people -- if you read some blogs and some newspapers, you'll read about the fact that we've replaced the prescription opioid epidemic with a fentanyl and heroin epidemic. I think that's such a nuanced way of looking at it, because clearly the number of people dying of fentanyl's derivatives far exceeds the number of people dying from prescription opioids. But the number of prescription opioid deaths hasn't fallen.

So whatever epidemic existed before the fentanyl epidemic, which started in 2013, is still there. So it's hard to, again, ignore it, even though it is trumped by the fentanyl death rate for sure. But the FDA has no role in addressing that whatsoever.
DR. HERNANDEZ-DIAZ: Thank you. Dr. O'Brien.

Sorry. Mr. O'Brien?

MR. O'BRIEN: Thank you for the promotion.

DR. HERNANDEZ-DIAZ: Anytime.

MR. O'BRIEN: Joe O'Brien. Just following up with what you were just speaking about, it becomes very confusing to me in terms of -- our first question was on patient population and who are we talking about here. And when I looked at the data from Dr. Goldberger yesterday, we have a large preponderance of everybody that had mixed drugs in their system. I don't know if there's data that tells me how many people are actually just opioids.

How many are just opioids, naive opioids, either from diversion or first-time patients that got more than what they should have got or took more than they should have had versus those that are substance abuse or otherwise misusing, or abusing, et cetera, what percentage of that is?

What I don't know -- and I appreciate if there's any data with that -- is that even with the
idea of the United States being so large in this opioid epidemic, which is clear -- I mean, you see that in terms of relative to other countries, but I'm not aware of having seen selective patient populations in that.

Is it a problem because we just had this general open distribution to anybody from toothaches to ankles, and we've applied opioids as being a medical management system? Is that the same rate that we have if we looked at cancer patients, palliative hospice patients, complex adults, and spinal deformity patients? Is that the same relative to the rest of the world when we look at it that way?

DR. HERNANDEZ-DIAZ: I don't have the stratified data, but unless we think that in Europe they have more [indiscernible] or both, which I don't think has been described epidemiologically. I think for most of these categories, the use of opioids is much larger in the U.S., and therefore, the opioid overdoses.

MR. O'BRIEN: Exactly. But my question is
are we just applying it to a broad spectrum of
patients, relative if we stratified it and looked
at specific patient populations? Who are required
clinically, that we've identified, that do need
opioids, and how is that different if we look to
the rest of the world?

DR. HERNANDEZ-DIAZ: That would be a great
question. I agree, yes.

I have a comment to follow up to
Dr. Marshall about interpretation of the data is
complicated by a confounding of who gets to the
high doses, and there was some discussion
yesterday. I think there is some concern that the
high-dose formulations leading to the addiction or
patients already in the addiction path seeking the
high-dose formulations. Maybe from a public health
point of view, we still need to worry anyway, and
it might lead to the discussion that we need to
identify who is at risk right before going to the
high doses. That was discussed.

If there are no further comments, I
will -- yes, Dr. Mikosz.
DR. MIKOSZ: Thank you. Christina Mikosz, just under the limit there it sounds like. I just wanted to expand a little bit on the discussion that was initiated by Dr. Marshall and Dr. Nelson regarding the data about prescription rates and how that affects, overdoses and deaths due to prescription opioids.

I think that some of what was presented during the course of this meaning is related to decreases overall in prescription rates, so the numbers of prescriptions that are out there, that number has gone down over the years. But I think we still prescribe a lot. I think we've published data showing that in 2015, we were still prescribing 3 times as much as we were in the U.S. in 1999. In the context of overall prescribing rates going down, if you drill down a little bit more into that data, it's a little bit more nuanced.

Some of the data that Dr. Woods presented yesterday started to get into this, but overall rates have come down, but some things have actually
increased. So the mean duration of prescriptions has actually gone up, and the rate of prescriptions that are 3 days or longer has actually increased in some recent studies.

I think, overall, it's coming down, but in certain subpopulations, prescribing is actually going up. How that plays exactly into where our prescription opioid overdoses are right now, I think that still remains under study, but there are some complicated factors in there when you're looking at the rates. Thank you.

DR. HERNANDEZ-DIAZ: Thank you.

Let me try to summarize the discussion for number 2. We agree that a higher dose increases the risk of overdose, although a lot of your population uses lower doses, and therefore the absolute number comes from that population. So to affect the absolute numbers, we also need to target the use of low doses.

We also discussed some difficulties in understanding the data about addiction, including the confounding for who gets the high-dose
formulations and the difficulties of ascertainment of the outcome addiction. There are studies underway to look at that in more detail, and the difficulty of interpreting the data in the context of other epidemics going on. The FDA acknowledged that in their briefing, so the high rates are hard to interpret when fentanyl and heroin epidemics of overdose are going on.

The difficulty because of the formulations cannot be identified in toxicological studies, meaning if the opioid was coming from a high-dose formulation or not. It can be easier maybe to compare the [indiscernible] level with the use and misuse and overdoses in other countries with similar populations where the prescriptions have been lower, and therefore the overdoses are lower, and the high doses are lower as well.

Finally, a comment that we have focused on addiction and overdose, but there might be other adverse effects of high doses, including effects on the endocrine system, neuroadaptation, et cetera.

Anything I'm missing or I've got
incorrectly?

(No response.)

DR. HERNANDEZ-DIAZ: We have a break schedule. I'm going to ask for permission, if you have the energy to skip the break.

We need a break? Okay. We need a break.

(Laughter.)

DR. HERNANDEZ-DIAZ: Okay. I just proposed, and it didn't work out. You have 10 seconds. Fifteen minutes, then, at 3:15, please.

(Whereupon, at 2:58 p.m., a recess was taken.)

DR. HERNANDEZ-DIAZ: We will now continue with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

We're at question number 3. I'm going to read it, and then if there is any clarification, we can ask for that.
Discuss the potential impact on patient health and public health more broadly, if FDA were to take any regulatory actions that resulted in reduced prescribing, access to, and use of higher dosage strength opioid analgesic products, specifically. Consider both positive and negative impacts on patients, healthcare delivery, and public health.

There are three aspects that we want to include in our discussion.

A) What currently available evidence is most compelling in predicting the impacts of taking such auctions?

B) What are the most significant uncertainties, changes in prescribing behavior, rates of transition of patients to illicit drug, in understanding the ultimate impact of such interventions on patients and public health?

C) What additional evidence could help address these uncertainties?

Any clarifying questions? Ms. Higgins?

Dr. Higgins?
DR. HIGGINS: Jennifer Higgins. I'm going to address A. I think I found most compelling the patient reports of the need to seek illicit therapies if the high dose was unavailable. I think that came out of the video, and I've forgotten now the presenter's name. But I found that to be compelling.

DR. HERNANDEZ-DIAZ: Thank you. Before we include that comment, any clarifying questions? Are we okay with the questions?

(No audible response.)

DR. HERNANDEZ-DIAZ: Okay. So we'll include them.

Dr. Zacharoff?

DR. ZACHAROFF: Hi. Kevin Zacharoff. I just want to touch on something that I've heard a lot of people mention today and the perspective in which I think about it, which is what would the impact be on patient and public health? When we talk about risk, which I guess we can talk about now, something that I have really incorporated into my thinking about this is the idea that this is not
a patient healthcare provider risk-benefit analysis anymore.

I have learned in the context of sitting on this committee that we need to take into account patient health, household health, community health, and public health overall when we're going to introduce a medication like a high-dose opioid or even an opioid into a household situation, and we've heard a lot of discussions about that.

But I've also heard people talk about what the potential negative impacts are. I think Steve Meisel mentioned what the equal and opposite action and reaction phenomena could be. And there was a really good case study published in February of the New England Journal of Medicine, and they used a phrase that I felt is something I need to incorporate into my phraseology.

They called this "structural iatrogenesis." It was a pain patient who was being very stably managed for 10 to 15 years on a relatively high-dose opioid medication. Changes were made uh, with respect to something that Dr. Katzman
mentioned, with respect to approval and preauthorization. That took this patient from a very stable, high-dose opioid regimen to ultimately seeking his opioids on the street, illicitly.

It had to do with access, and when we think about access, I think we often think about people just going to the pharmacy and being able to fill a prescription, but we don't necessarily think about people who might have trouble even getting to the pharmacy, and all the challenges that could be there.

When I think about what the potential impacts could be on patient-level health, I worry about the structural iatrogenesis that it may cause with respect to people seeking their opioids from illicit sources. We've certainly heard discussion about suicide and suicidality as a result of this.

I think when I think about the most compelling evidence, I would just restate what we've heard a number of people mention today for the sake of being brief. And that is that it seems like it may not necessarily be the higher dosage
strength opioid analgesic products that are necessarily contributing to either the patient or the public health. It's probably more about our decision to employ opioids than whether or not they ultimately end up on the higher dose opioids.

That's where I have to say I still consider the educational gaps to be, in a very large part, responsible because almost every educational effort we talked about at this meeting and past meetings involves training healthcare providers who are in practice already. It's not about necessarily talking about people who are in training and to consider these issues.

So I do think that education has been responsible for the decreasing number of prescriptions that are written. I think that it remains to be seen as to what the impact of decreased prescriptions and increasing opioid deaths, what happens over the course of the next few years. It certainly doesn't look promising. But I really worry about the structural iatrogenic causes and negative impacts that might happen to
patients who all of a sudden see the rug pulled out from under them.

We really haven't brought it up here, but there were a number of comments submitted to the docket for this meeting, and I was particularly overwhelmed by the volume of patients who talked about the fact that their lives would essentially end if access to these medications didn't continue. And it didn't necessarily mirror what we heard in our public commentary, but I highly encourage people who have access to take a look at the docket and see what the lion share of the comments had to say if we want to think about negative impact.

Thank you.

DR. HERNANDEZ-DIAZ: Dr. Becker?

DR. BECKER: Will Becker. So it seems there may have been some consensus growing that high dose needs to be available, but that the ability to prescribe high dose should be constrained to experts, or at least to settings where the monitoring capability matched the need for monitoring, and where the ability to pivot to
medication-assisted treatment is readily available.

Then there was discussion, well, how are we going to have access to all these pain specialists? I want to introduce to folks the concept that there can be other types of providers who can do the monitoring function, who can do the close follow-up, not necessarily MDs or prescribers; less expensive people who can manage complex chronic pain adequately.

If you consider the model like a Coumadin clinic, where pharmacists do the requisite monitoring and make decisions on dose titrations, this is the kind of distributed model that might work to help, again, preserve access, yet ratchet up the amounts of appropriate monitoring and specialization that will increase safety, and do so in a way that can be done with scale-up and spread; so using pharmacists and other allied professionals who can provide that continuity of care. Thanks.

DR. HERNANDEZ-DIAZ: Thank you. Overall, can I ask -- we'll have to structure the answers to these three points. When you make a comment,
they're all great comments. But if you can, could you [indiscernible] if you think there is currently available evidence or we will need evidence to support that the change will do that. I'm not going to ask to repeat.

DR. EGGERS: This is Sara Eggers from FDA. If it's helpful, yesterday morning in the booklet with my slides, there are slide 11 and slide 9, and that might help structure and focus in the discussion.

DR. HERNANDEZ-DIAZ: Thank you. So again, the discussion is, if these actions were to be taken, what would be the consequences, and if you have enough evidence or what is the most compelling evidence to support those impacts versus their uncertainties? Then we'll get at the end to where we need more evidence. I understand it's very hard to differentiate, so we can do A and B at the same time if you wish, and then we'll go to C.

While we open the slides, Dr. Katzman?

DR. KATZMAN: Thank you. Can you just go back to the question? Or maybe not; that's okay.
I still don't think there's enough evidence that changing clinicians' prescribing behavior has really lowered the overdose deaths. As a matter of fact, I think that we have done a very good job as per Dr. Sandbrink's talk in the VA perhaps with lowering -- that clinicians have done actually remarkably well with lowering new prescribers, lowering the dosage, the MMEs, lowering the co-prescribing through national efforts like the CDC, and the VA DoD joint guidelines, and the recent HHS interagency task force, a lot of national efforts, and the National Pain Strategy, and so many things kind of layering on top of each other.

I think that we're kind of missing -- so that's really what I would say, and that I think we need to more target -- the fact that we could do a little bit better job with a targeted response -- I'll just leave it at that -- with looking at the fact that many of these patients do transition to heroin or other medications, and buprenorphine, and we can lower their overdose
death rate burden by giving them take-home naloxone
and other things. That's where I think there's not
enough compelling evidence with what I said at
first. Thank you.

DR. HERNANDEZ-DIAZ: Dr. Goudra?

DR. GOUDRA: Basavana Goudra from Penn
anesthesia. For me, the whole thing looks like a
QI project, probably the biggest QI project ever
undertaken. Unfortunately, FDA cannot shy away
from this. The reason I'm saying this is if you
try to fix one problem, there is another problem
coming up. You fix the prescription drug, then you
have a street drug.

Even the evidence, deep prescribing for
example, the man power and the money needed, I
don't know whether hospitals can afford to do that.
Just an example, I get patients in GI endoscopy on
high-dose opioids. Just a simple endoscopy, they
asked for opioids postop. What are they going to
do with these patients? I know very well just an
upper endoscopy cannot cause this much of pain, but
they just come for this because they need opiates.
The issues are too complicated. I don't think we have evidence to go one way or the other. We'll be here again in two-years time probably dealing with something new that might crop up as a result. Genetics play a part, I'm sure. In one area, I speak to my friends. Dentists have certainly stopped prescribing. It is too much of a pain for them to prescribe. A friend of mine who is a pain clinician also desists nowadays from prescribing.

I think the answer is to keep doing whatever we're doing. It seems to be working. There will be criticism no matter what. I guess that's it.

DR. HERNANDEZ-DIAZ: Dr. Marshall?

DR. MARSHALL: I have a comment on B. We have B; is that fine? Okay, great. Brandon Marshall. I wanted to comment on the transition to illicit drug use. We've heard a lot of, I would say, strong anecdotal evidence of transition to illicit drug use following abrupt non-patient-centered discontinuation. There's not a lot of strong large scale epidemiologic evidence
that supports that, so I would argue we really need
to focus on building that evidence base.

My team did publish two weeks ago in Pain
studies showing that receipt of high-dose daily
MMEs greater than 90 in a VA population led to
transitions to heroin use, and this was a
prospective study. So regardless, it seems like
getting up to 90 MMEs can be a risk factor for
transitioning in the first place. What I've heard,
though, is it seems like the risk really depends on
what happens after getting to that 90 MME in terms
of the actions taken by the provider.

But nonetheless, this is why I support the
CDC guidelines so strongly because they talk very
clearly about avoiding increasing to 90 MME in the
first place among patients first starting opioids.
So I think there is increasing evidence to support
those CDC recommendations. For the folks now on
high-dose MMEs like Dr. Becker mentioned, that's
sounds like a much more challenging patient
population to deal with.

DR. HERNANDEZ-DIAZ: Dr. Hoffer?
DR. HOFFER: Yes. I'd like to also talk about 3B as well, and the actual same uncertainty that Dr. Marshall talked about. That is that very small changes in the populations of people on high-dose prescription opiates who come off those drugs, or being kicked out of pain clinics maybe because they recreationally used cocaine or something like this, it only takes a very small percentage of those patients to greatly increase the number of people using illegal drugs. In 2010, when oxy was changed to an abuse-deterrent formulation where people couldn't inject it anymore, that's when we saw the big uptick in people injecting heroin, and then later, fentanyl.

So I think, going back to Dr. Becker's comment about keeping people high right now and then trying to figure out the taper is important, especially considering the misunderstanding of the CDC recommendations, which don't say anything about that, but have been misinterpreted in that way.

DR. HERNANDEZ-DIAZ: Ms. Robotti?

MS. ROBOTTI: Suzanne Robotti. The evidence
I found most compelling was Dr. Darnall's presentation on titration and weaning people off of high doses; the fact that voluntary participation could -- she felt that we could taper people more quickly and safely. Adding into that, the VA presentation talked about how there's such a significant risk in the 3 months following a major change in dosing.

It was also interesting, Dr. Darnall's comment, the characteristic of those who dropped out of the voluntary titration were higher on depressive symptoms. These are all great clues, I hope, as to how we can help people be successful on voluntary titration; that and of course the behavioral therapy and chronic pain self-management.

I'd also like to say we've been focusing or we've been hearing mostly about titrating people down from high doses. It's not easy to get off of low dose. It's just not easy to get off this stuff. Yes, it's important to titrate people down from high doses, but I think that there should be a
lot of consideration for support on people who are on what are considered low doses, helping them get off of it.

I have personal friends who are on 10 milligrams 4 times a day, and 3 weeks later are physically dependent on it, and he doesn't know what he's going to do to get off of it. He's got nowhere to go. So let's include the big numbers of people, too, not just the very small number of high dose.

DR. HERNANDEZ-DIAZ: Dr. Sprintz?

DR. SPRINTZ: Thanks. Michael Sprintz. In terms of the potential positive and negative impacts, I saw both. There was compelling evidence on the possibility that we can decrease people safely down. I've seen it in my own practice, which is more anecdotal and Dr Darnall's comments yesterday and the data that's out there, and I've worked with -- or not worked with, but there's a pain and addiction psychiatrist who's done a very effective job in decreasing patients off of opioids in the Medicaid population with chronic pain, so
that was impressive.

At the same time, there's also evidence that was compelling in terms of -- from a negative perspective, that we still have increases in overdose deaths of opioids in general. So when I look about, okay, let's say we decrease it -- let me stop for a moment.

I want to reiterate one thing that I know Dr. Zacharoff has said again and again, is that we really need to help providers have the tools to help patients, to educate, to identify, and to manage them effectively and appropriately. And by doing that, I believe that we'll be able to have a much more impactful solution to this problem rather than a reactionary one, which is resulting in a lot of the problems we're seeing.

So from a positive standpoint, impact on patient health and public health, I believe that you'd have possible overdose rates that could decrease, and that's assuming that we institute technologies and systems to identify patients at risk or with substance-use disorders; that we have
an infrastructure or expand the infrastructure, as well as access to care to help those patients safely and effectively decrease and/or taper off, as well as address the psychological issues relating to chronic pain, addiction, and the life changes that occur when long-term opioid use is decreased or tapered off.

The number one question I always get when I have that discussion about de-escalating is, "So how are you going to treat my pain?" And I have that discussion. I have an answer for that. We need to give a lot of the other doctors out there the same tools to be able to do that. Thanks.

DR. HERNANDEZ-DIAZ: Just try to go back to the question. Everything you said is related, but I think we are going more into the discussion of the high doses, while the question specifically asks about if the FDA were to take any regulatory actions that resulted in reduced prescribing access to or use of higher dosage strength opioid analgesic products.

What would happen if there were not or easy
available products with high doses in the formulation? What would happen if they were not easily available?

DR. SPRINTZ: You'd have an --

DR. EGGERS: Sara Eggers, FDA. If you can go to -- well, if you want to go back to slide 11, I think what would be very interesting -- and we did this on our own -- just try to draw the arrows, or maybe it's a flat line, about what you think might happen to these both behavioral effects and key public health outcomes of current regulatory action; actions that reduce or target higher dosage strength; or actions that reduce or target higher daily dose. Then if you see where there are big changes to you, that would be interesting to hear.

DR. HERNANDEZ-DIAZ: Dr. Mackey?

DR. MACKEY: Sean Mackey. With regard 3B and specifically focusing on the potential impact of regulatory actions reducing prescribing or access, there's a lot of uncertainties that we have here, and to get at those uncertainties, we need better high-quality data in real-world patients.
that are undergoing these reductions or this potential impact.

We need to track better our patients' physical, psychological, and social functioning. We need to get a sense of their employment status and what happens if these patients are taken off. We need to get a better sense of healthcare utilization. Are we simply shunting them from one problem to another, where they're now showing up more in emergency departments?

Dr. Darnall did a great job yesterday in showing a couple of patients in her particular study. And the first patient looked like they were doing pretty darn well. But if you noted the second patient actually, who was in fact coming down, that patient had a rather dramatic worsening of that patient's cognitive functioning. And I was left scratching my head saying, "What's going on with that? Why is that person not cognitively functioning as well?"

There's so much we don't know about the implications of this, and once again, we need to
track these patients. We also need to be mindful that a large number of these patients are, by definition, rather vulnerable. This is an incredibly vulnerable patient population, and we run the risk of destabilizing them. So we need to understand well and track the data on what happens if we just destabilize them.

So just as closure, I think we need much better quality data to help inform us.

DR. HERNANDEZ-DIAZ: Dr. Hummel?

DR. HUMMEL: Michele Hummel. Thank you. I think the committee, again, really needs to be conscientious about the consequences of taking these high-dose products off the market. I'm trying to bring an element of practicality into this, and I'm not sure how many of you are aware, but last summer there was an opioid shortage in this country.

When I was staffing at the hospital, low dose IV morphine and hydromorphone were not available. What we had to do is we had to substitute with the high-dose products.
Thankfully, those products were available because we were able to cut the dose in half.

Here lies the conundrum. All the opioid manufacturers right now in this country are facing litigation and lawsuits. Hypothetically, what if these companies folded tomorrow? This would be a moot point, right? We would have no opioid products on the market.

So again, I just want to try to bring the element and practicality into this that, again, a lot of these high-dose products aren't really used all that much, but if there were a shortage in this country, at least patients that needed them for pain would have an option.

So I think, again, the committee should consider the practicality of issues, and manufacturing, and things like that, and what opioid manufacturers are going through today because there's a very strong likelihood that a lot of these companies today will not survive the lawsuits that are out there. I mean, look at Purdue Pharma at 2000 lawsuits. What's the
likelihood that that company will survive?

So again, the point of high-dose opioids being on the market, it may not even a year from now be a discussion point.

DR. HERNANDEZ-DIAZ: Mr. O'Brien?

MR. O'BRIEN: I've tried to look specifically at the question in 3; reduced prescriptions, reduced access to the use of higher dosage strength analgesics. And I'd like to focus, I guess, not exactly with your slide 11, but for me, it's always been on these panels, we look at the risk-benefit. So what did I see or hear the risk-benefit as specifically just related to that, and not the overall issue of opioids, which is a real problem.

I look at patient's healthcare delivery and public health. Clearly, on the risk side, I see a lot of risks associated with that for the patients, in particular, and in the healthcare delivery, some of that's combined.

Probably the best example of that is the misuse or misunderstanding of the CDC guidelines,
and we now have -- I think it was
Dr. Marshall -- no, Dr. Becker that indicated
before, in some elements, what we've done is we've
shift the opioid epidemic to a patient-care crisis.
There is now more feedback from patients and
concern and alarm that they're not getting what
they need. Wherever that genesis of that problem
is, that's there.

So I see a lot of risk in terms of them
getting access and all of the ancillary issues with
that, whether that be diversion to internet or
street drugs; or whether that be higher suicidal
rates, which is on the uptick or the use of other
drugs that are there; or whether that be from
alcohol to fentanyl; whatever the case may be, I
see that as being a very high risk.

On the other side, for patients, I don't see
great benefit from it. Just looking at patients,
what's the benefit if you were to do that, I don't
see any compelling evidence that shows that there's
benefit for the patient.

Healthcare delivery, the same thing. I see
there's potential confusion. We're not going to have -- if we did it with the CDC, if you support it -- and once there's education and everything else to really make sure it's understood what we're going to do, you really run the potential of having other issues with giving access and being able to provide.

I've had in my own cases doctors saying they don't want to lose their license. They're afraid. In some cases, it results in torture because you have untreated patients for what they want to do. And again, that the opposite side would benefit, I haven't seen -- or to me, I just haven't noticed any great evidence that shows that there's going to be benefit for healthcare delivery by doing that.

Now we're left with public health as the last issue, and public health is very difficult. We're going to have pain addiction and death, those three elements, they're going to always exist. And they exist in some relation to one another, and it's a huge problem to try to deal with that and to really ferret out what are the really key issues.
there and what we can do.

But as it relates to this right here, if you were to do those changes -- again, I would love to see Dr. Marshall's recently published data, which we unfortunately haven't seen, so I could ferret out and understand what that really is saying, because on the surface, it sounds like one thing, but it's always the devil in the details, and I'd like to understand the devil in the details.

That being said, we don't have that. What we have seen over the last two days, I haven't seen any compelling evidence that there's going to be, really, a great reward. We've discussed about it. We've seen a reduction in prescriptions and access, but that doesn't change the death. That hasn't changed the addiction. We still have that, and we have suicide rates that are going up. So in essence, in some ways we've actually created more problems by taking away, in some regards.

Again, I'm left with, when I do my little diagram, I have all of the risks in each box, and on the benefits side, I just have question, my
question, my question box, and I haven't seen any compelling evidence, unfortunately, on that side. As much as it would seem reasonable, I just don't see it.

DR. HERNANDEZ-DIAZ: Dr. Meisel?

DR. MEISEL: Steve Meisel. I just wonder if we are being asked to answer the unanswerable. This is an expert panel convened to offer expert opinion. Typically at these meetings, there is some new drug we're being asked to assess, and there's the evidence; and there's all the clinical trials; the outcomes, both positive and negative; and different assessments, and this sort of thing. We're basing it on science and to the best of our abilities.

In this case -- and Joe, you phrased this really articulately, and I commend you for that -- we have no evidence, one way or another, that any of the things we're talking about would make a difference in anything. It's all speculation. There's a tendency to want to do the right thing, so we do things that we think are
going to help, but we have really no way of knowing.

You think back to the REMS programs. Yes, there's evidence that the REMS programs are being adhered with, but there's not a whole lot of evidence that the REMS programs are achieving the outcomes that they're designed to achieve up and down the line. So could we be falling into the same trap here of doing something that maybe feels good but doesn't have the evidence supporting it?

So it makes me wonder whether this entire conversation is premature; whether we should be looking towards the research community, the medical community, the clinical practice guidelines, and the professional organizations to establish what is and isn't an effective means to achieve an end. And by doing so, that will help further inform whether regulatory actions would enhance or detract from that. Right now, I don't think that we can answer any of those questions. It's all speculation.

DR. HERNANDEZ-DIAZ: Dr. Marshall?
DR. MARSHALL: Brandon Marshall. I'm trying to think of the framework to conceptualize this. I'm an epidemiologist; I'm just going to stay in my lane. There's this large prevalent pool of people on high-dose opioids already, and then there's the incident pool, people that are at risk of getting up to high doses.

It seems to me like the problem is that we fear that interventions to try to prevent the new initiates might have unintended consequences on the prevalent pool. It seems like that's what happened with the CDC guidelines. The focus, rightly, was on avoiding folks getting up to 90, and then misapplication of the guidelines targeted this prevalent pool.

So my question for the FDA -- I just don't know enough about the tools in the toolbox here -- are there regulations we could conceive where we may be able to see benefit in the incidence, reducing the incidence of high-dose prescriptions without negative consequences for the prevalent pool?
How refined are the tools? Can we have different regulations for people initiating these medications versus those that are already on high doses?

DR. HERTZ: This is Sharon Hertz. I suppose we could try to construct something to look at that or to try and achieve that, but it would be quite difficult to craft. I don't know how we would necessarily enforce it, and I really don't know how we would measure the outcome.

Some kind of prospective study might be possible in some health systems to look at that outside of what we could do. I could imagine perhaps an interventional study with adequate support in case people were getting into trouble as a result. But I'm not sure that I can imagine a regulatory approach that would create the opportunity to get the same kind of data that some type of more rigorous prospective study could.

DR. STAFFA: This is Judy Staffa. I'd also like to weigh in on that. We learned some lessons from the ER/LA REMS program, where we had such
difficulty of trying to assess nationally the impact of a voluntary educational program. And I know many on this committee attended that discussion and discussed that with us.

As we have implemented the new opioid analgesic REMS, where we've brought the immediate-release products into that, we've taken a bit of a different approach. What we're trying to do is much of the data you need to evaluate an intervention like this and what you're proposing are not really available on a national level. The national data don't have that granularity because our healthcare system is not all linked together.

So the approach we've taken is to use the national data as more of a barometer or surveillance approach to understand the context in which things are happening, but then to be encouraging the sponsor group to be trying to look into certain health plans or microcosms where the more granular data are available to be looking at interventions and being able to control for the factors you would need to control for.
So you'd have some internal validity to a study like that, and then we can argue about the generalizability or the external validity of it. Again, it's too early in the process to understand what will come of that but that's the kind of approach because of the challenges of exactly what you're raising. At a national level, it's rather difficult to do that, but that's what comes to mind when you suggested that.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Lesar?

DR. LESAR: Tim Lesar. You've kind of answered the question. But what I was going to address was that there's a current state in which we have this problem population that we have to deal with. There's also the future state, which would be if we reduce the development of that population, they're going to have quite different concepts.

So thinking about this, what you do here may impact how many people enter that pool of problem patients. That may be better, but also might increase it or might decrease it.
I think I think of these things as impacting only the current state, which would be it's only benefits are negative. Also, it has to be thought out in a parallel way or concurrently of how it affects patients who are administered opiates for the first time today. Do we impact their progression toward problem patients?

DR. HERNANDEZ-DIAZ: Dr. Zivin?

DR. ZIVIN: Kara Zivin. I wanted to speak to this question based on conducting research on the impact of other FDA warnings, whether that's black box warnings, or communications, or other different approaches and other classes of medications, or other specific medications; and whether that is guidance to reduce either specific dose or reducing daily dose.

We've looked at this in relation to antidepressants as a class, as well as specific warnings for citalopram related to cardiac outcomes. We've also looked at decreases in recommended daily dose for women using zolpidem relative to men.
What the literature on the impact of these types of warnings or guidance or communications shows is that it can be the case that they are effective at reducing the intended behavior that comes with a warning. So if the idea is that you should reduce daily dose, then you look at populations of patients, whether it's Veterans Affairs, or large health systems, managed care organizations, or Medicare or Medicaid, and you can often see that providers do respond, especially if there are concerns not only about litigation for the drug companies, but also for providers that are worried about what might happen to them if they do not adhere to these FDA warnings, whether the warnings are well founded or not.

But what you often also see is that there's a concomitant increase in substitution medications, or use of multiple medications, or doubling up on lower dose pills or other things such that you can increase some of the negative outcomes that we are potentially considering here, whether that's destabilization hospitalizations, emergency
department use, rehospitalizations, and those types of things.

There's also research to show that sometimes people, not only do they follow the recommendations, but it extends beyond the recommendations. So in some cases, say for citalopram, we found that not only did people not use lower dose, they just eliminated using citalopram altogether. Or in a case where there were black box warnings related to antidepressant use for potential risk of suicidality in children, people not only stopped using some doses, they stopped using any doses, and even therapy, psychotherapy decreased. So then you have an increase in suicidality because you're not being treated.

So I think we need to be mindful of the unintended consequences when thinking about these potential actions. Thanks.

DR. HERNANDEZ-DIAZ: Mr. O'Brien, do you want to comment?

MR. O'BRIEN: I just want to follow up on
Dr. Marshall's comment. While it sounds great, I think for study purposes it's great. But I would just caution if it got to the point of implementing any type of regulatory with silos of before and after, that gets very complicated because we've heard there clearly is clinical indications where you're going to need new entrants who are in fact high dosage patients. So you're going to have a consequence on them if you just have this before and after type approach. So it's more complicated than just simply A/B, that type of thing.

That's all I want to say. To that extent, I'd rather see the money in innovation and just threatened the companies to say if they don't in five years come up with a non-addictive drug, they're going to lose what they have.

DR. HERNANDEZ-DIAZ: Thank you.

Let me try to summarize A and B, and we're going to do it together because one was what is the evidence and the other is what is not the evidence, and I think the consensus is that there is no really evidence. Most of what we have said is
based on informed experiences and not speculations.

Evidence is mainly coming from the patient perspective. Taking away high doses can destabilize patients and can lead to lower quality of life and suicidality. Taking away those high doses will put difficulties in access for individual patients, and the individual patients do not see any benefit from it. There is no clear evidence for the delivery, and they didn't see [indiscernible] a clear risk with evidence based for public health.

Then there is evidence coming from the clinical experience describing how changes in approval end up in patients even looking illegal opioids, and how we need to have a system in place to take care of patients on these high doses, including a system that can treat addiction and maybe limit the use and the prescription of these high doses to experts that can manage these patients; and not only pain doctors, but also maybe other healthcare providers that take into account patient's health but also the household health and
the behavior of the patient as a whole.

We emphasize the difference between the initiators and naive opioid users, where these higher doses will not be indicated. The patients that are already in high dose, what the situation is, is more challenging. For that, we did discuss some evidence from studies, including that there is evidence that the prescriptions over 90 milligrams can be a risk factor for addiction, but the studies could not address what to do after the addiction, and these accidents after addiction might be crucial.

There is some evidence from the VA and other studies we saw yesterday that with some targeted efforts, we can reduce prescription and lower dose with titration. But we still need data on interventions to reduce that, like some naloxone prescriptions.

There is data to support that providers do respond to FDA warnings, especially if there are legal consequences, but we have to keep in mind that sued physicians can have negative outcomes and
an unintended consequences. And one thing that also was brought back to the table is it's not clear that the higher dose products are responsible for more overdoses and addiction.

I think in conclusion, from this table, we can say that interventions to change the dosage strength products availability will probably change prescribing, but we don't know. We don't have the evidence to say what would happen with the misuse and abuse and what would happen with public health. So we have speculated, but I think we agree that the issue is too complicated to predict what one action in one block of that complicated framework -- what are the consequences that will expand through the tree of possibilities. There is so much we do not know about the implications, so most of our comments on impacts are not evidence-based.

Anything that you will disagree or you will add?

(No response.)

DR. HERNANDEZ-DIAZ: Now we can briefly go
to 3C, what additional evidence could help address these uncertainties? Again, focusing on the implications of actions that will affect the availability of these high-dose products and the kind of evidence we will need two to have in order to address that question.

Dr. Sprintz?

DR. SPRINTZ: Michael Sprintz. Additional evidence would be how the daily alcohol use in chronic pain patients have increased since regulatory changes and what percentage increases there have been in sedative hypnotic prescribing. Regarding opioid-related overdoses, the percentage that were patients that had a prescription for opioids but without any previous illicit exposure.

DR. HERNANDEZ-DIAZ: Dr. Litman?

DR. LITMAN: Thanks. Ron Litman. A couple things come to mind. I'm not sure how feasible they are. But the most obvious thing that pops out is some kind of a patient registry. If you're on a certain high dose, whatever you want to define it as, possibly creating a national registry as best
possible -- obviously, it's not going to be a hundred percent -- of what happens to these patients over time as far as overdoses, as far as tapering, and as far as just what happens to their pain. I think that will be worth funding.

I wrote something else down here that I can't find right now, but that would be the main thing. Thanks.

DR. HERNANDEZ-DIAZ: Mr. O'Brien? Sorry, no. Dr. Shoben?

DR. SHOBEN: Thanks. This is Abby Shoben. Just two quick seemingly minor things, and I don't know how much they would actually help, the thought experiments where you study prescriber behavior in these hypothetical scenarios in the census. So there's a little bit of discussion about what happened if you cut back on different types of drugs, but saying get a group of physicians, and try to get a good sample of them, and see how they would titrate new patients up, and see how they would do things under different potential settings.

Then the second question that's lingering in
my mind is this issue of is it actually safer, both
for the patient and for public health, to have many
more of the lower dose strength products compared
to a smaller number of the higher dose strength
products; so looking at safety events in terms of
missed taking of the prescription, or dropped
pills, miscounting, or the lost pill count sort of
things that could be done potentially in an
experimental setting.

DR. HERNANDEZ-DIAZ: Dr. Hoffer?

DR. HOFFER: This is Lee Hoffer. I think
it's interesting because I think information from
patients and narratives, that is evidence. I think
what's tricky is quantifying it in this context
that you just talked about, where it's a complex
situation. There's been this call to apply systems
and complex system approaches to this problem that
make it very difficult to quantify any large scale,
or rates, or things of this nature that we would
like to do, I think, usually in epidemiology.

I'll give you an example of that. People
want to know how effective syringe exchange
programs in referring people to services. That's a
great question, and we know that some people do
that from their stories, but actually tracking them
through those systems becomes very difficult
because of just the regulations of, of research.

So I want to put that in there just to say
that I think there might be some things that we
cannot collect data on in the way that we want to
maybe with rates, and probabilities, and things of
this nature; just to be sort of aware of that.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Litman?

DR. LITMAN: Thank you. Ron Litman again.

I just remembered, the PDMP, speaking of
registries, is sort of this inherent data
collection tool. I'm no expert, but I haven't seen
anything that's been analyzed from it. I know at
least I've inquired about it in my own state of
Pennsylvania, and from what I can gather, it's very
difficult to get the data.

Imagine if the states talked to one another
and combined their data. It can even be done in a
de-identified manner if you just assign patient
names, code numbers, or something like that. Anyway, that would be, at a very superficial level, a way to track these patients and get at least some data.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Urman?

DR. URMAN: I just want to follow up on what Dr. Hoffer said about difficulty in collecting data, and specifically what is being prescribed, which is easier to get versus what's actually being taken, what's being consumed. I think that's a challenge for a lot of the studies that we do, retrospective studies versus designing something that's more prospective and certainly reaching out to patients; so sort of having some patient-centered tools to assess if you're going to conduct a study like that to actually study impact, amount, and the dosage and outcomes to find out what's actually being consumed versus not going somewhere else or whatever it is. That's one of the challenges I think with a lot of the studies being done.

DR. HERNANDEZ-DIAZ: Dr. Zivin?
DR. ZIVIN: Another thought we've learned from our studies is that it might be useful to talk to providers in the sense that people specifically who are prescribing, they absorb information differently, depending on whether it's a pharmacist, primary care physician, mental health professional, or recovery specialist. They can come from different sources when guidance is given from the FDA, whether that's emails, or other bulletins, or provider education; so thinking about more targeted approaches for different types of recommendations, for different types of providers or settings, I guess in the sense of gathering more evidence that way, so either qualitative data or surveys.

Just as everyone might realize, providers are being faced with dozens of warnings or guidance on all different classes of medications all at the same time. We're very focused here today on opioids, but that is just one element of all the different other information that is affecting them, as well as things like hard stops and other things.
in the electronic medical record.

DR. HERNANDEZ-DIAZ: Dr. Katzman?

DR. KATZMAN: Yes. I think that other additional evidence that could help some of these uncertainties would be just to get a more robust idea about the actual -- we're starting to do that with some studies, but some ideas about suicide rates with de-prescribing and what that might be.

Then I think what Dr. Zivin and others have talked about, or maybe some kind of qualitative focus groups with clinicians about what really is happening in their practices; that they're changing their behavior, but what really is going on regarding which patients might be the best to start de-prescribing efforts on, and which patients are more difficult.

Finally, I'm just wondering if somehow maybe all of us in the room are really painful focused, and neurologists and anesthesia and pain, but just maybe so much of what we're talking about is substance -- Dr. Sprintz, thank you for having addiction chops, but so much of this is
substance-use disorder focused. I think that there is even more overlap here, and so many of these patients, as you know, have transitioned to heroin, illicit fentanyl, and the states have gotten this STR money for every state, and it's not -- the reason why it's called STR money is because it's a strategic targeted response.

We know that in opioid treatment programs, that's really where things like take-home naloxone, it's almost a one-to-one ratio. When you give someone take-home naloxone in an opioid treatment program, they go on to reverse almost every community member that they see who's overdosing on heroin.

So I'm wondering if we might be chasing the wrong -- that things like take-home naloxone with buprenorphine, or take-home naloxone with methadone in a maintenance program, I know that this is not the right framework here. But things taking away the data waiver, or mandating take-home naloxone, or co-prescribing of naloxone with some of these high-dose products, things like that might be
really beneficial in decreasing overdose death rates. Thank you.

DR. HERNANDEZ-DIAZ: Thank you.

Mr. O'Brien?

MR. O'BRIEN: Thank you. Several I had was just mentioned, so I won't repeat. As we had said earlier, to me it would be very helpful to have more stratified data regarding the entire epidemic, so we can get it down to pools of populations comparative to other countries to see, really, if we can isolate down to where the nucleus of the problem may be so we can become more granular in our approach to the solution of it, rather than more general, that it seems to be.

We had mentioned over the last two days, to the regard of those populations, and whether it's substance abuse, or mental health issues, or whatever the case may be, that it would be interesting to see whether or not a prescreening approach made a difference in the behavior, or the dosage, or the result in outcome with the patients.

If you developed a screening tool mechanism
to screen out substance abuse or some of these other things, and compared to those that don't have that to see what happened with those two particular groups, I think that would be very interesting to see whether or not legislatively that should be a requirement of standard of care, to have a screening tool that is provided there.

The other thing is to become more granular regarding alcohol, which I think Dr. Sprintz mentioned, and in particular, its rate. I've heard several times that opioid is sort of the gateway, and it doesn't seem to me that it is. The experience seems to be that alcohol is the first drug that kids are taking, and particularly with younger ages and older ages.

In our population, we see that they're not getting in trouble with doing all these other street drugs. What they're getting in trouble with is maybe taking too many martinis at the same time that they're taking the opioids, and that is probably the first one. Binge drinking is a real problem with our youth, et cetera.
So I think the more we understand alcohol and its impact as a gateway to other things is important in looking at the whole problem.

DR. HERNANDEZ-DIAZ: Thank you.

Let me try to summarize 3C. We talk about creating a patient race here [indiscernible], something like the PDMP, to know what happens to patients overall in their pain, overdosing, and tapering, and considering the impact of characteristics like alcohol use, other abuse behavior, or co-prescription [indiscernible] in these patients. In that context, we can study what patients do under different strategies in this experimental settings; for example, comparing many more small doses versus high dose formulations.

That was one option for research. We also talk about qualitative data or surveys considering certification by patients and clinical settings to understand the challenges. Daily focus groups could be with clinicians to understand the behaviors in prescriptions, and with patients to understand their risk for suicidality, pain, and
disability from not having the high doses, and
considering co-prescribing naloxone or
buprenorphine, or other interventions and
discussing them in this qualitative research.

In both types of studies, there was an
emphasis on understanding the patient variability
to identify groups that can benefit and might have
a lower risk; for example, with this prescreening
approach of who might be a higher risk of abusing.

Tracking patients through observational data
in this setting might not be possible because of
the challenge of following these patients through
the system, and also because of the challenge of
distinguishing the prescription from the use. So
there is a reason to focus on these other types of
more ad hoc studies.

That was it. I wanted to clarify that when
I say not evidence-based, it was not the right way
of saying it. Things are hard to quantify by
experiments, but I do agree that experiences from
patients and clinicians are still evidence that we
take into account, so thank you for noting that.
Anything to add or correct for my summary?
(No response.)

DR. HERNANDEZ-DIAZ: If not, we can move to question 4.

Question 4, considering the discussion on all the previous questions, discuss whether there would be value in FDA taking any new regulatory actions intended to target or reduce prescribing and use of higher dosage strength opioid analgesic products.

A) If FDA were to consider potential new regulatory actions, how might FDA define the products that would be subject to such actions? We will discuss that first.

B) Discuss any other actions FDA should consider to improve the safety of higher dosages strength opioid analgesic products; for example, actions not specifically intended to target or reduce prescribing and use.

Any clarifying questions regarding the wording? Anything that's not clear in the wording?
(No response.)
DR. HERNANDEZ-DIAZ: If we are okay, let's focus on A, and then B, if possible. Dr. Mackey?

DR. MACKEY: [Inaudible - off mic].

DR. HERNANDEZ-DIAZ: You will be first in B. A, Dr. Becker? Oh, a clarifying question?

Yes?

MS. ROBOTTI: I'm not sure. How might FDA define the products that would be subject to such actions? I'm not sure what products mean in that sentence.

DR. STAFFA: This is Judy Staffa. As you heard us talk about earlier, there's no set definition for what a high dosage strength of an opioid analgesic product is. So for the purposes of allowing us to have a discussion, we use 90 MMEs in terms of -- we use two definitions. One was 90 MMEs per unit or tablet, and then the other definition was, at the minimum label dosage, taking this product as directed would take you over 90 MMEs per day.

So that's the definition we use simply for discussion. What this question is asking is, is
there a better way to define a high dosage strength
opioid analgesic product?

   DR. MEISEL:  Just additional clarity, the
fentanyl patches, does that fall automatically into
this?

   DR. STAFFA:  I think for the purposes of our
analyses, we only focused on oral and transmucosal,
but we're open to hearing how you would want to
define them. And if that definition includes
transdermal, we'd like to hear about that.

   DR. HERNANDEZ-DIAZ:  I think Dr. Higgins was
first.

   DR. HIGGINS:  Jennifer Higgins. If the
committee wouldn't mind, I need to leave a little
eyearly to make my flight. May I answer A and B
combined? Okay. Thank you.

   For A, I would concur with the 90 MME, based
on my limited experience. I felt like that was
expressed greatly throughout the presentations as a
standard. And with respect to B, my suggestion
with respect to any regulatory actions would be to
include a more robust naloxone campaign or
education campaign; increase the patient monitoring by physicians. This would even follow after the stopping of a high-dose medication.

We learned that that's a critical point, which suicidality may happen or other kinds of decomposition. Then I would also hope that there could be some cautionary labeling regarding prescribing opioids to patients with substance-use disorders and mental health histories.

So that's concisely what I would recommend in terms of regulatory change.

DR. HERNANDEZ-DIAZ: Thank you.

Ms. Robotti?

MS. ROBOTTI: Hi. Suzanne Robotti. It seems that the FDA is focused solely on high-dose products, particularly with these questions. So don't get mad at me, Dr. Hertz, but you don't get to high-dose products without starting with low-dose products.

I think new regulatory action should include -- should be targeted also to initiating, first, opioid prescriptions. And -- I hope I'm not
going too far off point; don't stop me -- labeling
changes that were described earlier in this process
yesterday seemed that they would protect the
pharmaceutical company from lawsuits more than they
would inform and educate the patients.

   Patients don't know that they will become
physically dependent on this drug between 1 and 3
days, as soon as between 1 and 3 days. I would
encourage the FDA to put a label on the
prescription bottle or on the bag from the
pharmacist that says, "This drug causes physical
dependence and cannot be safely stopped without
tapering." Maybe you even want to add to it,
"Don't save the extra pills. Dispose of leftover
meds by" ABC.

   I know you can't do that, but there has to
be a way because the patients aren't getting the
message. Ambien, all these other drugs, they don't
get it. They don't get that they can't stop
without tapering. And if they knew that, that
would pause a lot of people. I talk to people all
day long; it's what I do for it, and these are
native patients who are less naive now.

DR. HERTZ: I appreciate all of your comments. You're right, we can't influence what's on the amber bottle. This comes up frequently. It's outside of our purview. The medication guide has that messaging. I know.

One of the potential benefits from using our new authority for packaging includes potentially more of a unit-of-use package, where some of this could be more readily delivered at the time the prescription is filled. We're also contemplating other ways to try and use new packaging configurations to spread more messaging. But I hear you, and don't worry about your comments.

DR. HERNANDEZ-DIAZ: Dr. Lesar?

DR. LESAR: Timothy Lesar. Just in terms of the definition, it is truly important. When we try to implement some process change, behavioral change, specificity is incredibly important because our feedback is going to come through physician order entry, order it, prescribing, computers. So if I were to make a suggestion, it should be very
specific. I would think that all long-acting opiates would be included no matter what the dose, and for short acting, every combination of dose and duration; for instance, any therapy over -- let's say a short is 1 week, you could have an alert in a computer with feedback as well, and you could set a dose.

You could decide on that, but I'm not sure what exactly that dose would be, simply because obviously the short-acting agents are involved in many of our issues as well. So my suggestion is specificity that would be identifiable through computer prescribing and easily identified through databases.

DR. HERNANDEZ-DIAZ: No more comments for A? Dr. Meisel?

DR. MEISEL: Steve Meisel. Picking up on Dr. Lesar's comments about long acting, I think that's valid. One of the additional -- there already is, on the labeling of the long-acting products, a caution about its use for acute pain. I think that is something that is routinely
ignored, and it's not uncommon for surgical practices to decide they're going to use OxyContin, whatever, 20 milligrams twice a day, to get ahead of the pain. And increasingly, there's a move afoot to be using drugs like methadone in that setting as well because methadone is inherently long acting.

I wonder if there is some strengthening of the labeling or other types of restrictions that sort of go beyond what's already there because what's already there could be interpreted that this is okay if you make the judgment that it's okay. But if we could label that more strongly, that provides a greater backing for hospitals or other organizations to say, no, that's not good practice; you can't do that. And that's one way I think of reducing the exposure of these kinds of products in the community; something to be thinking about.

DR. HERNANDEZ-DIAZ: For A -- sorry.

Mr. O'Brien, you wanted to say for A?

MR. O'BRIEN: [Inaudible - off mic].

DR. HERNANDEZ-DIAZ: We are wrapping up A.
You can hold it for a second, for B.

Dr. Hoffer, is it about A or B?

DR. HOFFER: [Inaudible - off mic].

MR. O'BRIEN: Well, whether it's A or B, as I've already expressed, I am concerned about the 90 MME as being an absolute target for regulatory because we've heard that there are many people that are beyond 90 MMEs for whatever the reason that they may be, and I'm concerned about the negative aspect of that. So with regard to any regulatory action for that, that would be a problem. I do have B, that I would suggest instead of that.

DR. HERNANDEZ-DIAZ: We'll go to B.

Dr. Hoffer?

DR. HOFFER: I'm stuck here on A, a little bit because of the regulatory action. I agree that people still do not understand about these drugs. They just do not understand how dangerous they are, and that they feel like they can share them, and it's just like an aspirin, or Tylenol, with codeine or something like this.

So I would really like to see the disposal
or don't share this drug with any other person, and
I know that that's on there with this prescription
that's been given to you. But I think in
basic -- I mean, it almost seems like the language
is too complicated. And I know that CDC guidelines
were very specific and they're very clear, but
they're almost too nuanced.

It should be just, "You know what? If you
get this medicine and you're not using it, you have
to get rid of it." It's not like -- you have to
get rid of it.

Then the second one, I think the 90 MME is
another one that there might be issues with the
actual dose. But I think the continuity with CDC
guidelines, for example, I think would be helpful
because of too many mixed messages here about
what's high, and if 90 is really a cutpoint even
though there's no real clear point there.

Just having the continuity with messaging I
think is very important in this context, as it is
in any public health arena where you're talking
about risk behaviors. You have to consider, well,
you know, "CDC said 90, but FDA says one 120, so what is it? And maybe they don't even know, so what does it matter?"

So I think that trying to at least provide some baseline and just simple guidelines would be helpful.

DR. HERNANDEZ-DIAZ: Dr. Meisel?

DR. MEISEL: Steve Meisel. Just going back to my comment earlier about unintended consequences, we talk about what products should or shouldn't be considered high dose. Wherever we draw that line, whether it's a 90 MME, or whether it's long acting, or long-acting plus, or you throw in the methadone, or the patches, or whatever, that has the effect of sending the message that anything that is not in that category is peachy clean and fine.

So if you don't have those special restrictions on the 5-milligram oxycodone, then that must be a pretty safe drug, and I can prescribe what I want on that. That's a subliminal unintended consequence message that gets sent, and
we know that the majority of the problems that we heard about yesterday, in terms of abuse, and overdoses, and all that sort of stuff, are with the lower dose, non-sustained release kinds of formulations.

So I think we have to be very, very careful about applying a solution to this narrow problem that may end up creating the psychology of making the bigger problem worse.

DR. HERNANDEZ-DIAZ: Dr. Katzman?

DR. KATZMAN: Thank you. Joanna here. I would just briefly say that I appreciate what Dr. Zivin said about the labeling and the black box warning, although you alluded to the fact that sometimes they also have the benefits and the unintended consequences.

I do think there might be some ways that it could help perhaps the majority of patients, on all levels of the opiates, both the short acting and the long acting, from all the doses, to, to Dr. Meisel's point. I think in addition to the new labeling that you have for the benzo and opiate
co-prescribing, I do think that there is maybe some room to consider adding its substance abuse potential, need for screening for addiction, overdose, and need to please consider co-prescribing naloxone especially at higher doses, or especially if someone has other risks, to align with CDC guidelines.

In academic medical centers, we show learners black box warnings all the time. We teach to this. So I really do think it has -- I just want to let you know, we teach to these FDA labelings all the time. It does have value.

Thanks.

DR. HERNANDEZ-DIAZ: Dr. Mikosz?

DR. MIKOSZ: Thank you. Christina Mikosz. I just wanted to speak briefly regarding the points being made about 90 MME and the CDC guideline. I appreciate, just for the sake of discussion, that that number was proposed to define high-dose opioid products just in the absence of a clear definition, and then using assisting guidelines like CDC's to help define that as the objective by which to frame
discussion.

I think it's worth making the point, again, that CDC's guidelines is not a regulation. We're talking about regulatory action. CDC's guideline is not a regulatory document. That 90 MME threshold was essentially chosen just based on existing data at the time that the guideline was written, looking at dosages associated with overdoses versus patients who do not overdose on what dosages they're taking on average.

So that's where that number came from, but as folks have noted, there's been a lot of discussion and recognition of the misapplication of the CDC guideline. So I just think that it's worth making the point again that that 90 MME threshold as defined in the CDC guideline is really just a point where clinicians should carefully justify increasing a dose above that. It's not a firm statement to say that this shouldn't happen, but again, it's just to give clinicians a point to pause and think about what their individual patient needs, and then to progress from there. Thank you.
DR. HERNANDEZ-DIAZ: Mr. O'Brien?

MR. O'BRIEN: Joe O'Brien. Sorry. And again, I don't want to cross over to B, but I do want to talk about other actions, but it may target or reduce prescribing and use, but they're not regulatory in nature to do that. So I guess I'll talk about it, and you can tell or not.

I do think it's important, carrying on what was just said previously, that I really recommend a robust communication program that's important, rather than a regulatory approach from the FDA.

Dr. Hertz, you've mentioned several times that there is a booklet, there is information there that I think is very important, whether it be on substance abuse or whether it be on the danger of this drug, the importance of tapering, the importance of minimizing the dosage, et cetera, I think that has to be brought to the public and to the patients directly from the FDA.

I think there should be a coalition of all organizations that are interested, on both sides of the issue, to bring them together as a true
coalition to try to resolve this problem. It's not any one organization's problem. It's not one agency's problem. And I think the FDA has an opportunity to do that, to really bring out their risk and benefits of this to the patient community directly, and the providers through that, but the patient community directly.

I think it should be a robust program going directly to that and bringing it here, rather than a regulatory process. I do think it's dangerous when we go from guidelines to regulatory, and that has really unintended consequences that's going to be a problem. Anyways, that's what I said.

DR. HERNANDEZ-DIAZ: Dr. Garcia-Bunuel?

DR. GARCIA-BUNUEL: Martin Garcia-Bunuel. I feel like, yes, in terms of the number, and not to get hung up on the number but sort of full circle, we started, and no one appropriately felt comfortable to understand what were the definitions; we don't really have definitions.

One, Dr. Hu's slide from yesterday, slide
number 11, just interestingly as we talk about numbers in the 90 MME, this was IQVIA data, and it was highlighted there, and it was defined as higher dosage strength products. In that slide, it was greater than 90 MME, and that's where we saw the most significant decline in prescribing from the data from 2013 to 2018; and then the reference to the CDC guidelines that, once again, were CDC guidelines.

The only reason I bring it up, it does beg the question of the power of a number that gets out there. It almost seems like the number's already out there, at least in relation to this, and it somehow has impacted how we're viewing this from a prescribing perspective and how information is being communicated.

I think from the FDA, from the agency perspective, I think it's a very important question because I'm wondering if it's already been defined. It might be a good idea to look a little more closely, since it's been defined at some level, what does it really mean, as some of the questions
have been asked. Is that number really valid? If it is, is that the number we choose? And whereas if it's chosen, that at least gives someone a reference point.

The flip side being if there's really no big changes between 90, 120, 180, when you look at the percent of prescriptions -- because that's what I was really looking for, was the data can help us define what's high dosage relative to what we're prescribing now as organized medicine as a community of practitioners. And if the data is not perfect data, it's telling me that less than 1 percent of prescriptions are for greater than 90 MME, that's a pretty slim proportion of prescriptions.

I'd have a hard time figuring out how we're going to push that number even higher to define high dose when we're talking such a small percentage. So food for thought for FDA. I sort of dropped that in your lap a little bit.

I think for the committee, I'm interested to hear how do we get past somewhere where we already
are. We grappled, even though over the last few years, and we were asking for guidelines, and I sat on this as a guest, once again, on this committee a couple of times, and people were grappling for guidance, and we were looking for blueprints, and we were looking for guidelines. Primary care was definitely looking for something to lean on because we had primary care practitioners prescribing hundreds and hundreds of morphine equivalents and no one blinking an eye, so we did ask for some structure.

I don't think it's fair for us to completely throw that out the window, is my point. I think we still have to take responsibility for these numbers and thresholds. We have to then be able to respond to them. I don't think choosing a number is going to have outrageously negative implications. I think it gives us a guidepost and something to keep responding to consistently.

DR. HERNANDEZ-DIAZ: Dr. Griffin?

DR. GRIFFIN: Marie Griffin. I just want to respond to that because I think there's confusion
about the dose of the tablet and the dose people are taking. I think the less than 1 percent is the less than 1 percent of pills dispensed are 90 MME. But it looked like about 8 percent of people are taking more than 90 MMEs daily. So it's still a significant proportion of people, and that still puts those people at higher risk. I think that's my read at the data.

DR. GARCIA-BUNUEL: I appreciate that. I think it still sits consistent with the idea we as a group have been struggling this afternoon in trying to make recommendations to address the implications. I felt a lot of the -- everybody's very apprehensive about what the implications are for restricting access or restricting the supply of these higher dosages. But either way you slice it, it's a small group of patients, and I think we need to figure out how to define it.

You're correct, and I said, yes, the IQVIA data was just another snapshot. I think we're already there. I think these are the doses that everybody is struggling with, and that's why it's
still important to address.

DR. HERNANDEZ-DIAZ: Dr. Katzman?

DR. KATZMAN: This is Joanne. To your point, Dr. Garcia, I think it would be worth maybe a conversation, like a merge conversation with maybe the addiction committee. I don't know if there is one, but substance-use kind of committee, there must be one, because I think that this crisis, this parallel chronic pain, unintentional opiate overdose crisis in this country is really in the chronic pain community, in the addiction community, and then outside in the intravenous heroin community, and those dying from illicit fentanyl pills and heroin combined with fentanyl.

What I'm getting at is, it would be really great to hear from kind of a mixed group of interprofessionals that have addiction expertise, in addition to Dr. Sprintz and others, to kind of understand -- as I see and I work so closely with addiction colleagues, I see a lot of these patients go into kind of opiate treatment programs and are benefiting so greatly from MAT combined with
naloxone. I think that this is really the next step in the reduction of opiate overdose deaths in the clinician population in this country, inside the healthcare system, if you will.

In the community, FDA really can't do anything. In the IV drug use syringe exchange program, patients getting out of jail, we need laws to give them take-home naloxone and stuff. So that's it.

DR. HERNANDEZ-DIAZ: Thank you.

Let me wrap up the discussion about dose to move on to B. We talked about the 90 MMEs, and there was some concern for the number and the false impression of clear cuts. Maybe if foreseeable, we could use continuity [indiscernible]. There was some caution with the misapplication of the guidelines that have to be applied, a point which more justification is needed, a point to pause and think.

We realized that the number is already out there, and changing it might be confusing by giving different cutoff points. On the other hand, using
it classifies only 1 percent of pills and 8 percent of patients at high doses. That might be small numbers to even discussing going higher. We discussed how all low-acting opioids should be considered and decide the dose and that that has to be identified easily in computers and databases as high risk.

Finally, it was acknowledged that the prescribers need structure and have something to lean on, but there is a danger in deciding a dose because it can give the appearance that doses lower than that are fine, while the majority of the problem might be at the lower doses.

Anything to correct about the dose?

(No response.)

DR. HERNANDEZ-DIAZ: Let's move on to B. Many of you have already commented, and I was taking notes. So if you already discussed other actions that the FDA should consider to improve the safety of higher dose strength opioid analgesic products, do not repeat it, but if you have new things, please go ahead.
I know some of you have to leave, so we'll try Dr. Sprintz. Oh, Dr. Becker, you were first.

DR. BECKER: Yes, I think when it comes to changing prescriber behavior -- and I'm convinced that that's what needs to happen -- that, really, the most potent drivers of that is regulation. Education is necessary but often not sufficient.

If we look at things that change prescriber behaviors in this space, you talk about the relabeling of hydrocodone from 3 to 2. and we saw, because you could no longer write refills of hydrocodone, major drops. For example, in Connecticut, there's a new law saying that you have to check the PDMP program before you prescribe more than 3 days of opioids. Guess what? The number of longer than 3-day opioid prescriptions in emergency departments has dropped precipitously.

All this goes to say that of the things that are in the FDA toolbox that I can tell, slide 16 from Dr. Ford's [sic] presentation, looking at an ETASU that can be attached to a REMS, where there would be a requirement for certification and
specialized training, is needed. I don't know if
the FDA has that lever or who, but that's where we
need to go with this, is my opinion. Thanks.

DR. HERNANDEZ-DIAZ: Dr. Becker? Sorry.

DR. MACKEY: All good. Sean Mackey. If
there is one thing that we could do to address this
issue, which would be both effective and
noncontroversial, would be to improve our patient's
storage and disposal of unused medications. You've
already heard this before, and I'm going to amplify
some of this.

We know from the data that at least half of
the opioids that are misused in this country come
from friends and family, not directly from a
prescribing clinician. We know from the data that
was presented that a large proportion of the
overdose deaths did not have an active prescription
on hand. There is this incredible supply out there
that we need to get off the streets, and there is a
tremendous unmet need to educate the public on this
particular issue.

While I was online, I took a look at the
FDA's medication guideline for patients, and while the information is there, it was rather boring. I'm not sure any patient's going to read it. However, I loved the website that you pointed us to a couple of few hours ago on the opioid REMS blah, blah, blah, and I forwarded that in a document over to our faculty, and within 20 minutes, I got three of our faculty that said, "This is really cool. Let's put this into play." The problem is everybody should know about that. Everybody should know about it, including the patients.

I'm struck by that huge pool of these drugs that we have out there. When you think about 80 milligrams of OxyContin, a 30-day supply, that's $2400 that is sitting in a person's medication cabinet. No person in their right mind would leave 2400 cash in that medicine cabinet, but patients do that all the time. Maybe we need to take advantage of that knowledge to get them to take it out of the medication cabinet and lock it up in a drawer or in a safe.

Sharon, you and I served on the Health and
Human Services endorsed National Pain Strategy, and one of the major strategic goals on the public education was to enact a nationwide public education campaign around safe medication use. So if you were to enact this, you would not only be addressing the needs of the FDA but also that major goal of the National Pain Strategy.

What was alluded to before, I'll amplify. This requires an interagency effort. This requires the FDA. It requires working with the DEA because everybody should be working together. For instance, with the DEA who does that prescription take-back effort, the vast majority of our patients are absolutely clueless about those efforts, and we need to do a better job in getting the word out and working truly collaboratively. And not only working from an interagency standpoint, but partnering up.

You've got a great opportunity. I served as president of our national academy in pain. I know most of the leaders in this space. We'd love to work with you on that type of an effort to get the
word out, and I know there's a number of people here who have been from patient advocacy groups and who are watching right now, that if you put the word out that you want to work with them on this safe opioid, this safe patient opioid storage and disposal, they'd love to work with you. Why? Because it's motherhood and apple pie. Everybody can get behind this.

Whether you are in the camp that wants to be able to provide opioids to patients who are in pain, or whether you're in the other camp that thinks that they should be just taken off the street, everybody gets behind this message, and we all want to work with you to help get these drugs off the streets and only used as they should be used. I think that's the number one thing the FDA could do. Thank you.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Litman?

DR. LITMAN: Michael, you've got to leave? Why don't you go?

DR. HERNANDEZ-DIAZ: Please, go ahead.

DR. SPRINTZ: Thank you very much. Michael
Sprints. I'm going to go actually really quickly.

Issues to consider; REMS. You need to change your REMS' program to make it clinically impactful.

Deliver clinical tools that help doctors better identify substance-use disorders and guides them on what to do when they see it.

You've required industry to make education available for prescribers. I'd suggest that the FDA require prescribers and associated healthcare professionals through ETASU; require the industry to offer prescribers to have a certain number of hours in addiction medicine training specific to pain management, primarily identification, appropriate opiate withdrawal management to minimize withdrawal symptoms, but not limited to taper scheduling -- including but not limited to taper scheduling and medication-assisted withdrawal; require risk assessment of patients and appropriate documentation for high dose.

I'd require prescribers to have either board certification or fellowship training in pain medicine or palliative care, along with specific
training in addiction medicine and opioid withdrawal management. I'm clear that because of the issues on a public health scale, it's probably not possible because we don't have enough people.

In terms of dealing with patients from identification, routine random drug testing; PDMP utilization, and actually using the PDMP, not just checking off a box; and technology to assist providers in identifying at-risk patients with substance use.

The bottom line is most doctors don't have any idea of how to identify someone who has a problem, let alone what to do with it. So there's a lot of tools out there, and I know Lewis talked about education. It doesn't necessarily impact in change in behavior. So if we can utilize technologies that can help make it easier for providers to do that and be able to deliver it in a way that that's usable and easy, that would be really helpful.

Then I would say require an enforce more robust postmarketing surveillance to truly support
decreased abuse and education and marketing,
meaning from the FDA. The messaging that we were
talking about to change the cultural stigma is
really, really important. Thank you.

DR. HERNANDEZ-DIAZ: Dr. Litman?

DR. LITMAN: Thanks. I'll be direct and
very brief because I also have to run, and I
apologize for leaving.

Michael already alluded to, basically, we
need to figure out a way to continue to provide
patients with high doses while keeping the public
safe. I believe there should be regulations that
physicians who take care of patients on high doses
should be required to check the PDMPs. Not all
states make that mandatory now, and that has to
change. And not all states release their data,
which to me, I don't understand. There must be
some reason that I don't get.

There should be regulations about monitoring
those patients to prevent diversion, so pill counts
and urine tox. I really do believe that there
should be a task force set up to examine in depth
what can be done to monitor these patients really closely to improve their pain relief, yet make the public safe. Thank you.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Jowza?

DR. JOWZA: Thank you. Maryam Jowza. There was something I thought could be a suggestion that could help improve the safety of not just the high-strength opioids but just all opioids, specifically to reduce the number of pills on the street along the lines that Dr. Mackey was talking about.

There are these Deterra bags which we use in our clinic. They cost $3 per piece, and you basically put the unused pills, and I think you add a little bit of water, and it deactivates them; perhaps making that available or asking the pharmaceutical companies to make them available, to be given to patients with each prescription, and that would also drive home the point to the patients that these are not medicines that you want to keep on hand, and these are things that you want to get rid of.
DR. HERNANDEZ-DIAZ: Thank you. Dr. Lesar, I know you have to run as well.

DR. LESAR: Tim Lesar. I just want to address that patient counseling, when you go to a pharmacy to pick up a prescription, you are required to give them the REMS. So it's put in a paper bag, and it's handed to the patient, and they're asked do you want counseling?

I would suggest that a REMS could be created given the situation, and a terrible situation has been created by this, that the pharmacist is required, not the technician -- to talk to the pharmacist, and they would have a simple message. If misused, this drug could be fatal. Never share this medication. Must store it. Must dispose. All the instructions are in the REMS.

That would be completely different than what patients experience at the pharmacy for all other drugs and would certainly put a focus on this problem and provide a second reinforcement of things that were said by the prescriber.

DR. HERNANDEZ-DIAZ: Thank you. Dr. Nelson.
DR. NELSON: Sorry. My ride is leaving.

That's why I'm going to try to go if that's okay.

A lot of what I was going to say has been said, and that's wonderful. I am a regulatory hawk, and I people probably know that because I always recommend these things.

But a good model REMS for this is the TIRF REMS. And some of the changes that went on with the TIRF REMS in terms of requiring documentation of opioid tolerance, something along those lines could be done here. It doesn't have to be that necessarily, but there could be documentation of some things, some key piece of information that would assure that the right person's getting the drug, and that they understand all of the issues associated with that drug.

In addition, I know Ron Litman wanted to create a registry for evidence collection. I think a registry is a great idea, just like it's being done for TIRF REMS. Given the relatively low volume of high-dose formulations, 1 percent, it
doesn't seem like it should be a tremendous burden, and it would allow us to provide tighter regulatory oversight of who's getting the pills and what the indications are.

I know we can't limit by indication, but it does seem to me to be a good way to monitor and control who's getting what. So I think just like the TIRF REMS, those two things come together very nicely.

The one thing I would say that always bothered me is the fact that you need to take an 8-hour course and pass the certification test to prescribe buprenorphine, which is a reasonably safe drug with relatively little abuse. And you need really nothing, a voluntary REMS, which nobody really takes, as far as I know, to give out a drug that's highly addictive, highly problematic, highly associated with all the things we talked about: hyperalgesia, tolerance, dependence, withdrawal, overdose, and death. And you really need nothing to do that except a license and a DEA number.

Now, getting rid of the waiver is one idea,
which is totally separate, but doing something to really increase the assurance that people that are prescribing these and people that are taking them are adequately trained to use those medications and understand all of the implications. That is not a voluntary REMS. That's a mandatory REMS with a lot of teeth. So that's my regulatory perspective on improving safety.

DR. HERNANDEZ-DIAZ: Dr. Zivin?

DR. ZIVIN: Circling back to -- we talked about this earlier -- the blister packs or some other physical change in packaging might be another way to prevent at least some of the grabbing handfuls of pills or not remembering if you've taken the pill already. Maybe if that packaging -- I don't know if it's metal or however it was -- could also have written on it, some of these risk warnings that we've talked about. I also agree with removing the waiver requirement for buprenorphine.

DR. HERNANDEZ-DIAZ: Dr. Marshall?

DR. MARSHALL: One thing that hasn't been
talked about much is the effect of direct to
provider marketing of opioid products on physician
behavior. We published a paper last year showing
that receiving even one free meal related promotion
of an opioid product can influence opioid
prescribing the next year.

There have been some states that have
attempted to regulate this. I'm just not sure if
that can be regulated federally, and if so, if that
falls under FDA purview.

DR. HERNANDEZ-DIAZ: Dr. Hoffer?

DR. HOFFER: This is Lee Hoffer. Actually,
just a follow-up on that. I think it would be
really exciting to do actually direct-to-consumer
advertising. The drug companies are allowed to do
this for these products, and some of them have done
that to unbelievable extent and are getting sued
for it. I guess I don't understand why the FDA
can't take out these big -- and I don't mean social
media here. I mean the New York Times, USA Today,
wherever people are reading information about some
of these issues that we've talked about.
Here, I would go back to Dr. Robotti's comment that it's the low-dose stuff. There's just basic information I think people still need, and consumers can put a lot of pressure on providers, not only to get drugs, but to not get drugs that they think are dangerous.

So I think some of that could work to our advantage with this problem that hasn't been used. It'd be really cool to see a full-page ad in the Times, or the Post, and various newspapers that runs every, I don't know how often. I don't think probably FDA can even do anything like that, but I think it would be nice to see -- and I know you have a communications program. I'm not on Facebook, but there's got to be some way to increase the direct-to-the-public information regarding the safety of these drugs.

Then the other one for me would also be training. I think medical school training, have the drug companies pay for it that make these drugs. Make it mandatory and pay the professors. There's got to be some incentives. The drug
companies have incentives to get doctors to prescribe those medications, so they should be able to come up with incentives for students to take those classes.

I think there are some different ways to think about -- and I don't think probably FDA can do any of these things, but I think it's time to step up the pressure a little bit, if possible.

DR. HERNANDEZ-DIAZ: Thank you.

Mr. O'Brien?

MR. O'BRIEN: Joe O'Brien. I guess at the end of the day, I just want to say that opioids have actually saved my life. I can say that. If I didn't have them at a particular point in time, then it would've been disastrous for me. On the other hand, it controls my life, and it provides risks both to me and to the rest of the people, to my family and everyone around.

The last couple of years on this panel, we've had companies who have come, and the focus has been on abuse deterrence, but it doesn't appear that abuse deterrence is realizing the outcomes.
that we would hope that abusive deterrence would do. It doesn't seem to be showing in the data.

We've had focus on patients and guidelines for prescribing, but I think we really have to do something about focusing on the companies, and really getting -- and not necessarily in a regulatory manner. I said it probably kidding earlier, but I guess I mean it. They have to be very clear that either they're going to be sued out of here, or they have to come up with a drug that's safer.

Pain isn't going to go away. Patients are going to need some type of pain management. And it's nice for all the modalities, but that by itself isn't going to work. We need a medicine that, a pain analgesic that works, that's not providing that risk that it does at this level. And if they don't get that now, then they're never going to get it, and I think you have to focus on them.

DR. HERNANDEZ-DIAZ: Dr. Goudra?

DR. GOUDRA: Basavana Goudra from Penn
medicine. Just two small points; I don't know, again, whether FDA can do anything about it. In order to save lives, I don't know why -- if FDA can make Narcan widely available, say in schools, in restaurants, McDonald's, or Dunkin Donuts.

The second thing is education. My son is a high school senior, and when I asked him have you had any classes or is anybody coming and talking about opiates, he doesn't know. I don't know whether it can be introduced in the school curriculum or somebody -- I don't know, again, whether FDA can do anything about it, but just two small points. Thank you.

DR. HERNANDEZ-DIAZ: Dr. Jowza?

DR. JOWZA: Maryam Jowza. Thank you. One last quick point. I just wanted to caution some of our colleagues that I heard suggesting liberalization of buprenorphine prescribing for addiction because addiction is more than just the physiologic process. I think it's a knee-jerk reaction to want to treat it with a medication.

I think that you need to -- if you're going
to have prescribing capability for medicine like
buprenorphine, then you should also be able to
provide comprehensive addiction care, which a lot
of practices that are currently prescribing
buprenorphine are not doing. And I don't think
we're doing anyone a service by just prescribing
buprenorphine, and we're just replacing one mu
agonist with another.

DR. HERNANDEZ-DIAZ: Dr. Katzman?

DR. KATZMAN: Sure. I'd like to just
comment to your point. There are two things about
the buprenorphine. We use buprenorphine
tremendously when we're worried about a patient
who might have the overlap of pain and addiction,
and we find it very successful in getting patients
off high-dose opiates time and time and time again.

We find it a much safer medication, and we
have three psychologists in our pain center and
embedded behavioral health in all of our primary
care clinics. Actually buprenorphine's been found
to be very effective, actually, with minimal
psychological services. But in our addiction
clinic, we have a lot of psychological services, so
I hear your point completely. So thank you.

I won't repeat anything in B that has been
said. I agree with everybody's points so far, the
safe storage, and take-back, and TIRF REMS. The
only other things that I'll add is I'm wondering,
from a regulatory standpoint, if it has to come
from the insurance companies or if high dose
opiates are approved, is there any way to regulate,
perhaps limiting the number of pills prescribed at
each encounter, for instance, like 14 instead of a
month, or 2 weeks instead of a month.

Then also perhaps mandating that in
high-dose opiates, whether or not we're saying
it's 90 MME or another specific dose, that the
patient has to be given a prescription, let's say,
of naloxone, something like that.

I agree with everybody else's ideas, though,
about the regulatory ideas, as well as removing the
data waiver. I think anyone who prescribes an
opiate needs to also know how to take care of
opiate substance-use disorder.
DR. HERNANDEZ-DIAZ: Dr. Urman, last comment.

DR. URMAN: Just very briefly, any way to lessen the economic impact on patients who get prescribed lesser dose opioids, but end up taking more pills versus higher dose, and that was discussed yesterday. There's a way, whether we work with the pharmaceutical companies or insurance companies.

If we're saying that that pushes people to prescribe high dose or fewer pills for people to basically buy, whether it's co-pays or whatever it is -- so anything that we can do to lessen the economic impact on patients who have to take a lot of these opioids and would end up getting a smaller dose but more pills -- they end up getting higher dose, fewer pills versus low dose, but more pills.

DR. HERNANDEZ-DIAZ: Thank you.

I'm going to summarize by mentioning the titles of everything that has been discussed because the details will be on the notes. We had two general blocks of comments. Some focused on
education, including simple language like the one on the website for example, and communication forums. We know there are materials out there. They have to get to clinicians as well as patients; having, for example, the quality to solve the problem from all sides, with a national effort like interagency and a work collaborative with other groups to improve the appropriate use of high doses and the safety.

We mentioned direct-to-consumer advertising, and I will add and stop the marketing from the companies, both for high doses but also for low doses. Training to medical students and practitioners, but even going to high school students for them to be aware.

Then there is another block that is more about regulations, including labeling, including the packaging format and messages, black box warnings about system abuse potential, and maybe co-prescribing of naloxone when necessary; the need for required training as we require for buprenorphine, including removing the waiver
requirement that is there right now, and having a
REMS that is not only education but it is
mandatory, even maybe requiring ETASU; and using
the PDMP, including making it mandatory, if
possible, so that all data is available. And the
registry can document who gets the drug and
oversight and monitor the use.

Finally, we mentioned limitations in the
number of pills. Naloxone came back a few times,
and keep in mind the economic impact for the
patients in all that, in trying to reduce it. I
know I just mentioned the titles, but you have all
the detailed transcriptions.

Before we adjourn, are there any last
comments from FDA?

DR. STAFFA: Yes. This is Judy Staffa. I
just want to thank all of you for the great
discussion. We've learned a lot. We really
appreciate your efforts. It's clear that you've
read this stuff, and really listened, and really
tried to give us useful information. And I thank
you very much for not critiquing our questions.
That's also very nice. Clearly, we've learned something from the last few meetings.

I'd also like to thank our guest speakers, although I think there's only one left. So yay, you're the survivor, and I also want to thank all the folks that came and spoke in the open public hearing. Again, very helpful, and we appreciate your efforts. So thank you and travel safe.

**Adjournment**

DR. HERNANDEZ-DIAZ: Thank you to the FDA for putting this meeting together. We kindly ask that all attendees dispose of any trash or recycling in the proper receptacles in the hallway, and do not leave any waste items on floor or tables.

Panel members, please remember to take all of your personal belongings with you, as the room is cleared at the end of the meeting day. Please leave your name badge on the table so that we can recycle it. Other meeting materials left on the table will be disposed of.

We will now adjourn the meeting. Thank you
very much. Safe travels.

(Whereupon, at 5:10 p.m., the meeting was adjourned.)