FOOD AND DRUG ADMINISTRATION (FDA)

Packaging, Storage, and Disposal Options to Enhance Opioid Safety

Exploring the Path Forward

Monday, December 11, 2017

8:30 a.m. to 4:20 p.m.

Sheraton Silver Spring

8777 Georgia Avenue

Silver Spring, Maryland

C O N T E N T S

PROCEEDINGS

(8:30 a.m.)

Welcome, Overview, Introductions - Irene Z. Chan

DR. CHAN: Good morning. My name is Irene Chan, and I'm the deputy director in the Division of Medical Error Prevention Analysis, and that's in the Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research. On behalf of the Food and Drug Administration, I'd like to welcome everyone to this very important discussion on Packaging, Storage, and Disposal Options to Enhance Opioid Safety.

The FDA is deeply concerned about the widespread epidemic of opioid overdose, dependence, and abuse in the United States, and we believe that packaging, storage, and disposal options have the potential to enhance the safe use of legally prescribed opioids, and the development of such options is an important component of our multipronged approach to addressing the current epidemic.

Through a cooperative agreement with the

FDA, the Duke-Margolis Center for Health Policy previously convened an expert workshop in June of this year to examine the potential role of packaging, storage, and disposal options. We intend to continue that conversation here today, and we want to advance our understanding of the specific problems that these types of options can help address, how they may be designed, and what types of data are needed to evaluate these options, both in the pre-market and the post-market settings.

We hope the information gathered here will allow FDA to continue creating a regulatory framework that supports and encourages the development and approval of these packaging, storage, and disposal options to enhance opioid safety.

There are a few housekeeping items and ground rules I'd like to review. The restrooms are located adjacent to the elevators, down the hall to the left. The WiFi network information is listed at the registration table. If you need shuttle

service to the metro, please see staff at the registration desk. If you have an emergency please also see the registration desk. Lunch options are available in the hotel as well as outside the hotel. For assistance, see the registration desk. Please silence your cell phones, smartphones, and any other devices if you have not done so already.

This workshop is being webcast and audiotaped. Transcripts and tapes of the workshop will be made available on the FDA website after the workshop. You were provided a copy of the agenda at the registration desk, and we will stick to the schedule, so please return from breaks and lunch promptly. Please do not interrupt the speakers. Public comment will only be taken during the audience participation periods as identified on the agenda.

The audience participation periods are at the end of each session time to allow for comments that pertain to that particular session. Please note that this workshop is not intended to discuss the merits or regulation of any specific product.

We ask that the audience refrain from asking product-specific development questions of our panelists.

During the audience participation periods, the microphone for audience participation will be located between the panelists and the audience, as you see there. If you wish to provide comments on the topic, please form a line behind the microphone at the appropriate time, and an FDA staff person will be there to assist you. For our panelists in the room today, as you speak, please make sure you are using the microphone in front of you, and please also identify yourself each time that you speak.

What I'd like to do is to start off with an introduction of our assembled panel of experts and stakeholders at the table. I'd like to ask that we all go around and introduce ourselves briefly. That includes both the FDA and the non-FDA panel members. So if we can start on that end with Dr. Bateman.

DR. BATEMAN: Good morning. Brian Bateman.

I'm chief of obstetric anesthesia at Brigham and Women's Hospital and associate professor at Harvard Medical School. I do research in pharmacoepidemiology, focused on opioid use during pregnancy and in the perioperative period.

DR. WALSH: Good morning, everyone. My name is Sharon Walsh, and I am a professor of behavioral science, psychiatry, pharmacology, and pharmaceutical sciences at the University of Kentucky and also the director of the Center on Drug and Alcohol Research. I do clinical research on opioid use disorder, treatments, and abuse liability.

MR. SMITH: My name is Chris Smith. I'm the director of federal public policy with the National Association of Chain Drug Stores.

DR. RAO-PATEL: Good morning, everyone. I'm Anu Rao-Patel. I'm a physician. I also work at Blue Cross Blue Shield of North Carolina. I'm here representing both my plan as well as the Blue Cross Blue Shield Association. In addition to my role at Blue Cross, which is primarily utilization

management, I'm leading an internal opioid work group, overlooking for strategies to deal with the opioid crisis. I also continue to see patients on a part-time clinical basis.

DR. MIECH: Good morning. My name is Richard Miech, and I'm professor at the University of Michigan and principal investigator of Monitoring the Future, which is a survey that tracks trends in adolescent drug use. We survey 40 adolescents ever year in the 48 contiguous states with a nationally represented sampling.

DR. MENDELSON: I'm John Mendelson. I'm an internist and a clinical pharmacologist. I'm currently at the Friends Research Institute where I conduct some clinical research. I'm also active in clinical practice, so I monitor the past as opposed to the future and the present. I'm an entrepreneur with a digital health start-up that's not related to opioids.

DR. GREEN: Good morning. I'm Jody Green, [inaudible - feedback] Development Center. I study misuse and abuse, burden of prescription in

patients, as well as pediatric exposures and safety of products in the home for consumer products as well as prescriptions.

DR. EMMENDORFER: Tom Emmendorfer with Department of Veterans Affairs, and I'm the deputy chief consultant for Pharmacy Benefits Management Services.

DR. CICCARONE: Good morning, everybody. Dan Ciccarone, professor of family community medicine at UCSF. My research is primarily around the public health aspects of heroin and opioid use.

MS. COWAN: Hi. Penney Cowan, founder and CEO of the American Chronic Pain Association. We provide peer support and education for people living with pain.

MS. WHALLEY BUONO: Hi. I'm Elizabeth Whalley Buono. I work within the patient medication adherence division of the MeadWestvaco Packaging Corporation.

MS. DORGAN: Hi. I'm Carolyn Dorgan. I'm an engineer and team leader reviewer of combination products team lead in the Office of Device

Evaluation at the FDA.

DR. BERTRAM: My name is James Bertram. I'm with the Center for Device and Radiological Health. I'm a jurisdiction officer, so I look at products that touch each of the centers in the agency.

MR. RAULERSON: My name is Patrick Raulerson. I'm a senior regulatory counsel in CDER. I work on combination products issues and other portfolio matters.

DR. SLATKO: Good morning. I'm Gary Slatko. I'm the association director in the Office of Medication Error Prevention and Risk Management in CDER.

DR. MEYER: Good morning. I'm Tamra Meyer. I'm the acting team lead for the prescription drug abuse team in the Office of Surveillance and Epidemiology.

DR. STAFFA: Good morning. I'm Judy Staffa. I'm also with the Office of Surveillance and Epidemiology. I oversee our office's activities in the area of opioids.

DR. MASUCCI: Good morning. I'm Iris

Masucci from the Office of Medical Policy in FDA's Center for Drug Evaluation and Research.

MR. TRAN: Good morning. I'm Paul Tran. I'm a pharmacist in the Office of Surveillance and Epidemiology.

DR. THROCKMORTON: I'm Doug Throckmorton. I'm the deputy director for regulatory programs in the Center for Drug Evaluation and Research. Among the things I help work on in the center are controlled substances.

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

DR. CHIAPPERINO: Good morning. I'm Dominic Chiapperino. I'm the acting director of the controlled substance staff in CDER.

DR. RAUSCH: Good morning. I'm Paula Rausch. I am the associate director of research and risk communications in CDER's Office of Communications, overseeing research related to drug and drug safety related issues, including opioids.

(Introductions inaudible - off mic.)

DR. KELMAN: Hi. Jeff Kelman, Centers for Medicare and Medicaid Services. I'm the chief medical officer for Medicare.

MS. MORGAN: Hi. Sharon Morgan at the American Nurses Association. I'm an RN and an adult nurse practitioner. I have over 25 years experience in acute care, hospice, palliative care, infectious diseases, and Third World health care. Thank you.

MR. WEBB: Good morning. Kevin Webb, director of government affairs and advocacy at Mallinckrodt Pharmaceuticals. I lead our corporate opioid safe use, abuse, diversion, and disposal initiatives for the organization.

DR. SCHARMAN: I'm Elizabeth Scharman. I'm director of the West Virginia Poison Center and professor of clinical pharmacy at West Virginia University; research in unintentional poisonings in children, and my research and teaching areas are clinical application of evidence-based research.

DR. TWILLMAN: Good morning. I'm Bob

Twillman. I'm the executive director of the Academy of Integrative Pain Management. We're a national, multidisciplinary organization for pain care providers.

DR. PATEL: Hello. I'm Ashesh Patel. I'm an internist practicing in Washington, DC. I'm also the governor of the DC chapter of the American College of Physicians.

DR. CHAN: Thank you, everyone. I would also like to identify the FDA press contact, Tara Rabin. If you're in the room, if you could stand. Thank you very much.

Thank you, everyone for introducing yourselves. Before we proceed with the workshop, I'm very honored today to introduce our commissioner, Dr. Scott Gottlieb, who will be providing some opening remarks. Dr. Gottlieb was sworn in as the 23rd commissioner of Food and Drugs on May 10, 2017. He is a physician, medical policy expert, and public health advocate who previously served as the FDA's deputy commissioner for medical and scientific affairs; and before that, as a

senior advisor to the FDA commissioner.

Dr. Gottlieb.

Opening Remarks - Scott Gottlieb

DR. GOTTLIEB: Thanks a lot. Thanks for having me. It's a real honor to be with such a great group today.

I want to thank you for joining us today for this discussion on how packaging options could play a role in driving more appropriate prescribing of opioids. It's widely accepted that the epidemic of opioid addiction has reached tragic proportions, and the scope of the crisis makes this problem very hard for us to fully remedy, and I think it's clear for all of us involved that there's no single solution and there's no magic bullet to this challenge.

No one agency acting on its own unilaterally can stem this crisis. It's going to take concerted, coordinated action by everyone involved, and it's going to take layers of different solutions to start reducing the rate of new addiction and helping those who are currently

addicted make the transition to lives of sobriety.

We need to be creative and take advantage of every tool and opportunity we have to advance these goals. Taking on this crisis remains my highest priority since I landed in this role of FDA commissioner, and it's one of the highest priorities, as you know, of the administration as well. And I believe how we package opioids can be a big part of our framework that drives more appropriate prescribing. That's why I think the discussion today is so important and why I'm so delighted to be here.

In conjunction with today's meeting, our opioid policy steering committee is also publishing a Federal Register notice that asks certain questions related to steps we might take to better address the crisis. The two actions, the meeting today and the questions we're seeking comment on in the new FR notice, share some common threads about the steps we might take going forward, and I want to share with you some of our thinking.

There are a lot of challenges when it comes

to the way that opioids are being prescribed. If there were not tragic mistakes being made, we wouldn't have the crisis that we now face. And because the epidemic has grown so vast, so pervasive, and so deadly, the kinds of actions we must consider to stem the tragedy are in my view going to be far more intrusive than the steps we might have taken a decade ago that could have slowed the rate of new addiction in the scope of the current crisis.

This meeting about the use of packaging solutions, more broadly beyond the use in limiting quantities of opioids available for misuse, includes the use of packaging innovations to improve storage and disposal and measure adherence. All this work has a goal of preventing misuse.

For example, improving disposal of unneeded opioids is another high effective way to reduce the supply on the market. But packaging can also be a tool to address certain aspects of the prescribing challenges that we face related to opioids. And with respect to those clinical challenges, I see

these broad areas of prescribing activity that we need to take new steps to try to address.

We know, for example, overprescribing for routine medical problems can probably be suitably addressed with non-opioid alternatives. This is, for example, the 30-day supply of Vicodin for a tooth extraction or for a routine musculoskeletal injury. Why couldn't a 3-day course of treatment be sufficient for a first dispensed or a trial of ibuprofen?

We also know that some of this overexposure to opioid drugs ends up fueling new addiction, and multiple studies have shown that excessive quantities of opioid medications are routinely prescribed for all types of surgical procedures as well as after emergency department visits for painful conditions. Most patients save leftover pills, so large amounts of opioids are unnecessarily made available for diversion.

Today I want to focus on this routine overprescribing of opioids for more common medical problems, including conditions that might be

appropriately handled with non-opioid alternatives. In my view, the question is this. How can we put some speed bumps in front of this behavior to tell everyone to slow down a little? That's where changes in packaging could be a part of a more comprehensive approach to reducing routine overprescribing.

Consider this one hypothetical scenario. Imagine if FDA worked with medical professional societies to create expert guidelines about what appropriate prescribing and dispensing should be for different medical needs. Under this hypothetical, the dental society might promulgate guidelines and stipulate that no dental procedure should require more than a 4-day course of treatment of the initial fill. If these guidelines were in place and had sufficient scientific support, under our current regulations we'd be able to incorporate this information into product labeling.

Once these were part of our labeling, it opens up certain possibilities about how we drive

more appropriate prescribing. We could, for example, require that the immediate-release drugs be packaged in units that comport with the majority of these consensus durations.

Let's say that recommendations for most of the medical societies cluster around proposals for 2-, 4-, and 6-day courses of therapy. Could we require certain drugs be packaged in these units like we see prednisone packs currently sold on the market? Could then electronic prescribing systems bring these options up as a default for clinicians? Then once we had more recommendations for shorter-term use and packaging that contained these shorter duration dispensed units, we could then consider linking quality metrics to these thresholds.

Educational requirements could also play a role. If doctors wanted to prescribe the packs of 4- or 6-day courses of treatment, they could continue to write for these drugs in the manner they prescribe today. But if they wanted to prescribe a 30-day course of therapy, they'd have

to go through some additional certification steps like mandatory educational requirements. You can start to see how packaging can become part of a more comprehensive approach.

In addition to the idea for a blister pack that has a defined duration of use that might be for only a limited number of days and doses, there are other considerations where packaging can play an important role. Other packaging innovations could make it easier to track the number of doses that have been taken, and still other options could work to improve storage and encourage prompt disposal to reduce the available supply and reduce the risk of third-party access such as a child accidentally ingesting pills they found in a medicine cabinet.

There are also technologies that could allow providers, pharmacists, or family members to monitor patient use of prescription opioids. FDA's committed to exploring our existing authorities to find new and impactful ways of regulating packaging, storage, and disposal options to improve

safety, all the while keeping in mind the balance we need to strike between those who need these medicines to function in their daily lives, which may be unfortunately filled with pain from a chronic disease or cancer. We need to balance our steps to address the opioid epidemic with the legitimate needs of patients with painful conditions.

At this meeting today, as it gets underway, we're also announcing in the Federal Register, as I mentioned, a public hearing we plan to hold and a series of questions we intend to ask in a new public docket. These two steps are part of one comprehensive policy effort that's currently underway at the agency.

The notice we released today and the questions we asked also foreshadow other ideas we're contemplating. Picture this as one example.

A doctor believes it's necessary to prescribe an opioid analgesic to one of their patients. When entering the electronic prescription to the computer, it prompted that the

number of pills they're seeking to prescribe is higher than the recommended number for a particular clinical need. And in order to proceed, the doctor would provide justification as to why the quantity he seeks to prescribe is medically necessary or consider alternative treatment options for their patient.

Importantly, this wouldn't take the place of a prescriber's best clinical judgment or limit access for patients for whom chronic use of opioids is the most appropriate therapy, but it would give providers a chance to carefully consider when the amount prescribed is proper for their patient or if there are non-opioid drugs that could be used instead.

Another approach the opioid policy steering committee is considering would require drug sponsors to create a nationwide prescription drug monitoring database, an approach that we believe could be more effective in helping healthcare providers identify patients that could be misusing or abusing prescription opioids and provide

real-time alerts about potentially harmful drug-drug combinations.

While we recognize that some of the ideas we're exploring were unprecedented, the tragic truth is that the crisis is so immense that we need to consider a range of more impactful options that we may not have considered before. Ultimately, we believe it's our obligation to identify and explore every option available to us. We're determined to make sure that when combined with other efforts we and others are taking, these new steps may yield meaningful results.

So I look forward to hearing the summary of what will be no doubt a very good discussion here today. I want to thank all of you for taking time out of your busy schedules to join us as we struggle to improve these public health challenges. Thanks a lot.

(Applause.)

DR. CHAN: Thank you, Dr. Gottlieb.

Before I move forward, I did want to take an opportunity to welcome Dr. Bosworth as well as

Dr. Izem in the room. If they could just take a moment to introduce themselves.

DR. IZEM: Good morning. I'm Rima Izem. I'm a team leader in the Office of Biostatistics.

DR. BOSWORTH: Good morning. I'm Hayden Bosworth. I apologize for being late. My flight was an hour and a half late. I'm a faculty member/professor of the Department of Population Health Science at Duke University.

DR. CHAN: Thank you.

Before we jump into the sessions, I'm going to walk briefly through how this workshop is laid out since this is not an advisory committee meeting. We've invited a diverse group of scientists, federal partners, manufacturers, patient advocates, payers, and other stakeholders with the aim of having an open scientific discussion over the course of the next two days.

Today, we will be walking through a narrative arc that starts with defining the problems that we hope packaging, storage, and disposal options can help to address, then thinking

about how to design these options that have the features and technologies that can truly address the problems and their associated behaviors. From there, we will talk about how the options may be regulated and consider the realities and challenges around integrating these options into the healthcare system.

Tomorrow will allow us to take a deep dive into the data considerations in both the pre-market and post-market settings and consider further also how the data will drive the labeling claims for these options. We'll want to explore existing research methodologies that can be leveraged and consider new methodologies that may be needed. We'll also need to explore whether in the post-market setting there are existing or modifiable data sources that could allow for detection of these options.

We anticipate it will be challenging to study these options, especially as we consider how to isolate the effectiveness of any particular option, considering the vast number of

interventions that are being directed at the opioid epidemic at present.

With each session, there will be an opening presentation or two to tee up the session topic, followed by a panel discussion where we will explore the answers to specific questions that FDA has crafted. Following the panel discussion will be an opportunity for comments from the audience, where they can provide input for the scientific discussion if they would like to.

There will not be formal presentations from the audience as you might see in an advisory committee or another formal meeting that FDA would hold. We have an esteemed panel of experts and stakeholders, but we also recognize there's a lot of valuable expertise out there that we could not invite to sit on our panel. And we do still want to hear your input, so please consider contributing.

In the interest of time, we will limit each audience participation speaker to 3 minutes during that session, but we do also have an open docket

where we encourage you to submit additional comments before February 12, 2018. The instructions are a part of the Federal Register notice.

For topics such as those being discussed today, there are often a variety of opinions, some of which are strongly held. And our goal is that today's meeting will be a fair and open discussion of these issues, where individuals can express their views without interruption.

Before diving in, we need to review a couple of key terms that we're going to use throughout the workshop. You will hear the FDA use the term "option" or "options." When we say options, we're referring to any packaging design, storage, or disposal product that might be developed or currently exists and could potentially play a role in enhancing opioid safety.

A "tamper evident package" is defined in the regulations as one having one or more indicators or barriers to entry, which if breached or missing can reasonably be expected to provide visible evidence

to a user that tampering has occurred.

"Abuse-deterrent properties" are defined as those properties expected to meaningfully deter abuse, but this should not be construed as properties that can fully prevent abuse. It's important to emphasize that FDA expects that no option can be created, when we're talking about the options today, that can fully prevent abuse.

The term "misuse" refers to the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse. The term "abuse" is defined as the intentional non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect. Abuse is not the same as misuse.

An "opioid use disorder" or "OUD" is the diagnostic term used for a chronic, neurobiological disease characterized by a problematic pattern of opioid use leading to significant impairment or distress and includes signs and symptoms that reflect compulsive, prolonged self-administration

of opioid substances for no legitimate medical purpose; or if another medical condition is present that requires opioid treatment, the opioid is used in doses far greater than the amount needed for treatment of that medical condition.

Session 1 Presentation - Irene Z. Chan

DR. CHAN: With that, let's go ahead and move into our sessions. I'm going to start Session 1 by talking about where we see a role for these options; in other words, what are the problems that we're trying to address? As a part of this discussion, I'll also share some preliminary ideas and raise some questions around how these options could be included in the product labeling.

The views and opinions expressed in this presentation represent my views. Reference to any marketed products is for illustrative purposes only and does not constitute endorsement by any of the parties listed on the screen. Any labeling statement examples in this presentation reflect preliminary considerations and are included to generate scientific discussion. They do not

represent FDA recommended labeling statements.

During this presentation, I'll be walking through four high-level problems where the FDA has identified a role for packaging, storage, and disposal options. These include accidental exposure, misuse, third-party access, and excess supply. It's important to begin with a discussion about the problems we're trying to impact because identifying target problems and their associated behaviors serves as a foundation for how to approach development of these options to enhance opioid safety.

Dr. Gary Slatko will be discussing a proposed development approach in Session 2 in further detail, but the general idea is to start with the problem you want to target, or problems you want to target, which will then serve as a guide for the development of design features and technologies aimed at specific behaviors. Once you've developed the design for an option, then you do need data to support that the option does do what it's supposed to. And if there's a meaningful

benefit demonstrated, that same data will also drive your labeling approach.

Let's begin by stepping through each problem. We'll start with talking about accidental exposure. When we hear the term "accidental exposure," oftentimes it's the pediatric population that comes to mind. It can be heartbreaking to see and hear stories about unsupervised ingestions of prescription opioids in young children, especially because in many of these cases, the child was exposed to a prescription that was intended for an adult.

In this study, the authors set out to examine the incidence and characteristics of hospitalizations attributed to opioid poisonings in children and adolescents. What they found was that between 1997 and 2012, pediatric hospitalizations for opioid poisonings increased nearly twofold, but the largest percentage increase in hospitalizations over time occurred amongst the youngest children.

In this investigation, the authors' aim to associate monthly trends of adult use of some

classes of drugs to trends in child poison control calls related to those same classes of drugs. The authors make a causal argument using analyses of whether the past data are a good predictor of future outcomes. The research suggests there is an association between adult medication use, specifically of opioids, and exposures and poisonings in children.

So why are these exposures and poisonings happening? After all, haven't we had success since the passing of the Poison Prevention Packaging Act of 1970? That Act required a number of household substances to be packaged in child-resistant packaging that is constructed to be significantly difficult for children under 5 years of age to open within a reasonable time, and Dr. Laura Bix will be speaking more about these testing protocols tomorrow.

Again, why are these exposures happening? To be clear, passing the Poison Prevention Packaging Act has saved lives, however, it is not foolproof. There are still failure modes that

exist that will allow for young children to ingest toxic substances, including prescription opioids.

For example, adults may improperly use the child-resistant closures. They could leave the containers open. They could incompletely close them. They may even transfer prescriptions from one bottle to another. In addition, there is also availability of non-special packaging or non-child-resistant caps for prescription medications. As a pharmacist myself, it would not be unusual working in the retail setting for there to be a request or something noted in a patient's profile indicating that they don't want child-resistant caps.

There can also be inadequate quality control measures by manufacturers that can occasionally lead to defective closures, and there is also the possibility of violations of the law by the pharmacists or the dispensing physician.

So what more should we be doing? We could focus efforts on decreasing the available supply of prescription opioids that the children can access.

However, since there likely always will be some available supply on the market, we could also focus efforts on making it more difficult for them to actually access that available supply, or there could be other interventions to consider.

An example of what can occur in a household is that a parent leaves a bottle of prescription opioid medication on a table or a counter, and it hasn't properly had the cap twisted back on. The toddler finds the bottle, easily removes that top, and eats the medication, resulting in subsequent hospitalization for a massive overdose.

If we can create a packaging, storage, or disposal option that reduces the risk for this type of use scenario occurring in the market, then the agency would want to consider how best to reflect this in the product labeling. Would it be reasonable to state that a packaging has characteristics expected to lower the risk for accidental pediatric exposure of a prescription opioid? And if we do so, it would probably be important not to suggest that these accidental

exposures cannot occur.

Now, let's move on to the problem of misuse. There are different published figures regarding the rate of misuse for prescription opioids in this country. These figures can sometimes vary and be difficult to interpret because operationalizing definitions of misuse and data sources can be challenging.

Many data sources have differing definitions with some combining the concepts of misuse and abuse. Regardless, misuse of prescription opioids is an important problem on which to focus. It has been noted that each day more than a thousand people are treated in emergency departments who are not using prescription opioids as intended.

When we think about misuse, it's important to understand that there is a spectrum of misuse that we're contending with. I break this slide down into unintended and intended misuse, though it's important to point out that the use of the term "unintentional misuse" or "unintended misuse" in this context is not to be confused with the

definition of misuse as the intentional therapeutic use of a drug product in an inappropriate way.

Examples of unintended misuse include a patient who forgets to take a medication or perhaps doesn't understand how to take the medication. As the spectrum moves towards more intentional behaviors, you now have examples where there is therapeutic use of a drug by a person other than the intended patient that may result from sharing of medication. For example, I may give my friend a Vicodin tablet for her migraine. Just to be clear, I wouldn't do that.

(Laughter.)

DR. CHAN: You can also have an example of an intended patient who uses more drug than prescribed to self-treat increasing or breakthrough pain. Another example is an intended patient who's retaining leftover opioids in case of future pain. In this example, the retaining of leftover opioids contributes to excess available supply, which could then potentially be accessed by others.

Based on the examples I just discussed, it

becomes clear that misuse could contribute to accidental overdose of an opioid. It could be a sign of developing addiction, it could contribute to excess available supply, and it could contribute to individuals not seeking necessary care from a healthcare provider.

If we create packaging, storage, or disposal options that reduce the risk for misuse of a prescription opioid, then again, we want to consider how to best reflect this in the labeling. Depending on the data produced, we might consider noting that the packaging has characteristics that improve patient compliance with labeled directions for use.

But of course, medication compliance is a complex issue, and medication use in general is governed by complex behavioral interactions and beliefs, so assessing compliance could be a high bar to reach, but perhaps the labeling would instead describe what a specific option does.

Perhaps labeling it has characteristics that would destroy an opioid after a certain number of

days, eliminating excess supply for example. Alternatively, there may be data that drives the labeling towards noting that the packaging has characteristics that would be expected to discourage the sharing of an opioid medication.

Let's now talk about third-party access, which starts to take us into the realm of abuse. It's important to note, though, that with abuse, like misuse, there is a spectrum of severity to consider. Abuse is a complex and nuanced issue, and it may be important to consider whether options are likely to be more effective or impactful with less severe opioid use disorder.

Having said that, I do want to emphasize that in some cases, a third party may steal a prescription opioid and use it for therapeutic reasons. Additionally, when talking about abuse, patients themselves can abuse a prescribed opioid; however, here we're going to focus on how we keep people other than the intended patient out of a prescription that was not written for them.

The next few slides are broken into

outpatient and inpatient considerations. In the outpatient setting, we could be talking about a scenario where you have adolescents in the home, or there are other family members, or it could be the person that's visiting your open house raiding your medicine cabinet. We're interested in thinking further about adolescent access of opioids in the home where curiosity or peer pressure might lead to first-time abuse or progressive severity of abuse of a prescription opioid.

In this report, the focus is specifically on drug overdose deaths for older adolescents age 15 to 19. What we see in this graph is that after tripling from 1999 through 2007, drug overdose death rates involving opioids for adolescents age 15 to 19 generally declined through 2014 but then increased again in 2015. So what we're seeing is an upward trajectory in 2015 where there's nearly 2.5 deaths per 100,000 adolescents age 15 to 19 that's involving opioids.

Let's not also forget what's happening in the inpatient or ambulatory care settings. There

have been various published reports of healthcare associated outbreaks or infections that are attributed to narcotic diversion by healthcare professionals. In some of these cases, nurses may be removing injectable opioid solutions from a vial and replacing it with another solution such as saline, so that it appears that the volume of the vial's content has not changed.

Now, you may be asking wouldn't someone notice that a cap has been removed from a vial. Unfortunately, it's possible to see a scenario such as that illustrated on this slide, where a hospital has an automated dispensing cabinet, but when the drawer is opened to remove the medication, there are injectable vials both with and without caps present. This can occur for various reasons. In some cases, due to the way a product's manufactured, the cap could have fallen off. In other cases, a vial may have been brought to the bedside only to be refused by a patient.

The main point I want to make here, though, is that there are vulnerabilities in the healthcare

system that can allow for these scenarios to happen, and it raises questions of whether dual tamper-resistant features or other packaging options could play a role in minimizing this type of third-party access.

So again, if we can create an option that reduces the risk for third-party access, then FDA will want to consider how best to reflect this in the product's labeling. Depending on the data produced, we may consider labeling that indicates the packaging has characteristics expected to reduce use by persons other than the intended patient.

So last, we get to the problem of excess supply, and as this slide notes, leftover prescription opioids from previous prescriptions account for a substantial source of non-medical use of prescription opioids among high school seniors in the United States.

You'll note that in previous areas of this presentation, I've alluded to how excess supply can in fact potentiate other problems. Numerous small

studies have assessed leftover pills, storage, and disposal after surgery, and these studies have asked patients various questions such as how many pills they used, or how many pills they had remaining, or even how or where the excess supply is being stored.

What these studies have demonstrated is that the median number of pills dispensed, consumed, and remaining differ by procedure, with the range being relatively large even for the same procedure. But what's also striking is that surgical patients who are prescribed opioids for their pain are frequently left with unused pills, and in some cases these are being stored in unlocked locations such as their medicine cabinets.

So if we can create a packaging, storage, or disposal option that reduces excess supply, whether that's by driving prescribing behavior towards writing for smaller quantities or driving patient behavior towards actively disposing of leftover pills, then FDA will want to consider how to reflect this in the labeling. As discussed during

misuse, perhaps the labeling will describe what the specific option may do, such as packaging that has characteristics to destroy an opioid after use.

This concludes my presentation to tee off the discussion in Session 1. Dr. Iris Masucci will now help begin our moderated panel discussion as we get the questions projected on the screen.

Panel Discussion

DR. MASUCCI: Thank you, Dr. Chan, for the presentation. And also, I'd like to extend another thank you to our panel participants and our audience members both in the room and online.

Again, I'm Iris Masucci from FDA's Office of Medical Policy in CDER, and I'll be co-moderating this session with Dr. Chan. We're going to pull up on the screen a list of eight or so questions that FDA has developed to spur the discussion. We have an ambitious agenda to get through in the next 60 minutes, and we obviously have a large number of panelists. So to best facilitate the discussion and allow everyone to be heard among our panel members, when you are

interested in participating, please raise your hand. My colleague Paul next to me will jot down names in the order that hands were raised, and we'll try to go through them in succession.

To start off, Dr. Chan talked about the four major problems that FDA has identified, where packaging, storage, and disposal options could have a beneficial impact, again, accidental exposure, misuse, third-party access, and the excess supply of opioids. We'd like to hear feedback to get the discussion started about whether our panelists have opinions on are these indeed the appropriate problems on which to begin our focus. So if we could turn it over to the panel, and if people would like to contribute, you can please raise your hand, and we'll get the discussion started.

MS. WHALLEY BUONO: This is Liz Whalley Buono, and I'll just start, because it seems like that spans a pretty good rep of the issue. My personal vision on these scenarios is based on unfortunate personal anecdotes that I'm sure all of us have at this point and late night CSI, which is

probably a pretty good source for some of these scenarios.

I guess my question is, do we know enough from the various poisoning prevention databases to know whether we've really got a visibility on the landscape of scenarios so we can consider whether the behavioral aspects fall into these categories? Has that work been done yet, or do we feel like there's more work there?

DR. MASUCCI: You have to get very close to your microphones, all of you.

DR. CHAN: I think the question is asking about do we know enough about the landscape to say definitively that these are the right problems to be targeting. And that's really the question we have. We think from gleaning what we do know and also from previous discussion at the Duke-Margolis meeting, that these seem to be the issues that rise to the top for people. These seem to be the issues that perhaps some feel are most compelling to begin with but not necessarily to state that these could be the only issues.

So with that, I'd like to actually turn it back to you and others on this panel. What other problems, then, do you see here? We're trying to understand if there is agreement that these could be areas that we probe with these options, but then also understand if there are other problems for which you think these options could be considered.

MS. WHALLEY BUONO: The only thing I'll add -- and the reason that I ask this question is, as Dr. Gottlieb noted, this is such a cross-jurisdictional issue. And I'm wondering whether we've had sufficient discourse with law enforcement and other jurisdictional agencies to know whether there's anything missing here as far as the behavior of third parties.

You've followed the path of the drug, and you've followed the path of the individuals that encounter the drug. Before we put a bow on the problems -- I don't know the answer to it -- it just would be interesting to know have we sufficiently engaged with the other stakeholders, if you will.

DR. CHAN: Yes, Mr. Webb?

MR. WEBB: Thank you. Kevin Webb with Mallinckrodt. I would add the phrase let's not let perfect be the enemy of good on this. I think this is a good place to start. The four scenarios which we present, I think it's an excellent place to at least begin the conversation, as long as -- I think to Liz's point -- we realize that this is not the only solution, but this is a part of the solution.

We also recognize that most of the diversion of unused opioids comes out of the home. So if we can start with the existing patient and move in there, I think it at least gives us a place to begin to move the conversation forward. This is an iterative process as we then continue to understand best practices, what is working, it allows us to continue to build on it.

So I applaud the FDA for putting this question forward because I think it's at least an opportunity for us to say this starts the process of addressing the issue of diversion and how to dispose of unused opioids [indiscernible -

feedback].

DR. CHAN: I think Dr. Kelman was next.

DR. KELMAN: Jeff Kelman. Are we talking about making the packaging a part of the label, and use outside that label, therefore misbranding? That would have a major effect.

DR. CHAN: Yes. I'd like to explore that further in terms of the major effect that you suggest. If you could speak a little bit more to that, how you envision that.

DR. KELMAN: So if it's misbranding [inaudible - off mic].

DR. CHAN: And I'd be interested to hear others' thoughts on that from other payers as well.

DR. KELMAN: I'm not sure there are any payers.

DR. CHAN: Well, I believe we do have a couple in the room, including closed system considerations as well. I think at this point we're still in early exploratory phases with regards to how that labeling would be implemented and what would be the appropriate input for the

labeling. I think fundamentally we would want to get this type of feedback exactly so we can consider the downstream effects, especially as we talk about the integration into the healthcare system and what might be some of those pitfalls.

So this is exactly the type of feedback that we need, and I think we'll have an opportunity also today, when we get into Session 4, about integrating these options into the healthcare system to definitely develop that further.

DR. THROCKMORTON: Jeff, I think we're thinking about this in a two-step, at least preliminarily, so begin identifying solutions that work for particular products and finding a way to potentially include them in the labeling, thinking like we're doing for abuse-deterrent formulations or something like that.

You're asking the longer-term question, once we do that, what happens to the products that don't have that labeling and don't have that packaging, and that's a harder question. If we think of the abuse-deterrent formulations of opioids and the

path that we're walking there, we started with labeling that predicted an effect, and we're working on determining whether or not in fact there is a real-world impact.

I'm not saying I know that's how we go here, but that's at least one way we might think about it. So we wait for that second step potentially. Once we determine that a packaging solution in fact has the impact we really want it to in one of those four areas, then your hard question would absolutely come into play.

DR. CHAN: Our next commenter is Dr. Mendelson.

DR. MENDELSON: Hi. I haven't had coffee yet, so this won't be organized as well as it should, but it seems there are two fundamental problems. There is misuse in the house, and that requires one set of possible packaging solutions. And there's misuse outside in the community, which is diversion, and that requires another set of packaging solutions. In fact, the packaging solutions you do for the house could end up being a

selling point for the ones in the community. If you have a nice little blister pack that tells you exactly what's in it, I think that actually might facilitate drug sales in many locations. So I think that some solutions will lead to other problems.

What I would actually like to know is the rate at which packaging failures have led to pediatric overdoses and the rate at which packaging failures are thought to have led to the diversion. It's fairly obvious that people will have excess opioids in their medicine chest, and if you will take them out, that's a packaging failure of a sort, and disposal might be the option there.

But if that's going to be the option, that you get rid of your excess medications, you're going to have to incentivize the patient so that they actually bring you the package material, a return and get $10, like recycling bottles or something. You're also going to have to think of the user experience as to what's in it for the patient.

Right now, if we give very small amounts of opioids to patients and there's no easy path for refill, the user experience for the patient will be crummy, and the user experience for the doctor will be worse, because on Saturday afternoon, there will be panicked patients calling that they're out of whatever you've given them. If we make it too complicated, we won't solve the problem either.

But my point is I think we ought to be driven by numbers as well. You should be tracking how often packaging failures actually lead to a bad outcome, if that's possible, to the extent that's possible. That will help inform your better packaging solutions.

DR. MASUCCI: Does anyone on the panel have a response to that question?

FEMALE VOICE: Just as a follow-up, for example, poison control [inaudible - off mic].

DR. CHAN: Dr. Green, yes?

DR. GREEN: Jody Green. There are several publications already that go into root cause analysis of things that have led to pediatric

exposures, particularly with buprenorphine in a recent publication, and many of the failures are human failures, not packaging failures, and that makes our job a lot more difficult.

I think that we know quite a bit, but I'm hoping that later in the day, today or tomorrow, we'll actually get to the data from some of those studies that might help us better inform Dr. Mendelson's questions.

DR. MASUCCI: Dr. Budnitz had a comment.

DR. BUDNITZ: Dan Budnitz, CDC. I think we'll get into the details tomorrow, but I think the fundamental question is not so much a failure of the packaging but the way packaging is fundamentally designed, either active mechanism where it requires the parent to put the cap on or whether it's something passive and automatic.

DR. MENDELSON: That is a failure. That's the whole point. That is a product failure. I mean, when you have a car, and you have an accident, and the steering wheel comes through your chest, that's a product design feature problem.

It's also a problem if the person was driving fast, or intoxicated, or in bad weather conditions. But that's a product failure, one way to look at it.

DR. BUDNITZ: Or one could look at the positive aspect where a seat belt is an active safety mechanism --

DR. MENDELSON: Exactly.

DR. BUDNITZ: -- but an airbag is a passive system. And it's not really a failure of each. They're just different approaches.

DR. MENDELSON: Yes, accepted.

DR. MASUCCI: Dr. Emmendorfer?

DR. EMMENDORFER: I'm the disposal side of the equation. In the Department of Veterans Affairs, we have the take-back receptacles that are DEA approved on site in over a hundred locations. But also as a convenience factor for our veterans, we also have the mail-back envelope option to try to encourage the removal of unwanted, unneeded medications from the home. And we do have a tracking mechanism for how many pounds we've received back, and through those two mechanisms, VA

has collected over 53 tons of unwanted, unneeded medications from the veterans, which is like the equivalent of 17 large elephants.

So I do think that there is a very strong component of being able to incentivize patients to try to clean up the unwanted, unneeded medications to help with the issue. Now, out of all those poundages, are all those opioids? No, because they can put anything they want into the envelope, but it is one component.

DR. MASUCCI: Ms. Cowan?

MS. COWAN: Hi. Penney Cowan, American Chronic Pain Association. I was thinking about the labeling, and I think when you're looking at the consumer, the labeling on most medications is not consumer friendly. The text is getting smaller and smaller. So without the education at the point of prescribing it by the healthcare professional and by the pharmacist to really reinforce the fact of what this needs to be, how it should be used, stored, and disposed of -- because I guarantee, most people don't read the inserts, and the

labeling on the bottle itself doesn't really give you those instructions.

So I would just encourage you to think about the number of consumers, the size of the text, the language that's used, the reading level that you're using in order to really have people understand what you're trying to tell them. I think education across the board on all these issues is really important.

DR. CHAN: So with that comment, I think what we're hearing, though, is that you're saying there is an option here. When we think about the development of packaging, storage, and disposal options, there is an opportunity here to actually impact, for example, misuse in that example where you're talking about you're providing education. I think that is what I'm hearing, or providing education with packaging itself.

MS. COWAN: Right. That's obviously not the golden answer for everything, but I think it's going to help. It's one of the many things that we can do. But I think for some people who've never

been told about putting their medications away, or using them appropriately, or not taking them off schedule, all those components, unless they hear it several times and then can read it and refer back to it -- and again, the labeling is just not user friendly right now the way it is.

DR. MASUCCI: I think it would be helpful to remember that when we're talking about incorporating some of this information into labeling, what we're talking about from the FDA perspective, with the first step, is in the professional labeling: the package insert, the information for the prescriber, which is obviously not meant for the patient. And that document is then the basis for FDA-approved patient labeling. And then beyond that you have what the patient may get out in the community for patient information, and how the prescription is actually packaged and the stickers that are on it. So there are multiple layers to what we're talking about when we're talking about labeling today.

MS. COWAN: Right. And I understand that,

but I know the stuff that I get from the pharmacy is not user friendly. Some of it I didn't have to look up because I actually read it, but it's not user friendly. And for many people, they couldn't even see it. The print is getting smaller and smaller.

DR. MASUCCI: Right. And FDA is certainly looking into that with some initiatives about patient medication information, and that's certainly part of the equation, is the readability factor for sure.

MS. COWAN: Great. But I also think the interaction of the pharmacist and the prescriber is also really critical in all of this, that that is communicated because not everyone is going to read it.

DR. CHAN: I think Dr. Bosworth also had a comment.

DR. BOSWORTH: Sure. I have a couple things to just comment on. Building upon what Penney just said, our own data would suggest about 38 percent of the primary care population is functionally

illiterate. So you can create whatever labels you want and provide whatever handouts you want, but just be mindful that a third of your population are functionally not going to be able to read it, let alone see it.

I think that's part of what I'll comment on, is when I look at the literature at the moment, right now, I think we're in phase 1, very epidemiologically focused, and I would suggest that there's a possibility of phase 2 and phase 3. Phase 2 is understanding the mechanisms that are explaining some of these issues, and then phase 3 is actually looking at interventions with a goal eventually of creating a toolbox.

So as I look at the slide with accidental exposure and misuse, third-party access, excess supply, creating a table with solutions that are actually going to help move that, I think the idea of creating one solution or thinking that labeling or packaging is going to get us X, it's just not going to do it.

So just to frame the conversation of what

are the pieces that we need to put on the table and, frankly, evaluate in any capacity, as we think about data, we can create and think about the best things we want. But I don't see a lot of data, and I would want to create labs, learning labs -- I don't mean experimental. What I'm talking about is real-life learning labs where you have the interaction of the healthcare system with a provider and the patients looking at these things in real time.

So those are models that we're starting to look at, and I think there are some really -- so we're not talking three-year trials. We're not talking five-year trials. We're talking about three months turnaround so you actually have data making informed decisions as you move forward. So to whatever capacity that's a possibility to put on the table, I would strongly recommend that because I just don't think -- we're going to create a toolbox if we do this right.

DR. CHAN: Dr. Rao-Patel?

DR. RAO-PATEL: Yes. I was actually going

to comment on her statement, which is I agree a hundred percent. I think there's multiple levels of education. Of course, education's not the only solution for everything, but I think some language simplification in terms of labeling, at least for what the patient gets, I think may help because half the times, as we know in clinical practice, patients often don't know what medications they're on, the names of them, and they often refer to them as like the pink pill or the blue pill.

So I think the education starts with the prescriber actually going over the medication and talking about a risk-benefit of what the medications are and side effects that would be expected, as well as perhaps making it in some ways mandatory that there is a consultation with the pharmacist.

I know right now it's generally asked to the patient if they want to talk to the pharmacist, but maybe that would be an additional speed bump to educating the patient about what the medication is and what it's used for, and disposal options and

storage solutions in terms of safety in their home, as well as labeling to make it simplified for the patient to understand.

DR. CHAN: I'd like to just reshift the conversation back a little bit and get back to the problems because, absolutely, I think a lot of what we're generating here, we start talking about discussions that go into the development of the features, the solutions, and what needs to be part of that design.

If we can switch gears for a moment, during the presentation, I talked a little bit about spectrum of misuse, spectrum of abuse, and that there may be different considerations depending where along the spectrum an individual may be. So do we think that package and storage and disposal options could meaningfully address abuse, for example, if we're talking about an individual, say, on the severe end of the opioid use disorder; or where do we think there may be the limitations to where these options can play a meaningful role?

I'd be interested to understand that a

little bit more from the panel and your thoughts around that. We can open up that discussion.

MS. WHALLEY BUONO: Liz Whalley Buono. As I think about what can we come out of the gate with quickly, obviously we have to look at risk profile of any of the interventions that we're looking at starting with. And even though looking at discrete issues associated with the opioid products is relatively new in what we're studying, we've been studying patient medication adherence for at least 10 years, and there's a lot that we've learned, a lot in the published literature.

We know that there are innovations that work, some moderately, inexpensively; some a bit more complex and reserved for really costly problems. But I think if we look at the adherence issue, there are certain aspects of basic patient medication non-adherence that are relevant to the opioid spectrum. And since they're low-risk interventions, I think there's an opportunity to learn on the fly with some of this.

So if we looked at what we've learned about

patient medication non-adherence in diabetes medications and cholesterol medications, we could start there I think because we know that educational components, reminder components, warning components, and links to ancillary patient support medication all make sense, and they're low risk.

There are things that we could do right now, then we could see are there other attributes of those types of packaging considerations that could be useful for things like identifying when pills have been diverted. I think there's an opportunity to really look at what we know works, what we know is safe, and to start to work with that right now because we can do that, and then monitor what the impacts are on some of the kind of addiction-specific behavioral issues.

DR. CHAN: I think what I heard was this idea of starting with behaviors -- if I'm hearing you correctly, what I'm hearing is that there are a lot of existing options or existing strategies that could be implemented. But it sounded to me as if

in those scenarios we were still talking about where they have more of a preventive effect. Right?

So I'm trying to understand with this question, though, if we have someone who has already developed down this path of more intentional behaviors, where could these options sit or could they be meaningfully applied for this population. So I'm hoping to get some feedback.

MS. WHALLEY BUONO: I'll just add to that. I think that's right, but I think there also could be value for established addiction, if you will. So when you think about expanding the concept of FDA capital "L" labeling, to include things that are not product specific, warning information about characteristics of overdose and things like that. That may very well have an impact on people that are intentionally misusing the product perhaps enough to, if you will, scare them into reaching out for support and things like that.

DR. CHAN: I believe Mr. Smith was next. No? Mr. Webb.

MR. WEBB: Thank you. From a manufacturer's perspective, we've looked at this from several different options as well. Trying to prevent an intentional illicit use of packaging is an incredibly difficult proposition. It's intrusive meaning that if you try to put something into the family or into the home with the caregiver, it's going to be very difficult to use, and costly. The timeline to implement something like that is many years down the road.

Until we have medications that spontaneously become inert or that type of technology, it still requires the patient to activate the packaging that's out there, to activate it on their own. It still requires the patient to be proactive and cause the medication to be neutralized or chemically neutralized. So it's almost an oxymoron of asking someone who has an illicit or significant drug opioid problem to ask them now to neutralize their medication.

So in the sake of expediency of a problem we're trying to solve, prevention through either

accidental exposure or trying to put in speed bumps to try to prevent a young teenager from experimenting with medication, if you can prevent them to getting to the point where they are an illicit drug user for long-term use, if we can prevent that from happening, we start to see victories.

So I would look at what can we solve today. And by today, I mean over the next 12, 18, 24 months, with packaging, and then let's stop the problem from happening, and then let's focus on how do you now get to the illicit hardcore user of medications.

I think that technology is still in its early stages, and I think for us to spend a significant amount of resources and solve something that is really an area that we can do a whole lot more good now, today, I would rather we just say, here's what we can do and have an impact there, and then worry about the -- because if someone's going to misuse, they're going to misuse, no matter what the packaging is. You can take a sledge hammer to

it; you're still going to get the medication out of it. But if you can prevent someone, say, they stumble across one or two of non-user of opioids, prevent them from experimenting with it, at that point, now you start to have progress.

DR. CHAN: Dr. Bateman?

DR. BATEMAN: I just wanted to make a point about how central I think overprescribing leading to excess supply is to the entire issue from adolescents who experiment to hardcore illicit use. If you look at the SAMHSA survey of people who use prescription opioids non-medically, far and away, the leading source is obtaining the medications from friends or family members. So if we can develop strategies that will lead clinicians to prescribe in a way that's appropriate to the indication, I think that's likely to have a very big impact.

There are now data from a wide range of clinical settings -- dental procedures, surgeries, primary care settings -- where we see that physicians prescribe greatly in excess of what

patients ultimately use and that patients hold on to the leftovers. To my mind, that's a critical point where we could really make an impact.

DR. MASUCCI: I believe Dr. Walsh was next.

DR. WALSH: I have two comments. I want to concur with Dr. Bateman. I think that if it's possible to use packaging to actually be an instruction set for providers, that would be invaluable. It's hard to imagine that in the current situation where this is in the news every single day and there's pressure on professional organizations, that we still see really inappropriate prescribing going on.

In my state, we passed a law for a new pain prescription for acute pain that could be no more than 3 days this past year. So what we're seeing is that physicians are prescribing the equivalent for 9 days or 12 days, but they're being written as a 3-day prescription so that they can obviate the problem of having a patient who wants more pain relief outside of the 3 days. So then you have young high schoolers going in and getting a

prescription that's reading 120 milligrams of hydrocodone a day. This is actually a real story. And then co-prescribing with benzodiazepines, for example -- and I know that there's a black box warning now, but it's just not sufficient.

So the whole idea that packaging could be used really to serve as education and reminders for physicians would be incredibly valuable. I at the same time know that it's really important to not limit access for the patients who need it, but I can tell you that the prescribing practices are still really alarming, from my perspective.

I work every day with people who have opioid use disorder. I also have worked really closely with the FDA on the abuse-deterrent formulations. I really have a hard time imagining that the most determined user who's physically dependent on opioids would be deterred by any packaging unless it had explosives in it.

I mean, I just can't -- no, I mean I'm really trying to think about what the technologies are. I just can't imagine that that's the person

that we want to target, because even with the abuse-deterrent formulations, as soon as one gets marketed, you can find how to extract the drug online. People are inventive and creative and very motivated. So I don't think that that's really the target population where we could make the most impact sooner.

DR. CHAN: Dr. Bosworth?

DR. BOSWORTH: As a trained psychologist, I looked at behavior. Two areas to focus on is linking the monitoring, so any successful behavior change really requires some form of monitoring, and then being able to report back to -- closing that loop to whatever capacity. I think incentives also people have mentioned briefly as well. Whether it's behavioral economics, whatever way we want to frame them, those are usually useful, but they're short term. That to me, the monitoring to whatever capacity, is one of the consistent issues that would probably underline whatever you look at.

I do want to make a comment that there's some reference to what I would interpret as

implementation science, but I also want to make people aware that there is a field growing that is de-implementation science, which in many ways I think is -- we try to think about getting all these successful products and programs into the healthcare system, but frankly we also have to think about how do we take the unnecessary or useless things out, and we really haven't thought too much about that as much, but NHLBI had sponsored a whole conference focusing on de-implementation about two months ago.

So I think while opioid use, we could look to adherence as a field, I think it's actually slightly different. It's not the opposite of implementation. De-implementation is a different field, and I think that there are some methods that we could look towards to help think about how we evaluate that and look at that. So I just wanted to raise that as an issue, de-implementation.

Lastly, I don't want us to forget the chronic pain individuals. I work in sickle cell and just really thinking about how do we create a

solution but also not throwing them out in the bath water either, so whatever capacity we can consider them as well.

DR. CHAN: Dr. Bosworth, you raise interesting points about monitoring potential technologies that might be integrated into some of these options that give feedback mechanisms, for example, and we've certainly seen some of these things out there.

So if we now add that to the equation, thinking about options that might be developed that could have these monitoring systems where a provider or a family member is notified, hey, someone's getting into this medication here, and I didn't expect it, in that scenario now, does that shift our opinions with regards to perhaps the value of some of these options in situations where you're looking at perhaps more intentional behaviors?

I'd let Dr. Bosworth start.

DR. BOSWORTH: I think that starts the first part of the solution, and you need that piece of

information. We see now, if I do look to the adherence literature, simply knowing someone is non-adherent is useless. What I want to know are the barriers and the facilitators. To me what that does is queue up that there needs to be the next step to understand what is going on and, frankly, training people.

So to whatever capacity, whether it's the pharmacist, or whether it's the primary care doc, whoever it is, we're not doing an adequate training. Just to simply put it back in their hands to assume they're going to close the loop I think is going to set us up for failure.

I just would look at it as a sequence. I think it's a starting point. It's really helpful. It's absolutely essential. But then thinking about what that incentive is to also create somebody to do that and try to think about how I can have solutions or tools to close that loop is really crucial.

DR. MASUCCI: I think Dr. Scharman was next.

DR. SCHARMAN: Yes. You were asking if

these were the appropriate problems to focus on. The one thing I think is not on this list are therapeutic errors. The number of patients on benzodiazepines, the number of patients with COPD taking these medications is a significant problem. So maybe it's not just opioid packaging preference; it's the co-existence of benzodiazepine packaging as well. I think we have to look beyond just simply opioids.

When it comes to labeling, maybe that goes into including the concept of prelabeling as well rather than educating the patients after the fact with a label that they take home like we do with other REMS programs. We will hand them a bunch of paperwork when it's dispensed. Again, when you get a vaccine, you're asked a series of questions before you get the vaccine; A, are you sick today, whatever? But we don't do that for opioids.

So the patient before they even get the prescription, is there pre-patient labeling where we make sure the patient is educated so that they understand if they're on a benzodiazepine, they

need to disclose. If they have a respiratory condition, they need to disclose. Did they understand that these medications are addicting?

I think we're in it so long, we assume everybody knows what an opioid is. We assume that someone knows hydrocodone is an opioid and is addicting, and I don't think they do. So I don't think patients can be advocates for themselves. I think pre-prescribing patient education so they can be their own safety monitors and advocates is very important. I think we need to think about that population as well.

DR. MASUCCI: Ms. Cowan was next.

MS. COWAN: When I'm thinking about disposing of these medications, I've talked to a very large, broad population. No one returns unused opioid medications because they're too hard to get, so they keep them, even if it's one or two pills. And I'm wondering if there was a way we could actually give people credit for returning them. In other words, so now their provider, their pharmacist, actually know that they actually do

return these, so the next time they need them, it wouldn't be so hard to get.

I don't know if there's a way of tracking that, not disposing of them in the places where nobody knows that they've actually returned them, but actually giving them credit for giving them back to the pharmacy to say, yes, I returned this, so now the next time I need it, I'll be able to get it. I don't know if that would help or not.

DR. MASUCCI: Ms. Buono was next.

MS. WHALLEY BUONO: Liz Whalley Buono. I think it's worth just revisiting electronic monitoring to answer your questions about that. There's a lot of experience with electronic monitoring both in the clinical trial as well as some in-market experience. It's not uncomplicated. And to Hayden's point, there are a lot of pieces that have to be put in place for there actually to be behavior modification. And it's also not inexpensive even though the price has come down. There are versions, whether it be a cap or RFID-fitted blisters, that are out there.

It's just important to recognize that there's got to be a backend solution to that so that the data captured can be analyzed and whether that's provided to the patient in the context of consumer convenience products, or whether it goes where it's more successful to the provider or the physician or the pharmacist so that you can look at what does the adherence pattern look like and discuss with the patients, to your point, why are you missing Tuesdays, that sort of thing.

So the cost really is not in the package itself, but the backend system and the fact that it's got to communicate with the various EHRs and things in order for that data to be used.

The last thing I'll mention is there's been some friction to uptake for in-market applications because nobody's quite clear whether if you put RFID fittings on a blister, does that then become a device, which causes the product to be a combination product, or is that merely a different type of packaging?

I think from a regulatory perspective as

well, if that's somewhere the FDA would like to go to see more of that, perhaps in a high-risk population where the cost is justified, there's got to be some clarity on how that's going to be regulated and how much data needs to be submitted behind that application.

DR. MASUCCI: Let's take two more comments on this question, and then we'll move on. I believe Dr. Mendelson was next.

DR. MENDELSON: Thank you. First off, what's not on your list is scheduling, drug scheduling from the DEA. If you are scheduled, if the opioid products are scheduled too, then you get into the problem that Sharon had. You get into the problem that if the doctor does not write an adequate amount of opioids, they're going to get called on the weekend and have to generate another -- you can generate these now on electronic health records. It's not difficult, but it's a big step of work that's uncompensated for primary care physicians. We primary care physicians, by the way, we're not illiterate. We do know our parents.

Someone said primary care, 35 percent were illiterate, and no, we're not. We know our parents.

But scheduling is a big issue, and I think if you're going to -- and you could propose dual schedules for small amounts of medication like 1 or 2 days worth dispensed. You could maybe go down a notch to 3, and then allow a certain number of refills and still stay within Schedule 3. That would be smart.

Most of us who treat opioid-dependent patients, you start with daily control in methadone clinics, and you move to some kind of weekly control, such as Suboxone induction or buprenorphine induction. And eventually you move out to some longer form of control. So as people slip out of control, you go back to more daily dosing. You move back to daily, supervised dosing.

The model exists, but the schedules the DEA uses makes it very difficult for physicians to implement that. And for pharmacists, I have patients we write every 2 or 3 days, and if the

pharmacist is off, the patient doesn't get their medication. It's cumbersome right now.

DR. MASUCCI: Dr. Bix?

DR. BIX: Several of the comments that came up brought something to the front of my mind. We do a lot of work with labeling, and one of the comments on de-implementation and the other comment about patients not really understanding the addictive properties of these drugs brought something that we hear repeatedly, both when working with institutional providers and also consumers as well. And that's that extraneous information gets in the way of critical information that they need.

I think if there's a hole in the label comprehension approach that we take, it's that we pre-suppose attention to information. We don't really objectively evaluate are people looking at these things and are they capable of reading these things. We go straight to do they understand them. And really, information processing is serialized in that you have to pay attention to it. You have to

be able to read it in order to get to understanding. So I do think that that's a weakness of the way we approach label comprehension and something that we could look at objectively.

DR. CHAN: Thank you. And since you raise the issue of labeling, we are going to switch gears a little bit. Would including information in the labeling -- because throughout the presentation, we talked about some labeling considerations. Would including information in the labeling about some of the characteristics of these options, could that actually encourage innovation in this area if we're supportive of that approach? We'd be interested to hear.

MS. WHALLEY BUONO: As a packaging manufacturer, I'll just say that, obviously, if there is a critical role that can be met by a specific package design, then I think the answer is yes. What's going to spur innovation is adoption of the packaging concept.

Some of the various platforms around calendar blister packaging have large, flat

billboard space that can accommodate information, whether it be drug-specific information or whether it be information about the addictive qualities, or whether it be support services that are available.

Don't jump on me, but my mind goes immediately to tobacco warnings. And I know that's not what where we want to go because we want people to take their medication. But we know that scary packaging information, labeling information, is effective in educating people.

So I think if you can craft information that educates patients that the medication should be taken as directed, but misuse can lead to some pretty terrible things, it seems to me that that's kind of a common-sense approach. And the concept is that information has got to be accessible to the patient. It can't be the kind of information that goes home and gets thrown in the trash.

DR. CHAN: So when we think about including information, I guess the question might be, are there characteristics for which including that information would be more meaningful depending on

who's looking at it? If we're talking about prescribers, patients, versus anyone else in industry, I'd like to get some thoughts around that.

DR. MASUCCI: Dr. Webb?

DR. CHAN: Mr. Webb?

MR. WEBB: Kevin Webb, Mallinckrodt Pharmaceuticals. As we think about labeling, one thing I would add -- and there are actually two comments to that -- is I would encourage the use of some type of a teach-back mechanism like we'd see in clinical practice where it's one thing to tell your patient to safeguard their medication or to lock them up, but without giving them the reason why; safeguard your medications because these things, to Liz's point, may happen.

We've done a significant amount of research with patients, and they yet don't see themselves as the source of the problem or as a part of the solution, so they're completely void of real engagement. But I would encourage healthcare providers to not just say do this, but they need to

ask the question what are you going to do with this medication when you no longer need it or if you have leftover medications. Have the patient tell you.

So if we can put it in the labeling, that way it engages the patients, and now you have a proactive dialogue with them, because if they say, "Well, I'm not going to do anything with it," or "I'm going to keep it for my kids," now that becomes a stop point to say, okay, well, we need to have a more in-depth conversation.

But the other thing to your point regarding labeling from innovation, again, speaking from a manufacturer's perspective, it needs to be standardized. If you just leave it to a manufacturer to do a thing and leave it up to the manufacturer, you're going to have a lot of disparities. You're going to have a whole bunch of different options out there. Some are going to do it and some are not.

When you look at most of these medications from IR opioids coming out of a generic market, if

one manufacturer chooses not to engage, now you have uncertainty in the market as far what's being said and what's not being said. So there has to be some standardization across the field, and then allow them certain features to be added to it. If the manufacturer wants to be innovative or a packaging company wants to be innovative, he can make a better mousetrap, but there has to be some kind of baseline then to say, okay, this is what it would need to include.

DR. CHAN: Is there anyone else from the product development side, either industry or packaging side, that could share whether or not having information in the label alone is incentive enough, aside from the public health benefit, obviously? But kind of the carrot and stick, if you have good supportive data showing that your product has an impact, is having that information in the label something that would spur you to pursue something in this area?

(No response.)

DR. CHAN: I won't take that as a no. I

will take that as no one wants to comment. That's fine.

MS. WHALLEY BUONO: I'll just answer. Again, Liz Whalley Buono. Anything that gives the alternative type packages value and makes them more commonly use makes it a market where more people are going to enter and try to develop IP or alternatives that will be purchased and used.

DR. CHAN: Ms. Green?

DR. GREEN: Dr. Green.

DR. CHAN: I'm sorry.

DR. GREEN: I guess the one clarification is do companies apply for this labeling, then would some products have labeling and not have labeling. Products with labeling are likely going to be a little bit more expensive and not generic, and then the generics and other products will still be available, so what's the likelihood of those actually being dispensed?

I think that there are a lot of considerations of what the framework would look like. Would it spur innovation? Sure, but at the

end of the day, you still have to be able to get that product out into the community. And as we know from the ADF products, they're a lot of barriers to that.

The theories are great, and it's great to have that, but if we know something works and protects patients and the kids in the community, then why would we not have that as a requirement to entry to the market as opposed to a competitive advantage of some have labeling and some don't?

DR. CHAN: So I do want to go back to the question we asked about depending who's looking at the label, what might be most meaningful to include. I am curious then about that for the prescribers. We focused a little bit of discussion here in terms of spurring innovation and the attractiveness perhaps from the industry perspective, if there's something meaningful to say about them. But for the prescribers, what would be meaningful for you in terms of making decisions about whether or not to prescribe them?

(No response.)

DR. CHAN: Any takers?

DR. KELMAN: [Inaudible - off mic]. What exactly were you thinking of in terms of labeling for the prescriber if you had a certain packaging unless the label actually limited the packaging under the FDA branding?

DR. CHAN: Right. Throughout the presentation, we had different examples of labeling considerations, some that spoke to a description of what the technology might do; this package X or whatever it is does Y, which is just describing what it's achieving. And then you could also have an approach more to the ADFs, which Dr. Throckmorton talked about, which was we expect it to do X, Y or Z. We have some data that leads us to believe that, so we expect this outcome, but that needs to validated in the real world.

Then you perhaps have an opportunity where, depending on the option and the way it's developed, and the data that's produced, you could actually say more definitively that in pre-market trials, this was observed. If you had a pragmatic trial

that was conducted, you were able to put that in.

So just trying to understand what's going to push prescribers and the payers as well for payment, in terms of adopting these?

DR. KELMAN: [Inaudible - off mic].

DR. THROCKMORTON: Jeff, you're asking a great question. I think the discussion this morning was loosely around the NDA model. The idea was that you'd have a specific product with a specific kind of language in it. You would lay out the advantages of that product then others, and typically that's done through NDA or something.

Now, a couple people, Dr. Green and some others, have just raised the idea of a standard, of a requirement used under one of our authorities saying all products with a certain characteristic will have labeling packaging of a certain type. So in that case, there wouldn't be an individual commercial advantage. They'd be required to be in an abuse packaging or something like that.

But for us the challenge is identifying what works, and that's going to be what we're talking

about in the next couple days, what we know works, actually works, sufficient that we would in fact impose that kind of requirement on a class of medicines. That's something we've been told to be pretty careful about, but if we got to that space, then that would, at least in this conversation, be related to safety.

I think to answer your question, it's at least in the realm of safety, but we'd have to know that it was a packaging solution that in fact did the thing it was supposed to. The alternative is to use individual product development as we collect that information. So it's a great tension. It's a great question. It's one that we're struggling with.

DR. KELMAN: [Inaudible - off mic].

DR. THROCKMORTON: It makes it what?

DR. KELMAN: Much more relevant to market uptake. You can put everybody in an abuse-deterrent packaging if you made it part of a requirement, obviously.

DR. CHAN: Dr. Ciccarone?

DR. CICCARONE: Dan Ciccarone, UCSF. To answer your question around what would make it easier for providers -- I'm sorry, what would motivate providers, my answer is make it easier in some way. So is there something about labeling or how the pharmaceutical industry interfaces with this type of drug that would make it easier on the provider? And the answer is to not add all these burdens about how primary care providers need to do this for patients. They're not doing it now because they don't have the time.

Maybe we can put it off for the pharmacists to do this with free education and stuff like that. Maybe the pharmacists don't have the time either. And maybe you can put it into a label and put the burden on the patients to educate themselves, and maybe some portion of the patients are medically illiterate or perhaps labeling is already so burdensome, they get this packet of paper and they toss it.

What can the role of the pharmaceutical industry be in terms of they see this with under

indications, with other diseases, where they support this, call this number for more information and join this location, social media, educate yourself about those types of drugs.

Perhaps QR readings where people could scan it. I guess that adds another burden in terms of literacy, but you can get a whole bunch of information through a video. We can even go on to the intrusiveness as Gottlieb brought up earlier. We can make this mandatory, mandatory for the patient that says you can't unlock the bottle unless you've watched this video.

I'm just thinking, to answer that question what makes doctors' life easier is to help patients become activated and educated and energized in ways that don't take up an extra 10 minutes in the clinic.

DR. MASUCCI: For our next topic, we touched on this a little bit, which is question 6. We heard a few comments about striking the right balance between something that would be helpful and something that would be overly cumbersome and

actually have negative consequences to patient access or clinical negative consequences.

Are there others who'd like to comment on any thoughts on how we might strive to strike that balance, recognizing actually what we say in question 7, that there's not necessarily going to be a one-size-fits-all solution via packaging to this problem? Dr. Bosworth?

DR. BOSWORTH: I don't have a good answer to that, but I can say that for every time we do an intervention or any program, there's going to be unintended consequences. So this again goes back to creating a really robust evaluation infrastructure.

To whatever extent you all decide, you have to be able to look to see what's going on. So whether it impacts the physicians, whether it impacts the pharmacy, the labeling, the individuals, just all too often we do something out of impulsivity and don't think about what the consequences are. So I just want to emphasize that.

DR. MASUCCI: Mr. Smith?

MR. SMITH: I would make two comments in terms of unintended consequences. One, if you're talking about the information going out to patients, the inserts or the labeling for patients, just take care that there's not duplication. There's already a lot of information going out to patients. If you are just adding on more information, and some of it may be duplicative or you're just inundating them, you may actually have a lack of effectiveness.

Second, when it comes to disposal -- and this kind of goes back to some earlier points about drug take-back -- there is a risk of actually promoting diversion with take-back to some extent. You can run into issues of diversion with mail-back. You can run into issues of diversion for people that are trying to put their drugs in a take-back receptacle, somebody who is seeking out that drug is waiting for people to come along, and then say assault them. They try to take the drug away from them; people breaking into take-back

receptacles.

We advocate various options in terms of drug disposal for patients. We've fought against ordinances that try to impose a sort of one-size-fits-all solution when it comes to disposals. Those are the two concerns I would raise on disposal and instructions or labeling to patients.

DR. MASUCCI: I think we had one final comment.

DR. EMMENDORFER: Let me just say for the packaging, one thing to consider for an unintended consequence, unit of use, for example, now are you creating a scenario where somebody may have previously used the child safety cap and the only way to get into the packaging is to pop them all at once, having a loved one do that? Are you actually setting up an example where that could be in a Dixie cup? I think most of us in this room probably have run into those types of patients that have those dexterity issues. I would want to throw that out for unintended consequences for packaging to consider.

Then honestly, I didn't think about it until John mentioned it, but are you creating -- and I don't know the answer to this question, but I do think it's worth exploring, is are you creating a marketing in the street value of a particular package because of the likelihood of that being the real opioid in there, is it higher?

DR. MENDELSON: Definitely. We should choose the nickname now.

DR. MASUCCI: Yes, final comment?

DR. COX: Thanks. Elizabeth Cox from the pediatric department of Wisconsin. I was thinking about the packaging thing, and thinking about it in a risk-based strategy. Obviously, we have people with dexterity or whatever issues who may have difficulty getting into these packages, but I've also had the experience clinically where I just offer an explanation about why having this medication in their household may not be safe, or having it not in tamper-proof packaging is not safe. So I look in the room and I see a family with a toddler and a 4-year-old, and they're asking

me for a script for pain medication, if I can just help them understand why not having that in their household may be the best choice, it's a much easier conversation.

So it makes me think about a risk strategy where you might have some key questions to ask people before they refuse child-proof tampering or tamper-resistant packaging as opposed to imposing it on everyone or allowing everyone to opt out without offering them information.

Audience Participation

DR. CHAN: Thank you very much. At this time, we're going to move to the audience participation session. If there are any audience members that wish to speak, could you please line up behind the microphone, and there will be a staff member to assist you if there's anyone who wants to come up.

We do ask that you focus your comments on this session's topics. I'm going to review the procedure for the audience participation. As mentioned earlier, you will be given up to

3 minutes to provide comments. There will be a light system that will keep time and notify you when the time is complete. Again, FDA staff will be available to assist.

The light system works just like a traffic signal. If the light is green, you can continue speaking. When the light turns yellow, that means you have one minute left for your time, and you should begin to summarize your comments. And then when it turns red, the blinking light means to stop speaking and please return to your seat.

Just as a reminder, any additional comments and information can be submitted until February 12, 2018 to the docket. And with that, we can have the first speaker come up. Please introduce yourself.

MR. IORIO: Hi. My name is Matthew Iorio, part of the public. I just want to raise the possible unintended consequence with any sort of solution that restricts the version of legal opioids. We just have to be cognizant to a shift potentially to other illegal drugs. I'll just put that out.

DR. CHAN: Thank you. Yes?

MR. LANGLEY: My name is Nathan Langley. I'm a co-founder and vice president of business development over at Safer Lock, a shameless plug. It's a combination locking cap for prescription bottles, tamper-evident, abuse-deterrent packaging, that we hope will be considered at some point to help address the opioid epidemic.

My question is, a lot of the comments I was hearing and questions were very population specific. And understanding that there is no silver bullet and that there is no one-size-fits-all solution, what population can you help?

I agree with a few of the comments that someone who's addicted or doesn't care, packaging might not help them unless there's an explosive in it. But to Kevin Webb's comment, where he mentioned maybe a curious teenager, of which at age 12 to 17, there's 3,000 kids that experiment today, which is over a million children a year, I think there is an opportunity there once the population

is identified.

I attended a very similar meeting which was on abuse-deterrent formulations. Something that they determined was an acceptable failure, and I believe they said that their population's more focused probably on someone who is addicted and further along, and they determined an acceptable failure rate for someone who wants to smash or melt a pill was I think 15 minutes.

So what would be an acceptable failure rate for packaging once we identify the population that it can help? The current acceptable failure rate, according to the Poison Prevention Packaging Act of 1970, is age 5. So do we increase that, and how do we identify that for determining what that is?

So my question I guess is what is the population that we can help and what would an acceptable failure rate for that population be?

DR. CHAN: Thank you for your comment.

MS. HOBOY: Good morning. My name is Selin Hoboy. I'm with Stericycle, and we're a healthcare waste services provider company. My comments are

related to a few different things, and I'll try to keep them brief.

One is, as some mentioned about bringing drugs back to the pharmacy or to the provider, we do need to be cognizant of the closed-loop system of the DEA regulations that prohibit that type of activity, and maybe looking at those regulations and considering are there some additional changes that can be made to the 2014 regulations that came out. I'd strongly suggest that that be done.

Then the other comment that was made regarding take-back programs and the different types of programs that are out there, both mail-back and for drop boxes, we've been providing services for that type of alternative for the last couple of years since the regulations came out, and we service a lot of the programs out west that we're kind of the frontrunners, and we haven't seen the types of diversion issues that were mentioned. We haven't had a lot of break-ins or people trying to attack people. We understand that that is part of the risk determination that many pharmacies and

retail facilities look at, but so far we haven't experienced that, fortunately. I'd like to recommend that that be looked at even further as well.

Lastly, keeping things simple for the general public I think is always the best, so we use a lot of pictograms on our boxes for people to be able to understand what it is they can and can't put in there. Maybe that's something to look at. Just like OSHA has the global safety information now, maybe that's something that can also be looked at from the pharmaceutical companies, to have pictograms that say, okay, here's the yuck factor, or here's the disposal type of container you can use to put this in there.

Just something keeping it simple for the consumer would be ideal because when we get the prescription information in that two pages of stuff, it doesn't talk about where do I go and what do I do when I need to get rid of this stuff. Thank you.

DR. CHAN: Thank you very much.

It looks like that concludes audience participation, as I don't see anyone else lined up. We're actually a little bit ahead of schedule, so I think we're going to go ahead and take our break a little bit earlier. I'm going to ask that people please return to the room by 10:35 and take your belongings with you. Thank you.

(Whereupon, at 10:20 a.m., a recess was taken.)

Session 2 Presentation – Gary Slatko

DR. SLATKO: A couple of quick announcements. Any additional comments that anybody wants to make, we do have an open docket that's been published. The way to access that is to go to the FR notice that's been published. You can find that FR notice on the meeting website that's available that many of you probably saw prior to coming to the meeting. So we do welcome public comments, and that docket will be open for a period of time after the meeting's over. Thank you.

I'm Gary Slatko. I'm the associate director

in the Office of Medication Error Prevention and Risk Management in CDER, and my presentation today is on Design Considerations for Packaging, Storage, and Disposal Options to Enhance Opioid Safety.

Here is my disclaimer, which is the same as Dr. Chan's earlier. I will say that I will be presenting some specific examples of different types of designs, and these should not be considered any endorsement or recommendation by FDA of any particular products or options, but are presented as examples for illustrative purposes only.

Here's an outline of my presentation. I'll pick up on the four opioid use problems that Dr. Chan discussed and present a conceptual design approach to addressing those problems. I'll discuss this approach in three stages, first, analyzing the opioid use problems for associated behaviors; second, considering three categories of potential design options: existing options, novel options, and integrated approaches. I'll then describe an end-user validation stage that

generates data about end user needs and can help anticipate implementation barriers. I'll finally conclude with some design principles to consider.

In terms of addressing the opioid use problems of accidental exposure, misuse, third-party access, or excess supply, these problems each have various behaviors associated with them. Some of these behaviors manifest in the patient themselves; others manifest in their home or community setting, including among family members, friends, visitors, healthcare providers, and others.

Options have been designed in an effort to try to deter or manage opioid use problems. Historically, some of these had been repurposed from other primary applications, such as adherence re-enforcement technologies. Recently, more innovative or tailored options have emerged that target certain behaviors that are associated with the different opioid use problems.

Given that background, I'll now introduce an approach to identifying target behaviors, designing

options with some examples of each, and then validating these options as a way to think about designing options in the future to improve opioid safety.

This graphic depicts the three stages of a possible conceptual design approach. It starts with analyzing the opioid use system to identify problems and associated behaviors. The identified behaviors then become targets for the selection or development of different design options.

The design should then be validated with assessments of end-user safety and effectiveness, end-user acceptance testing, and determining their ability to use or implement the design.

This then generates data that can help to inform design modifications and may necessitate additional end-user validation. In this sense, the third stage is iterative with the second stage. Finally, the data from the validation process can be used to support regulatory submission.

I'll now dive a bit deeper into each of these three stages. The first stage of the design

approach is analysis. This entails analyzing how the opioid use system may fail, leading to an understanding of the behaviors that could be associated with those potential failure points. These behaviors in turn become targets for potential design options that are intended to deter or manage those behaviors.

For example, in the second line, the healthcare provider prescribes excessive amounts of medication as a failure of the system. The associated behaviors may be that the healthcare provider is unaware of the appropriate amount of medication to prescribe or they may simply be in the habit of prescribing a set amount of medication and a set dose and supply. A unit of use blister package with a limited supply may be one potential design option to address that type of behavioral failure.

Analytical methods exist like failure mode and effects analysis, or FMEA, and probabilistic risk assessment that can prospectively analyze processes or a system for potential failures and

associated behaviors as targets for future designs.

The second stage of the design approach is considering three broad categories of design options that can address the targeted behaviors: existing, novel, and integrated approaches. Existing options are basically preexisting designs that are being applied or repurposed to be used with opioid medications. Novel options are new designs developed to prevent or deter, detect or track, or monitor or manage targeted behaviors associated with specific opioid use problems.

Integrated approaches combine the first two and/or use a multimodality approach. This can include redesigning an existing tool or combining designs to address multiple behaviors concurrently. Another integrated approach could be to integrate a design within a healthcare management program like a risk evaluation or mitigation strategy, or REMS, or into a delivery system program.

I'll talk about some examples of each of these to illustrate some features and possible strengths and weaknesses of each. In terms of

existing options, there are different types that are or could be used or repurposed for opioids, and we heard a little bit of discussion about some possibilities already. These could include calendar blister packaging; packaging that limits supply; designs that control access such as locking caps; tamper detecting or resistant packaging; and deactivating or disposal approaches.

Here is a marketed example that many of us have experience with, the zithromycin or Z-pack. It limits the number of days' supply of a medication and visually tracks medication consumption. There's also space on the packaging available to communicate instructions to the patient. And, as Dr. Gottlieb mentioned this morning, the Medrol Dosepak would be another example of this type of packaging.

This approach has the benefit of being a lower end technology that does not substantially alter the patient's medication-taking routines, but it is limited in that it doesn't control medication access or limit the rate of consumption. There

have been some recent innovations with blister packaging that could allow the detection and cellular technology reporting of when a blister has been opened, as was mentioned a little earlier.

Another marketed example is a locking cap, which controls bottle access. Again, this is a lower technology approach. It is relatively passive, with only a minimal impact on patients' medication-taking routines. In this example, the bottle itself is also opaque and therefore conceals the bottle's contents. However, this would not limit the frequency of bottle openings or the amount of contents that could be accessed with each opening. It could also slow down access by intended patients.

A third marketed example is medication deactivating systems or solutions. These are also lower technology and could be used on oral as well as other types of formulations. The disadvantages of these is that they do require additional discretionary steps be taken by the patient, and some of these do have out-of-pocket expenses.

A second category of design options are novel options that target behaviors associated with opioid use problems. A number of these more novel technologies are in development or have been introduced. They include tracking bottle cap openings with Bluetooth technology; embedding an ingestible sensor inside the pill or capsule; cellular modules that report blister package openings; and systems that control and track dispensing.

These are all more targeted and more information generating than the prior category, but they do have greater complexity associated with their use. Many have several higher technology component elements with associated costs, and active actions are often required of the patient and/or the healthcare provider.

Additionally, they may not be universally available to individuals who don't have smartphones, or WiFi access, or access to other technologies.

One novel example is the Abilify MyCite

product that was recently approved. The ingestible sensor in the tablet signals ingestions to a skin patch, which in turn reports to a smartphone application and Web portal.

This technology confirms most but not all ingestions, and it can include healthcare provider oversight of medication taking. Additionally, the sensor could provide a way to track individual tablets. However, there are a number of active steps required for this higher technology approach, and it has both financial costs as well as requires healthcare provider time to ensure that the patient is capable and willing to use it. It does not manage access or consumption rate, and detection delays may occur.

A third category of design options is designing and/or combining options together or integrating options with other healthcare programs or systems. An existing option can be redesigned to better address a target behavior. Options can be redesigned or combined in ways to address multiple target behaviors concurrently. These can

be also integrated together within safety management programs like REMS or healthcare delivery system programs like prescription drug monitoring, MTM programs, or other initiatives, as well as some of the things we've heard about earlier about special education programs, training programs, and those kinds of initiatives.

An example of an integrative approach is Lazanda. It combines several existing interventions and uses these within a transmucosal immediate-release fentanyl, or TIRF, REMS program. Here, there's a child-resistant container and a counter that tracks doses used and doses remaining. The packaging limits the total supply to 8 doses per bottle, and the packaging includes a separate disposal pouch to facilitate product disposal.

This packaging is tied together within the TIRF REMS Access program in which the healthcare provider must enroll and review the educational materials. Outpatients have to understand the risks and benefits and sign an agreement. Pharmacies must enroll in the program and agree to

comply with the REMS, and wholesalers and distributors must enroll and distribute only to authorized pharmacies. This does not control the rate of dosing and is vulnerable to errors and use. For example, someone might forget to re-store the spray bottle in the container.

The last step of the conceptual design approach is validation which generates data about the design option. Data can be used to help inform the design and/or design modifications, as well as to support regulatory submission. I'll talk a little bit more about this last step since we'll be talking much more about data tomorrow.

Data can be generated to validate safe and effective use by the patient to demonstrate that patient needs are being met and to show that patients are able to use the option successfully. This work can look at whether a patient finds the design acceptable and are willing to use it, they're able to comprehend how to use it, can demonstrate that they're able to use it, and it considers patient preferences in the design.

The validation should be undertaken iteratively. It can help inform the initial design of the option or modifications that may be needed during the design process, and the results can provide data to support the submission.

Another important consideration in design is anticipating and addressing potential implementation barriers. These barriers could include requiring the patient or healthcare provider to undertake active steps in medication taking or to undertake manual activities. Both of these could potentially be mitigated by more passive and/or automated design features.

Designers should also think about how to enable the design to be used on a sustained basis over time by patients. They should consider and attempt to mitigate potential unanticipated consequences of their design. They should also consider the possible use failure, generating use-failure data from such as we heard about earlier like data that might come from packaging use failures and use that information to help

design improvements that would avoid such use failures, and they might consider building redundant features into the packaging design.

Finally, designers should think about the healthcare delivery system into which the design is going to be introduced and distributed. There are potential system integration issues that may have to be addressed, such as the feasibility of distribution; timeliness or availability for legitimate patient use; the availability for repeat use; the affordability of the option; and other considerations.

I'll conclude with four principles that designers should keep in mind that I've covered today. First, use an evidence-based approach to analyze the use problems and identify associated behaviors to target for designed interventions.

Second, design with the end user in mind, addressing one or more target behaviors, while minimizing foreseeable end user errors, and potential implementation barriers.

Third, anticipate possible second-order

effects of the option. Expect and mitigate unanticipated consequences, and consider designing redundancies to offset possible use failures.

Finally, consider the real-world programs and systems into which the design will be used. Designs could disrupt other options or existing safety programs or delivery systems, and redundancies may be required to back up and prevent failures of implementation. Thank you very much.

(Applause.)

Panel Discussion

DR. CHAN: Can folks hear me? We're doing a little better with the mic now. Okay. Thank you, Dr. Slatko.

We have developed questions to guide the panel discussion for this session on design considerations, and I think we're trying to get those up on the screen now. We have five primary questions that we'd like to discuss over the next 60 minutes. As mentioned in the last panel discussion session, Paul, who's sitting here to my right, will be assisting us to make sure that we

call on you to provide comments to the session. If you'd like to comment or a question, please just raise your hand.

So let's begin with the first question. Oh, we've got a comment even before the question. Yes?

DR. KELMAN: [Inaudible - off mic].

DR. CHAN: I'll repeat the question since we're having some mic issues. The initial question to the FDA was whether we see these as drugs or devices. I think it's a little early to say. I don't think we know, and it's going to depend really on what's being developed. I think at the end of the day, depending on what's developed and depending what it's purporting to do, that's going to drive the regulatory pathway under which it may come in. And we will actually get into some of this discussion a little bit further after lunch when we go into the regulatory considerations in Session 3.

Moving on, in the prior session, we walked through four high-level problems where we thought there could be a potential role for these

packaging, storage, and disposal options, thinking about accidental exposure, misuse, third-party access, and excess supply. We had some good discussion around potentially other problems as well.

In this particular session, Dr. Slatko has talked about thinking through the associated behaviors with those problems and a framework in terms of a design approach in order to develop these design features and technologies that can actually address those associated behaviors.

What we'd like to better understand now, to start, is what steps or approaches do packaging developers currently follow when designing these packaging, storage, and disposal options? As a sub-question to that, we'd also like to understand to what extent are developers thinking about implementation into the healthcare system; and more broadly for the panelists, does that need to be a component when thinking through design?

Who would like to begin this discussion? Liz, please go ahead.

MS. WHALLEY BUONO: You're going to turn off my mic pretty soon. This is Liz Whalley Buono. I can just speak from the N of 1 in answering this question. When thinking about innovative packaging considerations, obviously we have to think about meeting regulatory constraints, passing CR testing. We have to think of FMEA and HFE type evaluations to make sure that the patients can use them; that they don't have difficulty in things like opening and closing.

We partner with organizations like the Arthritis Foundation to get markings around ease of use, especially in specific populations. There are environmental issues. There has been a big transition from plastic base to biodegradable paper base.

Those are kind of the design evaluations. We've spent the last 10 years or so taking a more scientific approach about evaluating the platform of calendar blister packaging, both from preclinical to clinical types of evaluations and publishing those.

I think the market considerations are also very complex, so there is tremendous investment in central fill organizations where drugs are put into bottles. The United States is a cap-and-vial culture, if you will, so to shift that to something like, let's say, calendar blister packaging is not uncomplicated. It requires a completely different filling process and different standards. In all of that, there's got to be a willing investor to do that.

On the pharmacy side, you have things like shelf space, additional NDC numbers when you've already got very crowded NDC lists and things like that. If you track the pill, if you will, there's regulatory, there's market, and then the patient usability issues are huge.

DR. CHAN: Thank you. I think we have another comment from Mr. Smith.

MR. SMITH: I just want to pair off of one thing that she said, and that was about the shelf space. One consideration, in any type of packaging changes is the bulk, the size. There is limited

space, and it occurs in multiple places. It occurs in the distribution centers where these things have to be kept in vaults. You have to think about the bulk of what you are packaging and how much space that takes up, and what changes would maybe need to be made, is there space, and what that cost is going to be. Then even when it gets into the pharmacy in terms of putting it in a safe, again, you've got that same issue.

So that's a good point. I want to reiterate it. A major concern for a pharmacy is the space involved, both at the distribution center and, again, at the pharmacy level.

DR. CHAN: Mr. Webb?

MR. WEBB: Thank you. Kevin Webb, Mallinckrodt Pharmaceuticals. I agree with what Mr. Smith and Liz were saying. The presentation, there's a whole litany of things that we as a manufacturer would go through. It's obviously a design phase. But the other thing that we'd also be looking at is intellectual property. Who owns this? What's the impact? Is this something that

we would be contracting out? Is this something we'd be expected to design in-house?

Then the timeline it would take to reconfigure the manufacturing lines, if this is just going to be a tray bottle that continues to come off the line and the retail pharmacist is going to repackage it, or a distributor, or someone's going to put it into a bottle that has the locking mechanisms, that's one thing. But if the manufacturer is going to be expected to reconfigure their lines, that just doesn't happen. There are a whole lot of discussions that have to happen. We have to look at the cost implications. Are we retrofitting [indiscernible] a line? Are we putting new lines in?

So there's a significant time delay as we look at speed to market and the sense of urgency. And that kind of goes to my other point of what are we trying to do now to start mitigating the problem. If this is going to be a very complicated design, you're looking at years in the process. But if it's something that we're just reconfiguring

the line or adding some different features to it, well then, that's a little bit more timely.

DR. CHAN: I've heard touch points with regard to implementation considerations, and I am curious, to turn this back, how much of that is considered currently in the design process?

MS. WHALLEY BUONO: Logistically, it can be done. Let's say, for example, how to put the drug in the package. There's a whole industry around packaging and contract manufacturing. Typically, that's the easiest route to market. We do have some branded manufacturers who are putting these lines in, so moving it in-house if you will, if it's a platform that they feel they want to run across several products for adherence purposes.

In order to have a customer invest in this type of packaging, there's obviously got to be an ROI and a willingness to invest. So all of those considerations are part of it, kind of idiosyncratic things. Like if it's considered repackaging, it's not a reimbursable product, so it's got to be manufactured origination packaging.

So there are a lot of issues that come into play in order for this to be feasible for the manufacturers to undertake. Retail pharmacy has also taken this on themselves and done it as part of their retail pharmacy packaging operations.

DR. SLATKO: Dr. Bosworth?

DR. BOSWORTH: I just want to make sure I'm understanding also part of your question. When you're using the term "implementation," are you using it in a scientific method or are you just using it in terms of the process of getting it out onto market?

DR. CHAN: Right. I think we're really just thinking about the practical considerations of getting something into the market and how much future thinking about that is actually taken into consideration early in the design phase.

DR. BOSWORTH: So as a researcher focused on the implementation side, I do think, though, there is something to consider because part of it is if you create the product and then think of the implementation, you've lost the battle. The

implementation has to begin almost as if you think from a drug trial from a phase one: how is it going to be used; who's going to use it; and why are they going to use it?

So I think that that transition to what I'm thinking of implementation science should be pretty straightforward and not taking the typical 17 years that we see in the literature. So again, it sounds like you're thinking about it in a different perspective, that I think the methods could be utilized to help -- and scalability and things like that, those are all fidelity. These are all components that you're probably going to think about that need to be considered as well.

DR. SLATKO: You had mentioned the repackaging is not being reimbursed. I can envision that there could be some technology that would be something that a patient would use and then have refilled, take that to a pharmacy to have refilled after they completed a course. It would be some kind of controlled distribution device. So it would be something that the pharmacy would take

back and would refill, refill a bottle.

I'm looking at you, but I'm not sure you're the right person to ask.

MS. WHALLEY BUONO: Those models exist. I think in the current U.S. regulatory infrastructure, those currently are only really possible under practice of pharmacy. CGMP and things like that, you simply can't package fresh drug, if you will, into an already opened container. But certainly under practice of pharmacy, pharmacists have a lot more latitude to do things like that.

They're outside the U.S. considerations, particularly in underserved regions around things like adherence boxes, if you will, where patients take them back to clinic and they're refilled with medication. But I don't see under the current regulatory standards here, in the U.S., how something like that would be appropriate as part of the FDA regulated manufacturer packaging process.

DR. SLATKO: Right. As a tool for getting feedback, for example visually, about whether the

rate of consumption was appropriate for the last course of therapy, bringing it back and visually inspecting it may not be sufficient as opposed to having some kind of ongoing tracking mechanism that reports the rate of consumption on an ongoing basis.

MS. WHALLEY BUONO: Yeah. I think the only way that could work is if you're talking about the secondary package type approach so that you could -- so the Gates Foundation is funding research in HIV and TB co-infection trials outside the U.S. where we've developed a box for them, if you will. And they take it back to clinic, and different drug blister cards are put into the box, and then the proxy event for adherence is the opening of the box.

DR. SLATKO: Right.

MS. WHALLEY BUONO: There are studies that show that the proxy event, opening the MEMSCap is equal in efficacy, if you will, in adjudicating adherence to let's say the SmartPill. So they've done head-to-head studies on that. So the opening

event typically is a pretty good proxy, but if you're talking about a box with different types of medication in it, you've kind of deluded when they're opening the box, what are they taking?

DR. SLATKO: Right.

MS. WHALLEY BUONO: And again, that's a device. That would be regulated as a device.

DR. CHAN: I think Mr. Webb had a follow-up comment.

MR. WEBB: Kevin Webb, Mallinckrodt Pharmaceuticals. I think the other question that needs to be on the table is -- it's kind of a chicken or egg scenario. The question is, is the FDA going to be looking to the manufacturers to come up and present some type of better configuration, or is the FDA going to come to the manufacturers and say here's what we want you to have in the labeling of what that blister or whatever that configuration can be?

If it's left to the manufacturers to say here's -- as many manufacturers as you have, all presenting something different, it's going to be a

chaotic process. And at that point, really, some are going to do it, some are not. But if there's going to be some labeling requirements to say here's what that new configuration needs to look at, in that way there's clear guidance to what it actually is the FDA wants for us to do, that's going to help streamline the process a whole lot more as opposed to just saying, okay, we think this is what we want.

Also, that's a question of what you were getting to earlier, the innovation of whose dollars. Is this something that we're going to work with someone like Liz's team in putting together some different concepts or is it that you have in your mind what we already want? So as we kind of meet in the middle, that would be very helpful.

DR. CHAN: The thing I would say is that I think we have to be careful in contemplating a question like this because I think what we don't want to do is stifle innovation that could occur. And that's certainly a consideration any time

you're talking about because we may have preliminary ideas collectively, whether that's in the agency or others, about what might work.

Data's going to drive a lot of this, which we're going to talk in a lot more detail about tomorrow. But I think in the interest of progress and continually being able to make a dent, I think we have to be open to the opportunity for innovation that may bring other features, other designs, into play that should be considered and should have a place in the discussion.

But I'm interested to hear others' thoughts on that because we've got one proposal on the table here, and I'd be interested to hear what others think about that. Dr. Scharman?

DR. SCHARMAN: Dr. Scharman, West Virginia Poison Center. Two comments on packaging. Looking at that group unintentional poisonings, you have to consider an amount to be toxic. If you've got a bottle of buprenorphine and you open that bottle, and it just takes one to be toxic, and you've packaged it in tablets of 15 to 30, that's not

really helping you.

So if you've got a product where it only takes one to be toxic in a child, then really a unit used packaging like blister pack is the only type of packaging that makes sense. So here again, if we're looking at the unintentional poisonings, we have to consider dose that's toxic to that population as part of that consideration.

The other thing, just as a reminder, one of the leading causes of decreased poisonings in children was the use of the Palm N' Turn child-resistant cap. Just as a reminder, that was not developed by an individual manufacturer. I think that was one of the pharmacy association committees that actually put out a clin test for package design. And people in the public and vendors got creative and submitted ideas to that project, and then one was selected, and that was patented. So different models other than having to charge one manufacturer dividing a product have been used successfully in the past.

DR. CHAN: Thank you. Dr. Mendelson?

DR. MENDELSON: Listening to this discussion, what approaches, the packaged and developed drugs, we physicians as packagers and developers don't do anything, so we're an easy target to work with. I think you have to think about -- I hear at least three groups that would benefit from being identified as either customers or users, and you have to analyze their user experience if you're going to be successful. Those are the manufacturers, obviously, but also the pharmacies and the patients.

The way you might get to the solution will be a contest, like actually put something out there. You just pointed out the little pop-top bottles. Someone invented those and did well with them by committee. But a contest or SBNR [ph] type process where you actually incentivize developers to actually consider the stakeholders and actually come up with products.

I think the user experience -- what I'm hearing a little bit here is this is a top-down process being envisioned here. What do we do to

control and not what we do to get people to actually use products in a way that actually works for them. So I would strongly encourage putting into the debate the user experience. Part of that user experience is patient, but part of it's also pharmacy shelf management. Part of it's manufacturers.

If you put out an RFA along those lines for technology, someone will respond who's relatively smart and will come up with something pretty interesting.

DR. SLATKO: Okay. I think we're going to move on to our second -- oh, you have one. Sorry about that. Mr. Berghahn?

MR. BERGHAHN: Walt Berghahn, Healthcare Compliance Packaging Council. What you're talking about is this marketplace, dozens and dozens of companies that put suggestions out there going back to 30, 40 years. I'm sure one of the things that this group will be evaluating is all of the technology that's out there on the marketplace. And it's a matter of defining what you want. You

can do almost anything. You can lock these things down dramatically with packaging and with near-fill [ph] communication. You have to know what you want.

DR. MENDELSON: Exactly. That's what's not defined, which is the user experience. That's the part that's missing.

DR. SLATKO: I think that does take us to our second question because I think there's an element of what are we trying to address and what are the behaviors that are associated with each of those problems that we're trying to deal with, which kind of drives what we're trying to accomplish with the design and the features of that design.

The question is, there are four target problems we talked about. What are the behaviors that we need to consider -- or say the most important behaviors we need to consider when we're designing packaging, storage, and disposal options? And given the behaviors, are there existing design features that might effectively address those

behaviors?

So let's take this in order starting with the accidental exposure issue. When Dr. Chan presented, she talked about accidentally leaving the bottle open, not closing it, transferring from the secure bottle to a different bottle as examples of behaviors. And there were some design features she mentioned.

Are there other behaviors and features that we should be thinking about -- I'm throwing those out there for discussion; other behaviors and features we should think about to include in the design of those solutions.

You had mentioned a single dose -- Dr. Scharman, you had mentioned making sure that if it had been a pediatric exposure, that there wouldn't be access to a single dose, to have that level of protection. I think that's an interesting idea because that's a very unique situation where one dose exposure might be lethal, for example.

Dr. Berghahn?

DR. BERGHAHN: Walt Berghahn. To continue, basically, if you go back and you look at the Poison Prevention Packaging Act and you look at the criteria that are there on blister packaging, it puts the onus on the manufacturer to define the toxicity in the product. What is going to cause harm to 25-pound [indiscernible].

So as the manufacturer, you make a decision what access is appropriate. Well, one dose is too much or 5 doses is too much. Your package style, you're waiting to get, and testing will be determined by what you envision the toxicity. But the problem is that that very criteria in the Act prevented companies from going [indiscernible] because they don't want to define the toxicity of your own product.

Who wants to say that? What is the toxic pill for a young child? So what the industry has done, as a de facto base, he said F1, absolutely block it down, F1. And in response to that, [indiscernible] there are tons of packages that are out there, and F1. But when you look at

data -- for instance [indiscernible], and there was a very specific product, all that happened is it went into a blister. It wasn't an F1 blister, but it still saw the poisons [indiscernible] and drop off.

Sometimes I wonder if PPPA is taking it a step too far because you put the onus on the manufacturer to determine the toxicity of their own products.

DR. CHAN: Dr. Green?

DR. SLATKO: Dr. Green?

DR. GREEN: That's a fantastic point, and as we were listening to the opening comments, 1970 was before I was born, and I'm not that young. So I'm not quite sure -- is it a recommendation that that act be revisited with today's environment, with today's technology and today's challenges, new challenges, for some of these products so that there's a more systematic evaluation or global evaluation of what is really the best intentions for these pediatric exposures?

DR. CHAN: Yes, Ms. Morgan?

MS. MORGAN: Hi. Sharon Morgan. American Nurses Association. With this discussion and certainly with the discussion previously, we are all here discussing a very complex situation with limited resources both as agencies and then in execution of anything that might be coming down the pike.

So really, where is our best bang for buck? What is the biggest problem that is going to give us the best results in addressing? Is it the poisoning aspect, the accidental poisoning? Is it minimizing the number of medications that are out there and education processes and packaging that goes along with that? So where really is our best bang for buck?

Then where is the biggest target audience? Is it the acute prescription area or the chronic prescription area? Do we then define packaging based on those two different areas or other subgroups of that? And then how can the packaging align with education, and labeling, and the use of social media to reinforce messaging about

appropriate use? Then who's going to be responsible for the reinforcement of what is being done; how it's being given the product, and is there appropriate use.

As I'm listening to everything that's going on, I really hope that we understand that we're not going to be able to address everything and that it might help to really kind of focus on where we think the best bang for the buck will be. Thank you.

DR. CHAN: So I guess my question to you then would be where do you think we get the most bang for our buck. And if we start there, then coming back to the focus of the discussion, what will be the behaviors we're trying to address here?

MS. MORGAN: I see, from a strictly prescribing -- we're talking about of all the complexity of the opioid issue, let's take a look at prescribing and how prescribing is being done. Where is the biggest areas for misuse and diversion and maybe targeting those areas. And do we need to redefine packaging for those areas or are there

other aspects to try to minimize the amount of medicines that are out there that have been prescribed that are now being diverted or misused.

DR. SLATKO: So there's a limiting supply aspect to what you're saying, I think, and then there is a disposal aspect, kind of reduce supply, limit and recover what's out there, to reduce the overall exposure to the population. Is that what I'm hearing?

MS. MORGAN: Certainly, but I would need to actually explore the evidence, is that where our biggest problem that is most likely to be best tackled? Is that it right there, and maybe it's not, or it's a subset of that discussion.

DR. CHAN: So maybe we can -- sorry.

DR. SLATKO: Did you want to comment?

DR. CHAN: Yes, Dr. --

DR. SLATKO: Dr. Budnitz?

DR. CHAN: Dr. Budnitz, yes.

DR. BUDNITZ: Dan Budnitz from CDC. Just to try to address this question about what are the behaviors and a way to target accidental and

supervised ingestions. I think there's basically two fundamental issues. One is that we're imperfect beings. We forget to put on the caps. We forget to put medicines up and away and out of sight. And the fact that by the PPPA, these are not childproof, these are child resistant. We don't watch our kids, so given 60 minutes, these caps can be defeated by many kids.

So when is this imperfect behavior issues? So then you try to prevent with packaging the need to do something. And that's an automatic protection.

The second issue is that we do things intentionally to transfer medications out of their packaging, when we want to travel, when we want to take it later. So then the issue is to make it unnecessary or inconvenient to get the medicines out of that [inaudible - feedback] that's been factored in. Ideas might be something like, if it is a blister pack, having perforated units so that they can be transferred -- that folks will intentionally take out individual opioids, take the

pill itself out of the package because their physicians are telling them to do that. Why? Because they can go travel or you can go somewhere and you leave the entire bottle, you're not getting anymore. So they'll be advised to take one and put them in a small, non-child-resistant container.

I think the point for what would be a way to address the behavior is make it so that each individual unit can be transported into our system.

DR. CHAN: Thank you. Ms. Whalley-Buono? Oh, we already addressed. Okay, great. Dr. Ciccarone?

DR. CICCARONE: Dan Ciccarone, UCSF. You suggest that your [inaudible - feedback], well what is the biggest bang for the buck? I think it's reducing supply, [inaudible - feedback]. There's just simply too many pills out there. So as Director Gottlieb mentioned, we're slowing down the doctor, and that would be an EMR thing because it reduced numbers of pills going out for prescription; so the blister pack like the Z-Pak idea with 3 to 5 to 7 days worth. Then we've got

to have some better disposal options. We have to find ways to incentivize bringing the pills back from the consumer.

DR. SLATKO: Ms. Cowan?

MS. COWAN: Penney Cowan, American Chronic Pain Association. I agree that we need to reduce the supply, but I think there are two different groups of people that take opioids, [inaudible - feedback] for they only need a little bit. So then you're looking at people who are on long-term opioid therapy but need these around the clock, 24. They've been taking it for years and years and years, and to reduce their supply to, say, 7 a day, the problem with that is access to care to get them to their -- they're elderly. There are so many issues.

So I think that we have to be very careful when we look at this, the acute, short-term use and then the long-term use. I think those are two different populations, and we need to consider that. We've heard from so many people who have been reduced to 7 days, and they've been actually

fired by their providers. So they're not able to do that, and so they're losing their jobs. It's just a snowball effect.

I think you have to look at the human factor of these decisions on people's lives and the access to care.

DR. CHAN: We'll take two more comments before we switch questions. Mr. Webb?

MR. WEBB: Thank you. Kevin Webb, Mallinckrodt Pharmaceuticals. I think also we just follow where prescriptions are coming from, to the extent that 89 percent of prescriptions come through the retail pharmacy, and then roughly 94 percent of prescriptions are for immediate-release opioids at a national level. So just by addressing where they're coming from or the immediate release for acute pain would give us an important place to start, and we can start to move the needle just addressing those two factors.

DR. CHAN: Thank you.

DR. SLATKO: Dr. Emmendorfer?

DR. EMMENDORFER: I would just like to echo

what Dan just said. I think the two main areas are supply and then disposal. We have the data within VA, and it's measured quarterly. The number of veterans on long-term opioids is defined as greater than or equal to 90 days of therapy in the reporting quarter or the previous quarter.

When we started our opioid safety initiative back in 2012, we were just over 438,000 veterans that are long-term opioid therapy, and now we have that down to 257,000 patients. And it's about appropriate pain management, so it's not the cutoff of the opioid, but it's about how do you appropriately manage that pain, whether it be increase in complementary and integrative therapies or whatnot. So I think that's one component.

Then I do agree with the disposal. Incentivizing the patients to return them and to dispose of them properly is a whole separate issue, but I do think those are the two big bang areas.

DR. CHAN: As a follow-on then, along the same vein, we touched a little bit on existing technologies. We talked about unit dose, which is

clearly something we're all very familiar, already exists. There are certainly hospital unit-dose blisters that are around.

So where do we still need the innovation in design or can we primarily rest our laurels on what's out there and say start there? I'd like to turn that over to the panel to think about, where is it that we haven't exactly hit the nail on the head with either design feature or some sort of option and technology that exist that we really need in this space? Yes?

MS. WHALLEY BUONO: I'll just start by saying, to Walt's point, there's a lot out there right now, and some of it's actually been pretty richly studied on issues like adherence and persistence, and some health outcome work. It hasn't been studied in the context of the opioid issues, and I don't think we have time actually. I would argue we don't really have time to really thoroughly study it for the opioid-specific issues.

We've taken 10 years and over a half million dollars to evaluate the platform of calendar

blister packaging on adherence and persistence in chronic, long-term medications like statins and things, so I don't think we have 10 years to do that for the opioid epidemic.

I think it's almost impossible to answer your question about have we innovated enough because I don't think we really understand what we currently have and how it's going to impact things like diversion. At the last meeting, we talked about perhaps something like blister pack will make it readily obvious to someone if someone has stolen pills out of the pack, which I didn't even really think about, but maybe it will. But we don't know until we've studied that.

So the question is, how much data is sufficient to understand whether what we currently have is going to work on these opioid-specific issues, and how do we get that information and not wait 10 years before we gather it along the formal traditional evaluation lines?

DR. CHAN: I think Dr. Green had a comment as well.

DR. GREEN: At the beginning -- well, actually from the June meeting, I did find it helpful to look at this in terms of the target population, the pediatrics, the adolescents, and the adults, and I think that might be some of the challenges with each of these questions, is that we're not posing them in terms of the target population and actually identifying what metric, what measure would tell us if we're successful or not.

If we went back to that table, I think this becomes a little bit more clearer discussion because while I completely agree with supply and the comments mentioned, any pill in the home is still a threat or a potential exposure to a child. It doesn't matter what the number is, the number of homes.

So there still has to be that packaging component, which to several comments, we already have data about. This isn't a novel issue with pediatric exposures; obviously, the Poison Prevention Act of 1970. And if it wasn't still an

issue, there would be no poison centers left in the country, but there are 50 of them. But we have good information about what types of interventions work for kids and how do we then apply them to the opioid issue.

Just speaking with Richard here, there are some opportunities with Monitoring the Future to actually ask adolescents what is a deterrent, what potentially could be a deterrent in that population. So let's talk specifically about what can we do with that population.

Then with the adult issues, those are even different, talking to providers and even potentially looking at poison data. There's a wealth of data about the misuse, unintentional or intentional misuse, of these opioids in adults that are reported to poison centers every year, so there's data there, too.

So I think that that there's a lot that we know. We should be sharing the actual data. I feel like we're just asking a whole lot of questions, but if we start narrowing our target

population, we might get a little further with each of these questions with those three target populations.

DR. CHAN: Thank you. Dr. Bosworth?

DR. BOSWORTH: I never follow directions, but I guess one question I would have is could you anticipate what you would want as an outcome or how you would determine whatever we discuss here is successful. I think about when we introduce quality improvement measures, everyone starts skating to that puck, and then there's innovation that occurs within the system.

So I think there's a lot out there. How you select what the right situation is for which group, I don't know. But I think when we see that we put indicators, and there's potentially consequences, whatever those may be, whether they're financial to the health plan, I don't know. But I do see that it changes pretty dramatically.

When CMS puts something in regarding our readmission for heart failure, oh my God, that was just like hands on deck and continues to be,

despite the fact that the secondary readmission has nothing to do with the primary. But nevertheless, it just made people at least start focusing on something.

I'm not proposing just throw something out there, but I do think that if you can envision what you want as an indicator, and you put that out or recommend that, I do think you'll see a lot more innovation that occurs and perhaps more data to separate the wheat from the chaff, if you will.

DR. SLATKO: Just following up on that, you're suggesting as a parallel activity even going to like NCQA to develop HEDIS measures for health plans, talking with CMS about establishing quality measures that would measure other groups' behaviors and performance, and that would drive down to those organizations, really the organizations. I think that's really interesting.

DR. BOSWORTH: You're much more eloquent than I am.

DR. SLATKO: No, but your idea --

DR. BOSWORTH: And I like the idea of

parallel, not to say that that's the solution, but I do think -- and we've seen now with these HEDIS measures what happens, and there is a big change, at least on the population level, changing and starting to focus in, trying to think of bundle payments. I know those are -- but the idea is just really trying to put together the right team and right effort. Having the people on the ground in those systems to try to figure that out gets a big win.

DR. SLATKO: The point here is that there are incentives that are tied to these performance measures. One of the things that everybody's been talking about, we talk about incentives of returning medicine, but where are the prescriber incentives? And this would be an incentive to win points, if you will, for compliance with these measures.

DR. BOSWORTH: Right. I think it doesn't even have to have a financial incentive; it could be public reporting. However, unintended consequences, we've seen this with surgery. When

we report quality indicators, all of a sudden we have cherrypicking things. So I think it's important, but if you do do it, do it right and evaluate what those indicators are. But I do think, in general, the process will change some things moving forward much quicker.

DR. CHAN: I think in the interest of time, we're going to advance. This question, I think we're going to actually, in the interest of time, move on to question 3 because those have been variants of question 2.

What might be the value in designing options that are intended to address more than one target problem? Here we're talking about combining features potentially. We've sort of been talking about each of these problems in isolation, but in reality, some of the features that have been tossed around the room could frankly work in more than one space.

I think what we'd like to understand is if there are some obvious values, probably inefficiencies and so on and so forth, we'd like to

better understand the value, but also what would be the pitfalls in terms of doing that type of an approach? Mr. Webb?

MR. WEBB: Kevin Webb, Mallinckrodt Pharmaceuticals. There are several pitfalls that would be associated with making something too complicated, and just by nature it's making something complicate. Sometimes they don't work. You're going to have returns. You're going to have supply or you're going to have space demands within the retail pharmacy.

We as a manufacturer have to think through every moving part within that supply chain and anticipate where things are going to fall apart. If you now have a supply constraint within the retail pharmacy, now you start getting into access problems. As we talked about, legitimate patients who need access to these medications, and the pharmacy can only store 5 of these new gizmos and their patient demand is 10, what do you say to the second 5 patients who are coming in later that afternoon for their script?

So I think we should always start with who is the patient -- let's not lose sight of the patient. I know obviously you're not, but as we think about how can this best serve the patient interest, we would want to take those types of things into consideration.

You have lack of standardization potentially as you have more complicated features. You have increased complexity. For example, if you have an RFID, you have to have someone now monitoring that, so now you're adding more complexity to the system and more cost to the system. And then you have the whole aspect of patients don't accept it, so you then have -- they will create a way to get around the new device that we put into place. So it gets back to the Dixie cup, and now we've just complicated the problem even more.

If we try to make it too smart, someone's going to figure out a way to undo the packaging that we just spent millions of dollars and years in development to create that solution.

DR. CHAN: Dr. Budnitz?

DR. BUDNITZ: Dan Budnitz, CDC. There are obvious values to address more than one problem [indiscernible], and there's, well, we did one thing and we have three different positive effects. The pitfall of course is one design option is not going to be perfect for all three types of problems you're trying to address -- third-party access.

To make this concrete, for example, an ideal option to prevent maybe misuse by a teen or adolescent would be make it obvious how many pills are in the pack and easy to detect. That might be the opposite of what you want for child ingestions. You don't want a packet that's clear and you can see all the different pills very easily. You might want it to be opaque and very hard to see, and of course that makes it harder to see access.

The only point is I do like the idea that Jody reminded us to highlight the problem we're trying to address, then take a solution, even if it's one solution, to recognize it may not be ideal for all, but it might be best for the overall effort.

DR. CHAN: The interesting issue that's been raised is this idea of we have to remember the user needs. We have to think about who we're designing for. But in some of these problems we're laying out, we're really not necessarily designing for the patient as the target, are we? We're thinking about -- for example, the third-party access, we're creating something that in fact is designed to prevent someone else, in the household for example, from getting in.

So that adds a nuance to this consideration because, yes, we absolutely want the patient to be able to use their medication, but what we're trying to achieve is an outcome that we would be measuring in someone other than the patient, which is quite a different way to look at this.

So I'd like to get some thoughts around that. Ms. Cowan?

MS. COWAN: Penney Cowan, American Chronic Pain Association. I think no matter what you develop, without the education across the board of all consumers -- you can develop a lot of things,

and as we've heard, there are ways to get around them. If we can educate people about the safe use of these but also the dangers if you're misusing them -- and I'm talking about getting education into the schools around these medications.

I don't know that that's in public schools right now, to educate consumers when they get them, to go into senior centers and start talking to older adults, community centers. I think education has to be part of all of this no matter what you develop, and it has to be across the board.

We have a public service announcement that we actually put in movie theaters on storage and disposal and not sharing. We actually did surveys and got 80 percent recall from people just watching that 30-second video. It's on our website. But it's that kind of go out to the whole public, not just to the people who are using.

DR. CHAN: If I could just follow up then. Are you saying that without that education component as to why a patient who I think previously you indicated may not perceive

themselves as being part of the problem or needing to be a solution for the problem, that without that education piece, you're going to have more incidents of these intentional workarounds being part of a new issue, so to speak.

MS. COWAN: Both that, but also around misuse by people who it's not intended for. I just think we need education across the board. Also, there's more to pain management than just taking a medication. So we really need to look at the whole balance approach and offer all the other alternatives of pain management, but that's another meeting.

DR. CHAN: Yes, Dr. Budnitz?

DR. BUDNITZ: Dan Budnitz, CDC. I'll just add one comment, one, to try to reduce harm for someone for whom the drug is not prescribed. But one twist on that is, of course, if the drug is taken by someone else, it's not being used by the patient to whom it is prescribed. So that might be another variation on ensuring the drug makes it to the person to whom it's prescribed.

DR. SLATKO: Just one more slight twist on this. For tomorrow, when we're talking about doing studies and studying not only the target patient but the people around the patient, how do you collect this kind of data to inform the design of trials around this is what we'll be talking about tomorrow.

DR. CHAN: Yes, Ms. Whalley Buono?

MS. WHALLEY BUONO: Liz Whalley Buono. To kind to try and answer that question, I mentioned before the expense and the time on some of the research conducted. But I do think -- depending upon what FDA would find a satisfactory amount of evidence, I think you could relatively, easily, inexpensively, and quickly evaluate through things like consumer panels as to whether individuals would find value in some of the packaging concepts for things like, A, to make sure you got your full script when you left the pharmacy; B, if you bracket age groups, would this package make you less likely to take a pill out of your mother's cabinet?

So I think you could do intercept work, and I think you could do panel work relatively quickly. Now, the scientific rigor around that evidence is going to be a lower bar, but it begins to sort of answer the question about whether these concepts have multiple layers of value in some of these issues.

DR. CHAN: Dr. Miech?

DR. MIECH: I just wanted to follow up on your earlier point that we're focusing on people for whom the drugs are not prescribed. Just to throw a wrench in there even further, we're hoping to focus on things that never happen. Right? We're hoping that the adolescents never actually take the drugs, so that's going to be pretty challenging.

I guess we'll get into this more tomorrow. Sorry if I'm being premature, but we would want to look at population levels of misuse of opioids by adolescents, and kids, and adults. But I just want to throw in there that we're looking at something that hopefully never happens, so that's going to be

a challenge.

DR. SLATKO: Our next question is about -- and we talked a little bit about this -- unintended consequences of certain design options. John mentioned this earlier, whether using unit-of-use packaging that identifies the content might make it more attractive for non-treatment abuse and increase its street value, for example.

But are there other untended consequences we need to think about and designers need to think about and anticipate as they contemplate designing these options? Dr. Patel?

DR. RAO-PATEL: This is Anu Rao-Patel from Blue Cross. Speaking as somebody who is in practice treating these patients, I would say one unanticipated consequence would be for a patient who has chronic pain and is taking these opioids for legitimate reasons -- two things, one making the packaging so difficult to access that they can't actually access their medications and also putting so many warnings, and labels, and all kinds

of things all over them that it almost stigmatizes the patient to take the medication.

There are a lot of patients I've seen in practice where in the practice I was in, we did both chronic pain management and addiction. I don't know if that was necessarily a good thing because a lot of the patients who have chronic pain, who have legitimate chronic pain, felt very uncomfortable in our waiting rooms, sitting with people who were there for addiction purposes or people who were there who were trying to access opioids for diversion or inappropriate misuse.

So I would say, especially with some of the patients who are older, who may not have as much social or family support, who live by themselves, and they have to manage their medications themselves, you wouldn't want to make it so difficult that they can't even actually take the medications that they need. That would be one thing I would be a little cautionary about.

DR. CHAN: Thank you. Dr. Scharman?

DR. SCHARMAN: The statement's been made

that it might make the street value more, but there's another side to that. If people are going to divert, they're going to divert. We see poisonings occur because they thought bought X, and they bought Y, so they got a dose that wasn't a dose they were used to, or they got a completely different drug, or hypoglycemic and their blood sugar dropped, or on haloperidol, and now we have dystonic reaction showing up, charging cares and ERs all over the city.

So in some ways, it's protecting that population. The needle exchange programs to help people that are going to inject drugs, in some ways, we're also helping to prevent unintended poisonings in people that are buying a substance. And right now, people are selling what looks like oxycodone or Xanax on the street, and it's really fentanyl. So in packaging, we might deter that market for people making fentanyl and heroin look like regular prescription drugs.

DR. SLATKO: Mr. Berghahn?

MR. BERGHAHN: Walt Berghahn. The next step

of that statement is the fact if you start putting these things into unit of use, coming in the back door of the pharmacy and going out the front door of the pharmacy, there is a law that's being rolled right now, the Drug Supply Chain Security Act. That is fully and active, and blisters will be serialized. They'll have a serialized bar code on them, and when they hit the street, you're going to know exactly where they came from, who dispensed it, and who it was prescribed to.

DR. SLATKO: Are you saying that as a good thing?

(Laughter.)

MR. BERGHAHN: I guess it depends on your chair [inaudible]. I think it's a good thing.

DR. CHAN: Dr. Cox?

DR. COX: I was thinking earlier when someone brought up the RFID stuff, that there's this consequence of things that happen when someone in the family realizes that someone in their family is surreptitiously taking their medication. So some of the unintended consequences may be family

strife, not knowing how to deal with this, and even interpersonal violence that we may want to think about, educating people or about where to go or what to do about that.

DR. CHAN: Dr. Bateman?

DR. BATEMAN: I wanted to comment on the idea of blister packs that are tied to particular pain indications. I think it's going to be a great challenge to sort out how much medication should be included. Pain is a really heterogeneous condition. Not all back pain's created the same; not all joint pain. Ideally, opioid prescribing would be really individualized to the indication but also to what you anticipate that the patient would need.

If a patient underwent a surgical procedure and is doing really well in the hospital on NSAIDs and Tylenol, you wouldn't want to discharge them with the standard amount for a cholecystectomy that might be greatly in excess of what they need. Conversely, if a patient has a high need for opioids during their inpatient hospitalization, you

might undertreat them if you dispense them a limited amount that's suggested as the amount needed for a particular surgery. So there's going to be a lot of thinking that needs to go into what that amount should be.

DR. CHAN: Thank you. As a follow-up to that, though -- you're absolutely right. There is a challenge. How much is the right amount for any given indication? In the absence perhaps of some of that data -- we've talked a little bit earlier -- there was discussion around consensus guidelines that might drive some of these things.

But if you put the packaging out there as a hypothetical -- so pick a number, it's a 7-day supply of whatever X, or a 3-day supply of wherever you want to go. If you put it out there, my question is, would prescribers perhaps be willing to uptake that just because it's a convenient option potentially?

So without necessarily needing to say for this indication, we should agree on X number of tablets being the standard, would by merely having

the option already generate that use of it because it's a convenient option? I'd like to throw that out as a follow-up.

DR. BATEMAN: So you're asking would providers be inclined to prescribe if there was package for acute cholecystectomy. I think it would be attractive, but again, I think you really run the risk of underprescribing for some patients and overprescribing if you dictate a set amount for a particular indication.

DR. SLATKO: Dr. Mendelson?

DR. MENDELSON: Again, I think this is an area where scheduling can make a really huge difference, so that you can get a lower regulatory burden for the physician to prescribe would be useful. Scheduling is complicated because it usually doesn't do anything to deter anything from anyone. It's sort of a seal of approval that you have a better drug. Like if you're Schedule 2, it's got to be better than Schedule 3 for abuse. In this case, I think it could help physicians come with more responsible prescribing practices.

On the note of blister pack forgeries, absolutely people are going to figure that out. If they already make a pill that looks like a Vicodin and it's got fentanyl in it, they're going to figure out how to put it in a blister pack. I think the diversion of the drug into the approved format will happen. There are a lot of clever of people out there with irons and glue guns.

But anyway, you really want to incentivize it for doctors that you've got to find a way to make it so they can prescribe it much more easily and in the right amounts. It could be small amounts. They could be refilled frequently. It can be daily. I really don't have a problem with daily refills. I think that's really not a bad concept. And people deliver now, so I think that's really not a bad way to go. You get two days, and you've got bring your packaging back or send it in a picture.

DR. BATEMAN: Along those lines, I think -- I'll make a comment. E-prescribing is something that might be quite useful in that

regard. If you knew that you could give that patient a refill without them having to return to the hospital, that would go a huge way and enabling physicians to write for less.

DR. MENDELSON: I don't do anything but E-prescribing, and I'm sure the other internists around the room -- do you guys even write prescriptions anymore?

DR. BATEMAN: Well, I don't just mean -- sorry. I was going to say, I don't mean just writing the prescription using an electronic medical record, but if you could write for a Schedule 2 medication without having the patient come back to physically receive the prescription, that would be --

DR. MENDELSON: You can do that.

DR. BATEMAN: I don't think those systems are widely in use around Schedule 2 medication.

DR. CHAN: So we've got a lot of interest in this. Let's go in order here. Dr. Cox?

DR. COX: I'm really intrigued by the shortening of the supplies how we might do that. I

wonder if there really is data out there about what is needed for a particular procedure and how we would get there.

Another thing it made me think of is the antibiotic overuse crisis in pediatrics that took place about 20 years ago. One of the things was having a contingency prescription available for people, so we talked about the issue with scheduling and being able to get a prescription; could you get a prescription that said if at the end of these 3 days you need 2 more doses or 4 more doses to get you through the weekend, you don't need to contact anybody about those.

So just thinking through the policies and ways that we might make this actually work seems really doable.

DR. CHAN: Dr. Rao-Patel?

DR. RAO-PATEL: Just a few comments about that. I'll say in North Carolina there's been some legislation passed and signed to law by our governor where it limits initial fills for acute pain for 5 days and post-op pain for 7 days. I

think there's a way to do that.

I will also say that I think it's an opportunity because, again, like my colleague mentioned, it's very difficult to quantify pain and say who would require more than somebody else and who has what pain tolerance, and what's appropriate for them post-op. What's appropriate for you post-op may not be appropriate for me and vice versa, either because I'm having more pain or I don't need an opioid at all.

So I think it's an opportunity not really where we could say for sure that if you have a total knee replacement that's elective, then you only get these many pills, but I do think it's an opportunity for specialty societies to get together. American Academy of Orthopedics, I'm a physiatrist, so I know that we're already having discussions about this -- the American Academy of Physical Medicine and Rehab -- about what is appropriate prescribing after certain procedures or certain indications for pain, low-back pain, knee pain, CRPS, whatever.

I'm not a dentist, but I can say that we can all recognize that a 30-day supply for oxycodone after a tooth extraction or a wisdom tooth is inappropriate. It may not be my position as non-dental person to say that, but I do think it's an opportunity for people within that specialty and within their own accrediting organizations to have these kind of conversations as well.

DR. CHAN: Thank you. Dr. Patel?

DR. PATEL: I do believe if there's a type of opioid prescription, that it would be maybe easier for a physician who's already potentially too lazy to look at databases to prescribe opioid Z-Pak for patients and maybe use, above and beyond, an NSAID prescription because it's easier to write for. As we all know, Z-Pak is already overly prescribed already because it's easy to write, easy to use.

DR. SLATKO: Mr. Webb?

MR. WEBB: Kevin Webb, Mallinckrodt Pharmaceuticals. We obviously support the fact that management of pain is best managed through the

physician and the patient. However, from our perspective, what we would see is that as you think about the patient and you limit that quantity to a certain number of days, when that patient needs more medication, that patient now has to incur another co-pay and go back to the pharmacist to get another prescription filled. Obviously, it's an inconvenience factor if it's a rural patient and just complicates the process of trying to be sensitive to the patient and the patient's pain.

The AMA has legislation out there that I think is a good model, that allows the physician to write X number. But in the event that the patient needs more medication, they can get the rest of their prescription filled for that month without having to incur another co-pay. So it mitigates some of the issues of financial cost burden that the patient may have to incur, but then allows the physician to be the one who determines what is the appropriate amount of pain management that that patient needs.

DR. CHAN: A partial fill type of approach

is what we're talking about. I think we are getting close to time here. We were supposed to move into our audience participation session. Before we move, any final comments before we close this out?

(No response.)

Audience Participation

DR. CHAN: So we're going to go ahead and move into the audience participation session.

DR. SLATKO: Anyone in the audience who would like to make a public comment, please step up to the microphone. As you'll recall from the last session, you will be given 3 minutes to provide comments. There is a light to keep the time, and we do have FDA staff available to assist you. The light will be green and you can continue speaking. When it turns yellow, you'll have another minute left to finish your comments. When it turns red, you'll be asked to stop speaking at that point in time and return to your seat. Please proceed.

MR. SUNDBY: Great. Thank you. Good afternoon. My name is Jason Sundby, and I am the

CEO of Verde Technologies. We manufacture Deterra drug deactivation and disposal technology, carbon-in-a-pouch people. Six years ago, we set out to develop a scientifically proven method to deactivate drugs. We did this under contract, an SBIR with the National Institute on Drug Abuse. So all of our science is validated not only in our labs, but Mercer University in Atlanta, and then again by NIDA.

As of today, there are multi-millions of units that have been dispensed throughout the country, which equate basically to about 155 million dosage units that are being deactivated and taken out of people's medicine chest. At-home drug deactivation is a tangible, cost-effective convenient and easy way to get rid of unused and unwanted drugs out of the home. It allows us now to close the pharmaceutical life cycle on drugs.

A few examples of how these are being employed. Two attorney generals, Pennsylvania and Kentucky, have dispensed them throughout their state to try and stop this opioid epidemic, and

Mallinckrodt Pharmaceuticals incidentally has purchased millions of units from us and have done the same. They've done a nation-wide campaign to get these out there.

We really believe that it's important for the FDA to expand their options for safe disposal. Right now it's kitty litter, coffee grounds, and saw dust, and flushing. There are technologies like ours that are out there now that can actually deactivate these drugs, and hopefully you'll expand those options. We're endorsed by the DDA Educational Foundation. We were added into the ONDCP and the President's Commission. We're recommendation number 17 of the opioid commissions.

So there's a much better way to sustainably get rid of unused and unwanted pharmaceuticals, and we hope that you'll take these comments and expand it. Thank you for allowing me to speak.

DR. SLATKO: Thank you. Next?

MR. SU: Hi. My name is Hoong Su. I'm the senior principal with Shire Pharmaceuticals. I'm a packaging engineer. I've heard a lot about unit

dosage and going from one platform of packaging to another platform of packaging. I would like to submit to the FDA if we are asked to go from one platform that is currently being distributed on the marketplace to another, to allow time for that because the stability study that we need to do for the product itself -- one of the main things of packaging is also the technique of the product.

The other thing, the time allowed for studying, the time allowed to change over the packaging lines when we're doing that, it's not a quick solution. It does require time to implement that, so please take that into consideration.

DR. SLATKO: Thank you. Hello?

MS. McNANNAY: Hello. My name is Jody McNannay. I'm with Curadite, and we have been working on packaging and also on medication adherence. We see a real overlap between medication adherence, as many panelists here discussed, and the opioid crisis. The thing that I've noticed and I really appreciate from a number of the panelists is the discussion on

incentivization.

I think it's really important. I know Drs. Bosworth, Ciccarone, Dr. Mendelson, Dr. Slatko all talked about this. And the reason that I stress this is because you do have a patient, you do have a physician, you do have a pharmacist. And there's always the question of who's going to incentivize and also who is going to be reimbursed.

I think there's some real crossover between these two so that when we think about how this problem is going to be solved and addressed, I hope that you'll take into consideration those groups and also those people who are active with creating packaging and labeling and so on and so forth. I thank you very much for your time.

DR. SLATKO: Thank you.

MR. GOODLOE: Thank you for the workshop and for the opportunity for the audience participation. Peter Goodloe, an attorney with the law firm Brownstein Hyatt. I spent most of my career working as a counsel in the House of Representatives working on legislation concerning

public health agencies, FDA, NIH, CDC, HRSA, SAMHSA, ARC. But here today, I'm representing a company that makes lockable prescription vials. We're not here to talk about specific products of course, but rather general principles.

So what's the objective? It stops pilfering in the home. It's a gateway issue. It's how kids get started. How do you fold it into the system? Earlier, one of the slides showed a locking cap. That was I believe an after-market product. The consumer would have to make the decision to purchase that. Perhaps a better way to do it is to try to seamlessly fold it into the existing system. It has to be affordable for health plans. It has to be easy for the pharmacist. It can't take that much time. And it has to be easy for the patient.

You add all that together -- and we need more data. But I've heard a lot of talk about what's the most bang for the buck, we can't wait 10 years, what can be done now. This is our work explored. Thank you.

DR. SLATKO: Thank you.

DR. LANGLEY: I'm going to piggyback off that because I also have a locking cap.

(Laughter.)

MR. LANGLEY: I was going to touch on question 1 because I wasn't sure if there was any closure manufacturers on the panel, and that question was the steps or approaches new packaging developers currently follow when designing new packaging. So I just was going to give a little insight at least our process. Our process might be a little different than traditional closure packaging company because we created this based off of a need. We weren't an original need packaging company.

Long story short, my partner's brother became addicted to prescription medication by taking one or two from his Mom after she was in a bad car accident. He was a teenager, and that's how he got started. From there, he actually became the neighborhood lawn mower and began going into all neighbors' medicine cabinets and taking one or two from them so it wasn't as noticeable.

So he figured if there's something around Safer Lock or locking cap that the existing prescription models, one could do without the other. One, he would have never started because there's a lock on it, or two, maybe it's not indestructible, and he would have broken it, but at least she would have known. She actually accused the pharmacist of shorting her on medications before she realized there's a problem in the home, found out to be very common. Not only does it prevent abuse, but it protects the patient because she was coming up short at the end of the month. She couldn't refill early, so she was actually going an extra few days or for a week in pain.

What we decided to do from that, as the market rises [indiscernible] situation, as we're all familiar with, we wanted to just design something that was disruptive to the industry but not too disruptive to the process. So we designed a cap that actually fits -- we're not a bottle manufacturer; we're a cap manufacturer, and it fits existing prescription bottles. So it's something

that can be implemented easily. It even fits with some of the pharmaceutical auto fills.

It's a mild disruption on the pharmacy fill process. The only real disruption is on the consult. It adds an extra few seconds to the consult to educate the patient on the need for support, which I think should be going on anyway. [Inaudible]. So theoretically, it's actually not adding too much because it's something that should be done anyway.

From that, we tested the product, Consumer Product Safety Commission, and showed it's child resistant but also senior friendly. Some people find this easier to use because it's not a press and turn but simply a turn.

I just wanted to share. One of the challenges, though, as has been mentioned here with us, is that it's a very light indicator of whether or not this is successful in past patients. We get a lot of anecdotal feedback from families saying they're so happy that they had this, but in reality how we even know if it really made a difference is

going to be down the road a year or two or a few years maybe when there's less treatment, because that's when [indiscernible] having less people go to treatment.

DR. SLATKO: Thank you.

DR. CHAN: It looks like, again, we're still a little bit ahead of schedule, which is always nice. I think we're going to go ahead and break for lunch. I would ask that everyone return to the room by 1:20, and thank you for this morning's discussion.

(Whereupon, at 12:14 p.m., a lunch recess was taken.)

AFTERNOONSESSION

(1:27 p.m.)

Session 3 Presentation - Patrick Raulerson

MR. RAULERSON: If everyone could fall into place, we'll resume the afternoon sessions. Hopefully, we'll keep them interesting enough to avoid people experiencing food-coma related narcolepsy.

My name is Patrick Raulerson. I am regulatory counsel for CDER, and I'm going to be discussing some of the regulatory considerations applicable to the options and technologies that we're discussing in this workshop. As Dr. Gottlieb and other FDA officials have already indicated, we believe the packaging, storage, and disposal technologies and options we're discussing today have a real potential to make a positive impact on the opioid crisis.

Accordingly, we need to develop and implement a regulatory approach that properly incentivizes and regulates these technologies. So this session is about the tools and authorities FDA

may be able to use to accomplish this.

I'm not going to read the disclaimer. It's the same one as in the other presentations, but I just want to mention that the views I express and the comments during the panel session that I may make are wholly my own and should not be taken as FDA's position or regulatory approach towards these options.

In addition, I want to emphasize that while my work at FDA deals with law as well as policy, I work in CDER, not the Office of Chief Counsel, so I don't speak for the agency on legal questions.

As an overview, this presentation is intended to provide some high-level content on the pathways and authorities that might apply, and in some cases are likely to apply, to these options. I'll also talk very briefly about certain aspects of the approach FDA has taken towards the regulation of abuse-deterrent opioids and how that approach may be potentially applicable to the regulation of the issues and topics that we're discussing today.

This presentation is not intended and should not be taken to represent FDA's views of how our regulatory authorities will apply or how any particular product will be regulated. This is largely novel regulatory territory, raises a lot of complex questions, but we really need to find answers; it's not just questions. Hopefully, the panel discussion will help us get there or start to get there.

We haven't issued guidance on this topic, but for now we will take a case-by-case approach, and we may be able to issue more public guidance in the future. We hope the discussion that follows this presentation will inform our consideration of these issues.

The first regulatory topic I want to mention is the basic benefit-risk paradigm that governs all new drug approvals. For any new drug application, not just for opioids, FDA will only approve the drug if it determines that its benefits outweigh its risks.

As for opioids in particular, FDA takes into

the account the significant abuse and misuse potential associated with these products, including the broader public health impact of such abuse and misuse, along with all other risk factors when considering the risk side of the risk-benefit calculus.

For example, for the fentanyl spray products, FDA reviewed the performance of the charcoal or carbon-line disposal pouches included with these products in connection with its consideration of the safety risks associated with residual fentanyl remaining in the bottle after the patient has completed or ceased using the product.

When any of the options and technologies that are the focus of this workshop are incorporated into a drug development program and specifically into a new drug application, or NDA, FDA would evaluate a known or reasonably expected impact of the technology on product safety. By the way, we'll also consider any expected or reasonably expected or shown demonstrated impact on product efficacy.

So while the focus of the workshop is on safety-enhancing technologies, we recognize that many of the options we're discussing could have efficacy-enhancing benefits as well, including but not limited to positive effects on medication compliance and patient-physician communication.

The next topic I want to mention as also part of the NDA review process is drug labeling. Prescription drug labeling must include the essential information needed for the safe and effective use of the drug. This standard generally applies to labeling, whether it's directed at prescribers or labeling directed to patients.

FDA can consider information about the options that we're discussing in this workshop appropriate for inclusion in labeling. For example, back to the fentanyl spray products, the labeling of those products, the NDA products, includes extensive descriptions of the disposal pouches included with those products and instructions for their use.

Also, as discussed in the first session

today and in part in the second, depending on the studies conducted, FDA may consider approving labeling statements about one or more clinical or public health benefits expected to result from the use of a particular storage, packaging, or disposal technology or option.

The next topic I want to mention is REMS. That stands for risk, evaluation, and mitigation strategy. A REMS is required whenever necessary to ensure that an opioid drug product's benefits outweigh its risks. As I'm sure almost everyone here knows, REMS have long applied to the extended-release and long-acting opioid products. And as I'm sure almost all of you also know, FDA has recently initiated the process for mandating REMS for immediate-release opioids as well.

REMS could apply to the technologies that we're discussing today in a variety of ways. To take a fairly trivial example, and one that we've already done, medication guides and communication plans are often included in REMS. A medication guide is information directed at the patient, and

communications plans, information directed at healthcare practitioners. They may be required to include information about the kinds of options, packaging or disposal options, that we're discussing today.

For example, for Subsys, which is a fentanyl spray product regulated under a REMS, the medication guide includes information on the Subsys child safety kit and references information in the patient-directed instructions for use on how you're supposed to use the included disposal pouch. In addition -- and this is more complicated -- FDA is also considering whether and under what circumstances it may be appropriate to require a safety-enhancing storage, packaging, or disposal technology as part of a REMS.

Next, I'd like to talk about potential regulation of the options that are the focus of this workshop as drug-container closure systems. Drug packaging is assessed to ensure the packaging is suitable for the product's intended use. This includes questions for all drug products, such as

does the packaging system adequately protect the dosage form for the duration of the product's expected shelf life; does it avoid reacting chemically; and does it avoid leaching harmful chemicals into the dosage form, et cetera?

But we also evaluate whether a container-closure system that is intended to have some other function, in addition to just holding or protecting the dosage form, actually functions as intended.

So for the packaging options that are the subject of this workshop, to the extent that they would qualify as components of container-closure systems, FDA's container-closure review conducted during the NDA process would include an evaluation of whether the product can be expected to have any safety-enhancing property or properties that the sponsor intends for it to have.

Now, I want to briefly touch on device considerations, which have come up several times already today, and I'm sure we'll talk about it more on the panel, and how they may potentially

apply. I'm not going to read this long definition of what qualifies as device, but I'll just mention that some of the options discussed in this workshop could, depending on their intended use, be considered devices; or if they were included as part of a drug development program could be considered device constituent parts of drug-like combination products.

For example, if an opioid drug sponsor packages its product with a locking technology and obtains FDA approval for a labeling statement that its technology can be expected to deter accidental exposure and/or overdose, FDA may consider the locking technology device a constituent part of the product and regulate it accordingly.

Now, with that said, I don't mean to imply that all or even most of the options that we're discussing today would be considered devices in all cases or that inclusion of them in a drug development program would necessarily result in a product being a combination product.

Unfortunately, I can't give you any

delineation of when it would and when it wouldn't be. This is a nascent area for FDA regulation, as I mentioned already, and these technologies present a lot of complex issues, device issues just being one of them. But I can say that we will work with drug sponsors as well as firms developing stand-alone technologies on any device considerations that may or may not apply on case-by-case basis.

Finally, I want to briefly touch on how our regulatory approach towards the options we're discussing today could reflect the approach we have already taken toward abuse-deterrent opioid formulations.

As a policy matter, as we all know, the goal is to make these opioid medications safer. So whether the safety-enhancing feature is a specialized formulation that resists snorting or injecting, or for example an innovative packaging technology that deters overdosing or deters a diversion, the potential positive impact on patient safety and public health could be significant. And

I expect FDA to be fairly agnostic as to whether that benefit arises from the formulation, from its packaging, or whatever other feature of the product that's under consideration.

One potential regulatory parallel would be labeling. Over the course of several years, FDA developed and publicized detail guidance on how opioid drug sponsors can show that their potentially abuse-deterrent formulations can be expected to deter abuse.

Consistent with the approach described in that guidance, FDA has today approved -- and I think I have this number right -- 10 opioid drug products with abuse-deterrent labeling; that is labeling describing their products expected abuse-deterrent properties. Those claims that include appropriate caveats such as the products that are undergoing additional study post-market, FDA may update or modify the labeling as needed based on the results of those post-marketing studies, et cetera.

As discussed in some detail in an earlier

session today, FDA could potentially take a similar approach to labeling, describing the expected benefits of safety-enhancing storage, packaging, or disposal options that are the subjects of this workshop, depending again on the data and studies that are submitted in support of those options.

Finally and more generally, FDA has stated regarding its regulation of abuse-deterrent opioids that it will take a flexible and adaptive approach to make sure we are utilizing our regulatory tools to appropriately support development and utilization of such formulations. I expect us to take a similar approach towards the safety-enhancing technologies under discussion today.

With that, I'd just like to thank you all for the opportunity to speak today, and I look forward to hearing from the panelists and other stakeholders on how FDA can use its regulatory tools and authorities to properly incentivize and regulate the potentially safety-enhancing technologies that we're discussing here. Thank

you.

(Applause.)

Panel Discussion

DR. BERTRAM: Mr. Raulerson, thank you very much for the overview of the regulatory pathways and considerations, as well as authorities for these products. Again, I had microphone issues earlier, so for those of you that don't know me, my name is James Bertram. I'm with the Center for Devices and Radiological Health. Before I get into the first question, I think I have two answers for low-hanging fruit.

Dr. Kelman, the answer to one of these devices versus drugs, it depends.

(Laughter.)

DR. BERTRAM: For attaching explosives, I think we'll have to do paper-rock scissors with ATF to decide.

(Laughter.)

DR. BERTRAM: With that, looking to get into this panel. Just a reminder, I won't go too far into the nuances of this, but we have a number of

focus questions that we'd like to use to direct the conversation. I believe there are 7 or 8 of them, so that gives us anywhere from 5 to 7 minutes per question. We've ordered them in what we think is maybe more fruitful in discussion, so if we don't get to the end ones, it will be okay.

With that, getting into the first question --

MR. RAULERSON: We're trying to put it up on the screen now. Sorry.

DR. BERTRAM: The earlier sessions, we discussed possibly incentivizing claims and technologies, or at least technologies, through labeling claims. I think the first question we're going to be looking at is taking a different perspective as at what point do we believe it's appropriate to require such technologies to be part of either the condition of approval or for the continued marketing of the product? With that, what level of proof do we believe the agency needs to have to make this a requirement?

I think this is actually a great question

coming back from lunch because I heard really a pretty vast discussion in the previous two sessions, being the agency should provide clarification so the industry as a whole knows what they're looking to address and pursue; others noting we're still early in acquiring what the problems are and what are the solutions to the problems. Also, depending on what technologies and at what stage we mandate, it could impact availability of the products for years to come or until they are available.

With that, I'd like to turn it over to the panel. Who would like to dip their toe in the water first? Just as a reminder, please introduce yourself when you talk for the transcript.

MS. WHALLEY BUONO: This is Liz Whalley Buono. The light bulb just went off with that presentation as to when we're talking about labeling claims. It wasn't really clear to me; that I think what we're talking about is an actual claim made around the effectiveness of the packaging innovation itself.

MR. RAULERSON: Right. So there's really two labeling issues. One is a mutual description of what the option is. Like if there's a charcoal disposal pouch included with a fentanyl spray product, it says that in the labeling, and it tells patients how to use it.

What we're talking about today, or in addition, is what you just mentioned, which is the potential for getting some sort of statement in the labeling, FDA approved, that that disposal pouch, or some other option under consideration, is expected to have some benefit we think significant enough to include in the FDA-approved labeling.

MS. WHALLEY BUONO: Got it. Okay. So that was something that honestly hadn't even occurred to me until just now it went off. I certainly defer to anybody else around the room, but the concept of adding verbiage onto the product around the functionality of the packaging, to me, I worry about, A, just adding more information to an already crowded label that really is not going to be I think of value to the patient. And I'm not

sure from a commercial perspective whether the packaging industry would really feel that that's necessary from a competitive advantage perspective.

The claims around the packaging, in my mind, the real question is what does the FDA need by way of proof to show that, A, the packaging is not going to cause any unintended harm, and that, B, it's actually going to help with some of the challenges posed by the opioid epidemic.

So just from a commercial perspective, I don't see adding packaging claims to -- the right to add a claim to the package is something that would be particularly attractive. I think it's really a question of what would the FDA need by way of evidence to approve these packaging concepts, and are they PAS submissions. How do we get that through most expeditiously as possible, where a manufacturer is willing to invest in these sorts of innovations?

DR. BERTRAM: So it does seem more of the view that what you're saying is the agency dictated and said tell us what we need to see, and we look

at how best to apply [indiscernible] that information.

MS. WHALLEY BUONO: I should say there's an educational component to adherence packaging, let's say as an example -- and I'm sorry to keep on bringing that up, but that's what we've been doing for the last 10 years.

Let's say on the adherence packaging down at Walmart launched through its pharmacy, there was language on there that said this package is designed to help you track your medication and take it correctly. Refer to the calendar, and then there were instructions around how to follow the calendar. And those were added because we learned from the pharmacy feedback and the patient feedback that the patients simply were not identifying the calendar because when that packaging was first launched, it was really a new concept.

So there was an educational component, and then once the patients were educated, oh, that there is actually a calendar and this is what I'm supposed to use it for, then obviously the

effectiveness of the packaging was heightened.

So there are components I think that are valuable to have in the labeling as far as the intention of the packaging and how to use it, but I think that's very different than some sort of claim, which I'm not sure would mean anything to a patient.

DR. BERTRAM: Dr. Budnitz?

DR. BUDNITZ: From a point of clarification, my understanding is that when they talk about the package label, it's not what the patient sees on their amber bottle or on the box. This is a package insert that's 15 pages long in a very small font, just to clarify.

MS. WHALLEY BUONO: And I think there's some crossover there with the different innovative packaging types because a lot of that material is then printed on the extra space on the adherence packaging. So there's a crossover.

DR. BUDNITZ: Maybe you have data to clarify what they're talking about for the increased claim. It might be something that might be used for

payers --

MR. RAULERSON: It might be used for promotional materials to prescribers as well.

DR. BUDNITZ: Promotional materials but not necessarily --

DR. BERTRAM: In Session 1, in Irene's presentation, there were several examples, like this technology is expected to reduce the risk of external exposure. I'm not getting the words right, but we don't have any words anyway. But that kind of thing wouldn't be directed at the patient. It would be directed to the prescriber.

So we would consider that. If they showed through substantial evidence, we would say that's -- depending on the technology and the data, we'd say that meets the definition of essential information for the prescriber to know about.

MS. WHALLEY BUONO: I'd just point out that sometimes there's value in some of that information for the patient, from an educational perspective.

MR. RAULERSON: We would consider that as well.

MS. WHALLEY BUONO: Yeah.

MR. RAULERSON: Can everyone hear me? I want to make sure we get to question 1 -- we should keep talking about labeling as needed, but under what circumstances do you think FDA should take that additional step of saying thou shalt to the manufacturer, thou shalt include some kind of safety-enhancing packaging or disposal or storage options?

MR. WEBB: Good afternoon. Kevin Webb, Mallinckrodt Pharmaceuticals. In the question regarding labeling, it's obviously a complicated issue. One of the things I think the FDA needs to also take into consideration is, to your point, a type of promotion activity. We support that, opportunities to be able to do that, but since most of the opioids are generics, generics don't promote their medications by default. So we're just looking at how do we maximize value with the distributor so that they choose our generic medication over another. At that point, you're looking at margins.

So we're probably not going to look to a labeling opportunity to differentiate it from a promotional capability. We're going to be looking at making sure it's a level playing field. We want to make sure that if we do this, everyone's doing it because we don't want to invest millions of dollars developing a new type of packaging when my competitor is not, and the distributor buys their packaging or their piece because it's 5 cents less expensive than mine.

It goes back to then the FDA saying if we're going to do this, this is what the manufacturers need to have as far -- again, I'll use a blister pack configuration just because of simplicity; that they all need to have it, allow us then to be innovative saying these are some of the features that might be different in one blister configuration from another, but we're all investing in the same thing. The guidance and clear direction of the FDA is going to be what we need to be able to move forward.

MR. BERGHAHN: Just kind of pushing back a

little bit on this point, [inaudible]. I look at 21 CFR 201, and what's on that package is it needs to provide another direction for someone to get adequate and safe use out of their product. And I think we're all sitting here today because it's not happening. It's failing miserably.

So I think we need to consider both, what is this added labeling needed for patients, as well as the procedures, as well as what you're describing.

MR. RAULERSON: I don't disagree.

DR. BERTRAM: Dr. Kelman?

DR. KELMAN: Jeff Kelman. I'm less worried about the labeling issue. But if the FDA gets information that actually changes the safety risk factor for a drug based on packaging, it's hard to see how it cannot require.

MR. WEBB: I just want to ask one clarifying question. As we think about the whole regulatory review as well as the question that we would want as a manufacturer, how much time -- I don't expect an answer on this, but as we look at what is the regulatory review process on this, as we bake that

into how quickly we bring something to the market, we would need to know is this a CB30 review, is this an annual report, or is this going to be something that's a prior approval. All that needs to be factored into what configuration we're looking at.

MR. RAULERSON: Any other thoughts on question 1?

DR. BIX: This is Laura Bix from Michigan State University. I do think that there is an example, a path that's been traveled, patterns, and that's the Poison Prevention Packaging Act. The language in that act may not prescribe a design, but you need to meet a certain performance standard. So it's specific, yet flexible at the same time. So it presumably allows for innovation, but it also mandates a performance standard. So to me, that's been a very successful path, maybe not perfect, but a successful path that deals with the problem 30 years ago, 40 years.

MR. RAULERSON: So expand on that. I know in some of the earlier sessions today, you've heard

FDA say we want to allow for innovation. We've heard from several panelists, FDA you've got to give us targets. So it's going to be important for us to strike the right balance. I don't know if anyone else has thoughts on that.

MS. WHALLEY BUONO: Liz Whalley Buono. I think that's a very interesting analogy, Laura. I guess I'm having trouble thinking about, so I love the idea of the flexibility, and it provides an open blue space for innovation. But then at the end of the day you've got a protocol that you test against. And it's for one problem, and it's for the problem of children getting into packaging.

When we're looking at what we're hoping the packaging impact will be in the market, I don't know, what do you say? A hundred problems? So what do you test against? And I guess my mind goes to when you talk about level of proof, I would say the FDA needs enough data to feel that the packaging will not do any harm versus a vial.

So that's the first thing. And you can certainly get there I think with an amount of data

that's digestible and probably we can get. But then when you talk about the hundred discrete problems and how do you test for diversion in the home, I'm having a hard time.

I guess that's a really inarticulate way of saying that I think once you get the benchmark of it's not going to do any harm versus a vial, then you start to look at perhaps more subjective type endpoints for data standards would be acceptable to begin implementing things.

DR. BIX: I agree, and think that that's something that I strongly recommended at the first meeting, and I think one piece of it is you have to prioritize how you're going to eat the elephant. So I would suggest that you have to prioritize which bite you want to take.

MS. WHALLEY BUONO: Just so we're clear. The evidence right now is not out there in the published literature. We did a very comprehensive, systematic review of all randomized control trials of a certain caliber up, and there just simply has not been the type of evaluations done and published

on packaging prior to the three that we put up, and if there's additional ones that I'm not aware of, but we've been kind of living and breathing this space. We can't really hoe that ground. It's not out there. So whatever we're looking for, we have to create moving forward.

DR. THROCKMORTON: Liz, I want to ask a clarifying question. You seem to be articulating a standard, no worse than vial. I'm having a hard time understanding that. It seems as though you'd need more than that to support a change in packaging that would lead to potential patient confusion and those kinds of things.

I think that was partly why we were talking about claim because we're trying to incentivize better than existing. We wanted people to be doing better than existing vials because we thought that was the direction we needed to be heading. We needed new technologies. We needed new ideas in these areas that we've talked about already. No worse than existing doesn't seem like a goal I'm overly excited about.

(Laughter.)

MS. WHALLEY BUONO: Yeah. I wouldn't imagine that you would, especially if you're talking about something like mandate. This is -- sorry -- again a non-articulate way of saying -- no worse than vial to me is it doesn't cause patient confusion.

What is the option? Right now, you've got a bottle or a vial full of pills and a very curved, small-font, round label, and then perhaps additional ancillary information that goes out with it. So I would just say from a risk evaluation perspective, you start with what's currently there, and that's what we've got, and then you decide what's the level of substantiation around things like confusion associated with a new packaging type.

Well, you can get that from usability studies. You can get that rather quickly from consumer engagement packets. You can get that sort of things. But you're not going to get all the way to bright in a short period of time. A, the

package needs to be out in the market to evaluate it unless you're talking about a randomized controlled trial, which I just don't think -- I mean, if we're talking about that, then we're years away from a solution.

So I guess I'm going with the whole first do no harm. So if you've got some concepts that are working in other areas, and you've got data that shows that they're not causing confusion, and you've got a common-sense approach to maybe they can help with some of these newer opioid-specific issues, it's a lower bar arguably from a regulatory perspective, but to me that's the only way you move the needle on this.

MR. RAULERSON: What are you anticipating as the regulatory impact that meets that lower bar? We would allow a description of the packaging. We would allow it to be part of the product where we would mandate something.

MS. WHALLEY BUONO: For you to mandate, you're going to need more evidence than that. There's definitely got to be a justification for

the increase of cost for the manufacturer, and hopefully you're looking at public health improvement.

MR. RAULERSON: Sorry. One last subpart to this first question, and then move on to the next, because this ties into something we've already heard a couple of times, which is -- and I think for Mallinckrodt and others, that if FDA doesn't require it, what's the incentive? What's the incentive for uptake by pharmacies, manufacturers, any stakeholders in the distribution chain?

If we don't have enough evidence to require it, but we simply allow it, we're in a position that we've been in with abuse-deterrent opioids -- at least this is a view that's been expressed to us in the past by several stakeholders, which is labeling isn't enough because I can't convince payers to preferentially prescribe my product even though I have this labeling claim.

We need more than that. I'm wondering if we have thoughts from the panelists. And that's not

FDA's position, but we've heard that, and I'm wondering, since we've heard similar thoughts today, if anyone has any additional considerations for us.

MS. WHALLEY BUONO: Well, I can just say, two, and I don't know how feasible they are, and certainly I would defer to the experts on this. But preferred formulary status would be one that would seem reasonable to me and some sort of improved reimbursement rate for drugs that come in those packages.

They're just two market incentives. I don't know how realistic they are because now you're crossing jurisdictional lines into CMS' area or managed care's formulary setting. Other than a mandate, those are the only two incentives that I can think of that justify the upcharge.

DR. KELMAN: The argument is going to be that if this were truly a preferential product that actually was safer and more effective than the other that exists on the market, the others should be off the market.

MS. WHALLEY BUONO: So you're not making a claim that the drug becomes more effective and safer because it's in a package. It's being offered in a package that can improve adherence, which is really what we're talking about.

DR. KELMAN: But your question is how is it marketed. That's why my question is about whether this is a device or a drug. Are we covering this as a drug with a technological safety element or are we covering a drug in a separate package? And if it's a separate package, it's unclear that that's reimbursable at all, depending on what the package features are.

DR. BERTRAM: Can I ask a quick clarifying question? You're saying drug versus device, so I understood that the way you described it to be is whether it's part of the drug packaging or maybe a combination product as compared to a stand-alone product.

DR. KELMAN: Does it have an NDA. That's what I'm really asking about, and to most payers, that will be the question.

MR. BERGHAHN: Walt Berghahn, HCPC. To Liz's point, you've got a hundred problems. You're going to have to prioritize them. And if one of the top priorities is that you want to reduce child ingestion of opioids, you've got a very clear solution. You're going to get into unit dose, and then you're going to see what additional benefits you get from that measure, which addresses some of the other 99 problems. There are no solutions that's going to hit all hundred, but when you prioritize the problems and see which ones are giving you the most problem, [inaudible] then we can target solutions.

MR. RAULERSON: Let's go on to question 2, which is what potential unintended consequences, for example, on availability or cost of opioid medications, do the panelists see if we were to require a mandate, some sort of additional safety-enhancing features along the lines of the things we've been talking about today?

MR. WEBB: Kevin Webb, Mallinckrodt Pharmaceuticals. As we think about the

manufacturer's perspective of who's actually bringing product to market, any additional burdens within the manufacturer would cause some of them obviously to leave the market. So I don't necessarily think, as we think about supply, that's a bad thing. But recognizing there's a value that manufacturers have with making sure there's a readily available supply of medications, that is we make the packaging too burdensome or onerous for manufacturers to absorb that incremental cost, some of them would just fold up their tents and go home and not even compete in the market anymore.

MR. RAULERSON: Can I ask a follow-up? Since we've been talking about -- and again, not trying to forecast what FDA's action may be. But since we've been talking about blister packs unit of use packaging, do you think that kind -- that's fairly simple technology. Would that alone be enough disruption to potentially cause problems?

MR. WEBB: It depends. A manufacturer like Mallinckrodt, no, it's not. We have the blister pack even though some do not. But I also want to

make sure that we understand that that's not something that we can ensure [inaudible] tomorrow. So there's still a significant amount of lead time that needs to go into retrofitting the existing line.

So I think there was a point earlier that was made during the general comments that we need to allow the industry enough time to absorb and make the necessary changes, but some just aren't going to be able to afford the infrastructure themselves just to redo the lines.

DR. MENDELSON: The problem with this question is the condition of approval. So if you take this to an advisory committee -- and many of us have been on committees -- the committee will demand perfect and will not accept good. And therefore, you'll end up with a thousand solutions that no one will ever use as the condition of approval, and it will never happen.

So I think you have to be very careful how you present this to your advisory committees because they will want it better than -- and

they're not focused on cost. They don't care about the cost of the product; they care about the safety and the efficacy. So I think condition of approval is a dangerous pathway to go unless you're ready to go, when you do accept one, that you pull everyone else off the market also. That's the other unintended consequence.

So you may end up distorting the market quickly, and you could avoid that by doing demonstration projects and then having some kind of other iterative process or just regulation from the beginning. But I think the biggest problem that you'd have is that your committees could run away. They might not approve something because it wasn't perfect, and they might insist on things that made it unmanageable or unimplementable for your product.

DR. SCHARMAN: I remember when the Duragesic patch first came out. It was a gel matrix, and they were cutting out the gel, and putting it on their tongue, and they were injecting it. And then later they came out with an embedded matrix, the

[indiscernible] gel, which is great. Now no one was sticking it on their tongue, and they weren't injecting it. But all the generic manufacturers were allowed to keep gel matrixes on the market. So they come in the pharmacy, and if the doctor wrote a fentanyl patch, the patient picked, and they got the gel every time.

So it did no value. So the company was very innovative and came out with a drug that stopped diversion, but it didn't work because the generic companies were allowed to not keep up with what the brand company had came out with. So I think if you're going to incentivize the brand-name companies to be creative with non-divertible products, they ought to get market exclusivity until the generic products can use that same non-diversion formula.

MS. WHALLEY BUONO: Liz Whalley Buono. It's an interesting analogy. The only thing that I'll raise is that I believe that the reason that the generics kept the gel products on the market is because the intellectual property was vested in the

branded manufacturers. You wouldn't have that with packaging.

No, you wouldn't because the intellectual property in the packaging is established. Unless a pharmaceutical company comes up with a brand new packaging type or exclusively licenses the packaging technology, which it's highly unlikely anybody would do that, it's a level playing field, so it's just a cost issue. There's not a barrier to entry there.

Does that make sense?

DR. BERTRAM: Thank you. Moving on to question 3, what are the benefits or challenges of mandating or otherwise including packaging, storage, and disposal options within a REMS, as opposed to utilizing FDA's authority so you can have more discipline?

MR. WEBB: Kevin Webb. One of the obvious issues, again from our perspective, is that through the REMS -- agreeing that the FDA has that ability to do so -- it doesn't adjust the reimbursement issue. I don't want this to be a cost issue

because it's not, but at the same time if the payers or the plans don't see the value proposition on this, is it still going to be a situation where you just have a better device of packaging with no incremental cost to be continued, the innovative [indiscernible] medication?

So I just would like to make sure that the FDA takes that into consideration that there needs to be a balanced approach. It's one thing to force the industry to change; it's another to say that the market is willing to accept it and pay for that information as well.

DR. KELMAN: You talk about a REMS. I assume it would be a REMS across all products, so it would be a level playing field. So if there were any cost increases, it would go to all products and not differentiate lower price and higher price ones.

MR. RAULERSON: Let's make that assumption. I agree that that's what we were thinking, yes. Whatever set of opioids the REMS applies to, if it included an element to mandate some kind of safety-

enhancing packaging, would that be of benefit to our ability to properly incentivize and regulation these technologies?

DR. KELMAN: It would clearly be an incentive. It would be a requirement.

MR. RAULERSON: It would be a requirement.

DR. THROCKMORTON: But an incentive to do better or just an incentive to maintain the status quo?

DR. KELMAN: I assume it's an incentive to improve, to be in line with the REMS.

MR. WEBB: I think it would raise the bar. It would level the playing field and give you the desired result that you're looking for. The market will catch up. So it's a pathway to allow you to do this.

DR. BERTRAM: Any other comments on REMS?

MS. WHALLEY BUONO: Liz Whalley Buono. I would just comment that REMS to me seems like the best solution so far because you have the opportunity to make it multifactorial. So you can then bake into a REMS counseling and all sorts of

different interventions that when you layer them could have exponentially greater impact than just mandating one particular innovation.

DR. GREEN: Another potential benefit of doing it through REMS is that you can take maybe a more risk-based approach because the REMS are a little bit more specific. For instance, the transmucosal fentanyl REMS and the buprenorphine REMS, you might be able to evaluate the risk associated with that group, whether a shared-group REMS or product-specific REMS, and then match those interventions or requirements with the risk of the products that are actually included in that strategy.

DR. BERTRAM: So going back to Dr. Kelman's point of whether it's an NDA or not, just to note, for devices, there are no REMS, so we don't have a REMS authority. So again, just contemplating, as you look at these technologies, if they are brought as stand-alone devices as compared to under the NDA, that may have an impact on the, quote/unquote "level playing field," but at the same time, as

being said, the point of this is getting to looking at consistency, should they be looking at this issue consistently irrespective of what the product type is?

MR. RAULERSON: All right. Let's move on to question 4, which is -- and I think this is something we are going to have to deal with -- if the option under consideration has already been on the market as a stand-alone entity, what additional considerations are warranted in evaluating its use with a specific drug? So if a drug sponsors wants to bring an already existing, stand-alone product into its drug development program to package or dispose of its product.

MR. WEBB: I'm sorry. Can you clarify the question, though? I'm trying to get my mind around it. Are you asking what would we need to do as an industry to bring something that already exists; or to invest and have more of an innovative blister pack, what do we need to consider?

MR. RAULERSON: The first.

MR. WEBB: What type of unit of use --

MR. RAULERSON: The first, that is there's already a stand-alone product that may or may not be regulated as a device. Let's assume for these purposes it's not. It hasn't sought approval. It hasn't sought clearance as a device.

For example, there are locking pill bottles available right now for sale. So the drug sponsor wants to bring a technology like that into its drug development program. Does it matter that the product already exists on the market in another form as a stand-alone entity? It may not. Our regulatory approach, we may be agnostic as to that. But I'm just wondering if that cues any thoughts from the panelists.

MS. WHALLEY BUONO: Liz Whalley Buono. I would say that the more you know about the packaging innovation, the better, because you know more about it, it's been used, and it's been hopefully evaluated. So you're just starting from a higher benchmark, if you will, of confidence that the innovation is at least safe.

I think what you'd need to do at that point

is identify the challenges that are specific to that product type, the opioid product type, and then look at what sort of evaluations can be done to give you a sense of confidence that they'll have an impact on the opioid-specific issues as well.

DR. BERTRAM: Dr. Mendelson?

DR. MENDELSON: How do you guys regulate enteric-coated products, long-acting products? Those are versions of packaging. They're somewhat the same questions, aren't they? No? Enteric-coated? An enteric-coated aspirin is sold as something different.

DR. HERTZ: They're not analogous. They're formulations, not packaging, so it doesn't work that way.

DR. MENDELSON: Okay. You can't learn anything from that pathway? You can't learn anything from how you thought about that pathway?

DR. HERTZ: We can. What do you think is relevant there?

(Laughter.)

DR. MENDELSON: I think you did clinical

trials for those. Did you do clinical trials or not? That would be the first question.

DR. HERTZ: So I'm going to turn this back to you. It sounds to me like you're suggesting that clinical trials may be the approach to take with these. Is that what you're suggesting?

DR. MENDELSON: Well, I'm wondering. I actually don't know the answer. The thing that would be the most convincing, yet the most burdensome and expensive, would be a clinical trial, an RCT of some kind, and I'm not sure how you'd actually measure some of your endpoints like diversion. And you still might not learn anything important. That's why I'm asking what you've learned from other pathways that I don't have much interaction with.

DR. HERTZ: Well, you've sat in on some of the advisory committees. You know the program for abuse-deterrent opioids, but that is -- I'm not sure -- do you see how that methodology could be applied here? So just for the general audience, there's a number of in vitro studies that are done,

and then there are actual clinical studies that evaluate behavior, but none of those outcomes I think are really -- I don't know how.

Like for instance, drug liking, willingness to take drug again, how high the drug makes you, those are the negative effects -- I mean, those are the kind of outcomes we measure in those studies. We've learned a lot from our experience with ADFs. And I guess if you wanted us to apply a clinical trial design, it goes right back to you, how do you foresee that?

DR. MENDELSON: I'm not sure I do want us to apply -- I'm sure Sharon could figure it out. I have no doubt that Sharon -- the explosives would be particularly good at your lab. There are a couple of post docs you could assign to that project tomorrow. I'm pretty sure you know them. Maybe me if I were working in your lab.

This question of how you're going to test these in an abusing population is going to be very complicated because your endpoint is, again, this non-user diverter type population.

MR. RAULERSON: Actually, tomorrow we're going to get --

DR. MENDELSON: We'll talk some of that --

MR. RAULERSON: -- the studies, the effectiveness of these options.

DR. BATEMAN: Can I just make one comment in response? There are probably some things you can measure in a trial context: number of leftover pills --

DR. MENDELSON: Exactly.

DR. BATEMAN: -- or did the patients dispose of the leftover medication. That might be quite relevant.

DR. MENDELSON: Yes.

DR. THROCKMORTON: I think, Patrick, for this afternoon, the reason why the RCTs are worthwhile is the reason people do those studies is because they get claims. They don't do them because we told them to do them; they did them because they saw specific language in their label that allowed them to differentiate their product from the ocean of other opioids out there. And

that was why we were talking about that paradigm here; is that valuable to encourage innovation and creativity, and doing the studies that I'm hearing people feel we're going to need to have?

FDA is not going to do them. We can require across-the-board changes in labeling and packaging, and things under certain circumstances, but we will not innovate in the way that we're talking about. The innovation through trialing was done for a labeling change with an indication, a claim if you will.

DR. MENDELSON: And the labeling change will have to be strong enough to displace competitors.

DR. GREEN: Or the other reason they're done is because there's a requirement for an F1 packaging with a certain class of drug or group of drugs. It can also be further discussed as alternative to capitalizing and not throwing the baby out with the bathwater in terms of the Poison Prevention Act of 1970 and the established criteria for the different levels of the -- the application of the Act and the grading of the different

interventions or mediums put into place.

Another technology that we've been evaluating with over-the-counter products -- and I know that there's not many liquid products within the opioid space, but the flow restrictors that have been put on the over-the-counter single ingredient in acetaminophen products and doing a lot of work in that evaluation, there might be some lessons learned there that we could apply then to the solids in terms of even like a flow-restrictor type as dispenser. The CDC PROTECT initiatives has done a lot of work on that that could share that knowledge, that might be applicable here as well.

DR. BERTRAM: Thank you. We're going to go on to question 5. As we know, depending on the technology and intended use, et cetera, these technologies may be either -- how they're distributed. It could be a stand-alone device or a stand-alone entity, combination products or a drug device, or simply just container closure.

Looking to incentivize as well as promote consistency, what does the panel think regarding

some of the benefits or the challenges of treating these products? Different? Consistent? Choose one that you think is best, and what can the agency do to ensure the consistency as well? Liz?

MS. WHALLEY BUONO: So my mind goes, obviously, to electronic monitoring. And the experience that we've had is that manufacturers are reluctant to do things like a Good Start program, if you will, which was one of the concepts that has been bandied about for a couple of years, where particularly expensive drugs are launched in an RFID fitted blister package such that the first couple months of therapy, patients can be monitored. Doctors or pharmacists can have a conversation with the patients about their adherence, their lack of adherence, side effects, things like that. The concept is that you get them off to a good start taking their medication correctly.

The resistance to uptake has been a lack of clarity as to whether these concepts would be devices or container closures. And without clear

understanding of that, manufacturers are reluctant to invest and put the product in market for risk of enforcement activity or that sort of thing.

The flip side is for them to be devices. And obviously there's a greater cost to bringing them to market, so it's a Catch-22. If it were up to me, it would be a risk calculation. So when you're talking about functional packaging like electronic monitoring, you're then talking about analyzing the data, providing adherence patterns, and encouraging a counseling moment. I'm not sure that rises to the level of diagnostic imaging. I think it's a risk calculation, and it's really the agency's to make in my mind.

DR. BERTRAM: Just to push you a little further regarding the cost, is it just the classification as a device that incur a cost, like the part 4 obligations with manufacturing?

MS. WHALLEY BUONO: It's kind of all of it. It's making sure you have sufficient data. It's the submission process. It's waiting for the approval. It's the manufacturing conditions under

which the devices have to be manufactured versus the container closures. So it sort of incrementally adds up to a completely different project, and within the pharmaceutical manufacturers, that's a big deal as to whether you're simply changing packaging or you're making a combination product.

DR. BERTRAM: Ms. Dorgan?

MS. DORGAN: Hi. Carolyn Dorgan, FDA. One point of clarification for that, I think you're assessing the cost associated with being either a device or a combination product versus container closure, not necessarily going under the NDA. I think some of the requirements you would need for a device or combination product would be quite similar as far as cost and type of data required.

Am I correct in saying that?

MS. WHALLEY BUONO: I think that's right, and I think some of this also is just a fear factor associated with do we really want to add a device our drug when we're really just looking at trying to change the packaging. So it's kind of a little

of all of that.

MS. DORGAN: And I guess I'll follow up on that and say, are there things the agency can do to reduce that fear factor?

MS. WHALLEY BUONO: Well, I think engaging with the FDA early and often is a good idea, but that's not always appealing. Things that we know that we're familiar with, like RFID-fitted blisters and MEMSCaps, I think probably there's a comfort level with the years of experience with these things, that perhaps there's an opportunity to set some ranges and issue some guidance and decrease barriers to entry.

But I can't speak on the part of the manufacturers. I can just tell you what we've heard in engaging with customers who invest an awful lot of resource into trying to develop these projects, and then dump them because they're concerned and they can't get it through their regulatory group.

DR. BERTRAM: Thank you.

DR. CHAN: Can I ask a clarifying or a

follow-up to that? If I'm hearing you correctly, you're saying there's this concern, maybe a lack of clarity around when do I get kicked into the device realm. Right? At what point do I cross that line? So I'm hesitant to go there. And perhaps this is why you expressed -earlier the position you did with regards to labeling claims because if I now want to say in my label that this packaging does something, then what I'm saying it achieves may be what kicks me into the device realm.

Is that what I'm hearing? Is that this double-edge sword here?

MS. WHALLEY BUONO: I don't want to speak for the manufacturers, but I've never heard a manufacturer tell me that they want to communicate a claim around the impact of the packaging. They just want the impact of the packaging.

DR. CHAN: So then if no information goes in the labeling in that example that speaks to that particular technology or whatever it is, then how -- I guess I'm wondering how you envision manufacturers then being able to go and let's say

promote on something like that?

DR. HERTZ: But I do just want to say that from our experience at the division level, we have had folks come in wanting a claim and wanting to be able to promote on it for a variety of ways or considerations that are relevant here.

MS. WHALLEY BUONO: That's why I said I really don't want to speak for the whole industry. Just the experience that I've had is that I haven't heard the manufacturers feel that there is enough of a competitive advantage that will increase their market share, if their product is in this package, to sort of justify seeking a claim. They just want the patients to take the medication as intended so it works better.

DR. BERTRAM: Mr. Webb?

MR. WEBB: Kevin Webb, Mallinckrodt Pharmaceuticals. If that's the question that we're trying to solve, I think we need a different workshop for that because you obviously have branded pharmaceutical manufacturers and generics. You have long-acting. You have immediate release.

Those packaging and those claims, there are some -- to your point, Sharon -- that do want to make claims regarding the fact that this packaging does something; the generic manufacturers don't. So really it depends on where it is that we want to insert ourselves into the dialogue.

To that point, where do we want to insert ourselves? The other question we need to ask ourselves is if we're going down the path that we're going to have some 7-day unit of use package, as a manufacturer, that's a little bit more complex than to say that we're going to continue to move a 100-count or 500-count bottle down the line, and then the pharmacist puts it into some type of a 7-day packaging. There are a lot of good devices out there.

So the question is going to need to be for the manufacturer, are you looking to the manufacturer to come up with a 7-day unit of use bottle with a lock of whatever it may be, or is the lock going to be attached at the retail pharmacy, and it's going to be put in some kind of bottle?

Those questions haven't been asked, so I think we still obviously need to think through the supply chain. But if they're looking to the manufacturer to do it -- and I think this goes to your earlier question -- are we comfortable with the devices that are already on the market?

It depends. It depends on the details and what's being asked, or do we just need to scrap everything and go back and say we need a bottle that holds no more than 7 tablets that's going to have to have certain type of locking capabilities on it? I don't know if that technology exists or not. So we would really have to do a lot more homework on it, but the devil's going to be in the details on that.

MR. RAULERSON: Thanks. And keying on that, since we only have a couple of minutes, I want to skip question 6 and go to question 7, which is, do the panelists think that FDA's existing authorities are appropriate to achieve the goals we are trying to achieve here, to incentivize and properly regulate these products, and if necessary, to

mandate them, including throughout the supply chain?

As sort of a brain teaser here, one option would be to seek additional authorities from Congress if we thought they were necessary. So all of the things being equal, we have container-closure rules, we have NDA rules, benefits have to outweigh risks, we have REMS, we have device regulation, are those existing authorities adequate or do you have thoughts on that topic?

MR. WEBB: Kevin Webb, Mallinckrodt. I think the ability to influence this through REMS obviously you have, but I think it's only going to get us halfway towards the solution. If we're looking at having an industry or an entire stakeholder engaged solution on this, I think it would require Congress to authorize you to do the things that you want to do. But I think in the environment that we're in, you would find probably an audience willing to have that dialogue or having that discussion.

MR. RAULERSON: Dr. Berghahn?

MR. BERGHAHN: Walt Berghahn, HCPC. It would seem that if you're talking about solutions that are created in the industry by manufacturers and by contract packages that are FDA regulated, then the answer is yes. But if you're looking at solutions that are going to be implemented in pharmacy, then obviously no.

MS. WHALLEY BUONO: I'll just add when you're looking at retail versus manufacturer -- because we've worked in both spaces -- the problem obviously with retail is it's not ubiquitous, and it's a highly competitive market. And pharmacy is governed by state-by-state regulations.

So I can't envision how you could have a mandate that crosses across all states and requires these hyper-competitive retail environments to do the same thing because they hate doing the same thing. They want to do everything different. So that just seems like that's so far out there, it's something that we probably couldn't achieve.

DR. BERTRAM: Thank you. I think with that, we can turn it to -- you made it in time, so turn it to our public comment period.

Audience Participation

MR. RAULERSON: Right. So with that said, any audience members that wish to speak should go ahead and line up behind the microphone. There's staff, and we're available to help you. We ask that you focus your comments on the session's topic. And I'm going to review the procedure, which we previously announced for audience participation.

You'll get 3 minutes to provide comments. The light system will keep time and notify you when your time's complete. And the light system works just like a traffic signal. Green means go, continue speaking; yellow, you have one minute left; and red blinking light means to go ahead and wind up. And just as a reminder, any additional comments and information may be submitted up until February 12, 2018 to the docket established for this workshop.

With that, can the first speaker please go ahead and come up? Thanks.

MR. GOODLOE: Hello. Peter Goodloe again. I'm an attorney with Brownstein Hyatt. I'm most interested in question 7, certainly the legal matter. There's a need to -- and again, I'm talking about lockable prescription vials. And I'm not talking after market; I'm talking about at the pharmacy. So it was already said that that can't be regulated. We're collecting data. Somewhere down the road we may have enough where FDA maybe wants to act, and then we reached at question 7, can act.

There are pilot programs going on around the country. Pharmacists voluntarily participate. They're educated about it. Patients are willing to take the lockable prescription vials. They receive some educational information, and then later on they're surveyed and teens in the homes are surveyed.

Let's say we get to a point where FDA thinks, well maybe it would be a good idea, at

least in some situations, if pharmacists offer a lockable prescription vial, not mandated but just offer it. So where are we? We've talked about REMS. My impression is that FDA is directly regulating the manufacturer and that the manufacturer turns around and enters into contractual relationships with pharmacies, a restricted distribution program for example.

So if the pharmacist violates it, has the pharmacist merely violated a contract with the manufacturer or has it violated the Federal, Food, Drug and Cosmetic Act?

Now, if you use your container-closure authorities, then you're talking about an FDCA violation. And bear in mind that the Act does regulate the pharmacies; 503B deals with prescription drugs. And it says you can't dispense a prescription drug without a prescription or it's an FDCA prohibited act. That's on the pharmacists. The Act goes on to require certain packaging requirements, so the Act's packaging requirements do apply at the pharmacy level.

As you know, in 1982, FDA implemented OTC requirements. That's on the manufacturer, but that was done under current good manufacturing practice authorities. And I don't see anything in 503B indicating that the CGMP requirements do not apply at the pharmacy level. So could you do at the pharmacy level here what you did for OTC back in 1982? And again, we want to be careful with any kind of mandates, but Dr. Gottlieb did say it may be time to get aggressive, even intrusive. Thank you.

MR. SULLIVAN: Hi. My name is John Sullivan. I'm the CEO of a company called Marjo, and we're actually developing an electronic blister pack monitor with artificial intelligence. The blister pack industry, especially electronics, have been around. The patents go back as early as the 1970s.

The difference with technology today is that we can actually put a liquid crystal display on the monitor with a countdown time or that tells you when you can have your next pill. And if you take

that pill 2 hours early, we add 2 hours to the next pill. But more importantly, we are able to record the consumption data, and that's the most important part because the first slide of the day was 21 to 29 percent of patients are using their bulk prescriptions. So out of 214 million prescriptions, that's 44 to 66 million Americans abusing opiates. So if we add that to the stockpile that people are using, which is 11.5 million, that's between 55 and 75 million Americans abusing these drugs.

So this epidemic is not going to go away if we don't know the consumption. And this is a very important discussion because if you don't know the consumption, you don't know what's going on.

So with a hundred percent take-back program, that monitor has to come back. Now, that's a reusable monitor. They reuse it over and over and over again, so it produces a cost of the overall program. But what I need from the FDA is that whatever the pill touches requires a child-resistant lock. And it's very difficult to

put a child-resistant lock on a blister pack.

Now, we can put that in a box, but I'm not comfortable with the box because a kid can still tear a box up. We're working on a child-resistant bag that this goes into. So the labeling part, the label that would typically go on the bottle will go on this blister pack. That gets thrown away at the end of the 30 days, and the monitor's taken off and reused.

So we need to have some sort of fast track on placing this blister pack in a child-resistant bag. All the instructions that you typically are printing out now, they get stapled to a white paper bag that they throw away immediately when they get home will now go inside of this bag, and the monitor's in the bag. The bag's got a child-resistant lock. The kid can't get in the bag.

So the important part of the overall program is that if you know consumption, you know addiction because you can look at somebody's behavior patterns and see that they're taking more and more

and more. And the other part of this scoring program is that at the end of the prescription you get scored a pass and fail. Fail is that you didn't return the monitor or you didn't take the opioids when you were prescribed, you took too many.

If you got a pass, no conversation. If you got a fail, a therapist is called to have a conversation, because a lot of these doctors have never been trained to look at addiction or know addiction. So the therapist interacts with the doctor and the patient when they fail their score. And that's very important because the early-stage treatment is key. Once it's a late-term addiction, it's too late.

So thank you, and I appreciate this opportunity.

MR. LANGLEY: Nathan Langley with Safer Lock again. I heard some comments about if we find some sort of better packaging that we might want to get rid of everything or the current packaging that's been used. I think current packaging might be

sufficient for certain populations, so we might not need to exchange all opioid packaging, and it might make sense to identify what population that we need to change the packaging for.

So we might not be looking to exchange all opioid packaging if we -- not we. You guys determine if this is a sufficient solution. For example, maybe 30-day prescriptions have a higher rate of diversion, so maybe that has a higher level form of packaging versus maybe a 3-day to a 7-day prescription that maybe somebody there doesn't have much diversion with that. Because there's a lower amount of pills, somebody might not want to go take them because they will notice.

This is all speculative, but just something to consider. Maybe we might not looking for a solution for all opioid packaging but specific populations.

MS. HOBOY: Hi. Thanks again for the opportunity. It's Selin Hoboy with Stericycle. I just wanted to mention -- and having been -- and all of you guys are in highly regulated fields as

well. On the waste side, we're regulated by a very weird myriad of different regulations. And one of the things that I heard from I think both sides of the table here is that you have to have some room for innovation, but we also need some guidance around it because I think when you don't have guidance or some type of mandate, then you are worried about where that innovation can lead you.

That's actually happening on the DEA side of things on the disposal side of things for us as an industry right now -- and the gentleman spoke earlier -- and that indecisiveness that's in the regulation on the DEA side has kind of stifled innovation a little bit because people are worried about, well, what if that product doesn't create what the DEA intended to when they wrote their regulation and put in a specific definition.

So I would just caution that maybe instead of saying there's no mandate or there is a mandate, talk about what it is that you would need to have in a mandate or a guidance that would get enough comfort level for that innovation to be able

to get out of the gate, because we're seeing that on the other side right now, on the disposal side. So that would be my recommendation as part of this, too. Thank you.

MR. RAULERSON: Thank you. I think that concludes Session 3. Thanks.

DR. CHAN: We're just a few minutes ahead of time, but we're going to go ahead and take a 15-minute break. We will resume -- we actually just say we'll go ahead and resume at 3:00, promptly though. So if you could please make sure you're back in the room at 3:00. Thank you.

(Whereupon, at 2:40 p.m. a recess was taken.)

Session 4 Presentation - Kayla Cierniak

DR. CIERNIAK: All right. Hi, everyone. My name is Kayla Cierniak, and I'm an ORISE Fellow here to introduce Session 4. My objectives are to walk through an ideal model of the medication use system that applies to healthcare settings in the United States, including key stakeholders and technologies. Although there are many variations

in the real world, I will be focusing on outpatient and inpatient settings.

As such, my discussion does not entail a comprehensive evaluation of all healthcare settings possible, including long-term care and hospice. I will identify how packaging, storage, and disposal options may integrate into existing systems through the use of examples.

The first example is a theoretical outpatient product, oxycodone tablets in a calendar blister pack for enhanced opioid safety. The second example will apply to inpatient scenarios. This is a "tamper-resistant" or "tamper-evident" hydromorphone syringe for prevention of diversion by healthcare providers in the inpatient setting.

Here is the basic framework of the medication use system which comes from the Institute of Medicine, the Joint Commission, and the California Health Foundation. This system is based upon the continuum of four steps: number 1, a prescription is written by a healthcare provider followed by order transcribing; number 2, the

prescription is prepared and dispensed through a pharmacy; number 3, the drug is administered to the patient; and number 4, there is monitoring for therapeutic and adverse effects.

There are two precursor steps shown in the upper left-hand portion of the slide, selection and procuring and storage. These steps set the stage for the process by establishing formularies and distribution chains.

We all know that processes within this use system are exceedingly complex requiring numerous handoffs and facing regulations in the full spectrum of healthcare settings. Some of the example stakeholders that are involved, which I may also refer to as users, include patients, providers, pharmacists, payers, regulators, manufacturers, distributors, policymakers, and other organizations.

So how might stakeholders who are healthcare providers learn about these new options? Here I list some examples of existing systems or platforms that might be evaluated for delivering this

educational content.

For example, continuing education is required of practitioners to maintain their license. Learning management systems are employed by larger organizations such as hospitals in order to deliver timely educational updates to their employees. Clinical decision support systems assist clinicians with decision-making tasks, and as we have mentioned earlier today, REMS portals may also be a vehicle.

Moving into our walk through the medication use system, I will begin with a discussion of our two precursor steps. Selection and procuring involves the formulary, which is a list of preferred drugs that a certain payer will cover. Formularies are designed to restrict the listing of drugs for cost-savings purposes.

On the smaller scale, local P&T committees, or pharmacy and therapeutics committees, make these decisions at the level of individual healthcare organizations. These are interdisciplinary teams of clinicians, including administrators and

pharmacists. On a larger scale, there are pharmacy benefits managers and third-party payers.

Note that some payers have more restrictive or closed formularies as is the case with the Veterans Health Administration. Of note, there may be a difference in the cost of implementation between closed systems and more open formularies such as the Centers for Medicare and Medicaid.

Once a formulary has been established, pharmacists and clinics must operationalize new purchasing, receiving, and storage workflows. Accrediting bodies and institutional policies might require strict specifications for, number 1, security of the medication; number 2, protecting handlers against accidental exposure; and 3, maintaining the integrity of the product, which includes accurate expiration dating and temperature control.

While we're on this topic of storage, and as we have mentioned earlier today in our discussions, storage is going to be a unique challenge between all the steps in the medication use process as we

integrate these new options, including adjustments in pharmacy shelf space, transport, and even considering storage at the patient's home, depending on how large or bulky the option might be.

We will now move into the first step of the medication use system, prescribing and transcribing. There is first clinical decision-making here by the provider to initiate drug therapy. This occurs with evaluation of the patient, drug choice and regimen determination, documentation in the medical record, and the result may be a verbal, written, or electronic prescription.

For successful uptake of new options for enhanced opioid safety, it is very important they be supported by the electronic medical record, or EMR, and computerized physician order entry, or CPOE, which are applications that allow physicians to send electronic prescriptions. These may be sent to outpatient pharmacies, inpatient pharmacies, and across the spectrum of health care.

Challenges in the system at this point might include a lack of provider education regarding new products, and in this example I describe an outpatient physician who is attempting to order oxycodone. They may type "oxycodone" into the EMR and be provided with a list of options to choose from in a drop-down menu.

If the provider is unaware that oxycodone now comes in a blister pack for enhanced opioid safety, potentially associated with a new proprietary name they have not heard before, the provider might just glance past the option in the drop-down list and select what he or she is already familiar with.

Transcribing also occurs during this first step and is a process where a healthcare provider or staff member receives a prescription and must check if it's correct. The user who is transcribing here may be a number of different example users: pharmacists, nurses, or even unit clerks.

The prescription may then be entered into a

completely independent order management system and linked with a pharmacy information system. These provide a wide range of pharmacy-specific functions, including order entry, inventory, purchasing, reporting, clinical monitoring, and billing functions.

A potential vulnerability at this stage might be the receipt of an oral prescription by a user who is unfamiliar with the novel product and who must manually enter this order into the independent pharmacy system.

For example, a prescription is called into a pharmacy for oxycodone to be dispensed in this new calendar blister pack. If the user who takes that prescription is unaware that the option exists, they may simply write down "oxycodone tablets," enter this into the pharmacy information system, and the pharmacist might end up dispensing the tablets versus the blister pack.

Although this is a similar challenge as that which I discussed with the prescriber, it presents the unique challenge of ensuring that not only

prescribers are aware of these new options, but a whole host of other potential users, including nurses, unit clerks, and others.

We will now move on to step 2. This is the preparing and dispensing. This step involves data entry and screening, preparation, double-check, and of course dispensing. The primary users here will be pharmacy personnel.

Regarding technologies, drug purchasing and supply-chain management systems allow pharmacy buyers to track inventory and to purchase accordingly. I also want to mention automated dispensing cabinets, which are shown in the photo below. These are drug storage cabinets that electronically dispense medication in a controlled fashion and are found in the inpatient setting. There is limited space in these cabinets, and drug storage compartments must be carefully designed.

One challenge in the integration of the example of the tamper-resistant hydromorphone syringe might be ensuring this product is not in the cabinet and becomes confused with another

hydromorphone syringe that is already on the market.

Shifting to our outpatient example, retail pharmacies must adjudicate insurance claims, which harness the technologies of payer prior authorization, payer medication therapy management, and prescription drug monitoring programs. At this step, certainly payer coverage might be a barrier. If a payer requires a prior authorization, for example, we must consider that prior authorization may require a day or two to process, which may result in an undesirable therapy delay for a patient who's prescribed a short-term course of opioids due to an acute injury and needs that prescription soon.

We will now move to step 3, administering. This occurs with the user checking the instructions, preparing the dose, and administering to the patient followed by documentation if in a healthcare setting. On the inpatient side, medications are recorded in the medication administration record, or MAR, which is ideally

integrated into the EMR.

There are also smart-pump infusion devices that have guard rails to help caregivers give IV medication at the appropriate rates. Bar-coded medication administration, as shown in the photo below, involves the scanning of the patient's identifier wristband and the unit-dose bar code into the MAR. Any new product that is purchased by an inpatient pharmacy will receive its own unique bar code or else an error will be generated at this step in the administration process.

If the nurse is unfamiliar with the new hydromorphone syringe, she may override this bar-code scanning step, or he, which is a workaround that may lead to medication errors. But considering that many of these potential options might be used in the outpatient setting, patients who are self-treating for chronic pain at home will not have this BCMA double-check. An available technology for these patients might include mobile medical applications or desktop software with reminders or information for the patient.

The fourth and final step is the follow-up and monitoring portion of the system. The patient will be assessed for therapeutic and adverse effects, providers will review lab results if necessary, and adjust therapy and document the encounter. Example of users include the providers and the patient.

The MAR will allow for monitoring inpatient, but for outpatient use, education and follow-up might be possible through patient portals and through REMS portals. In addition, many larger health systems offer a patient portal where patients can go online and view their electronic record anywhere they have internet access. Telemedicine also falls in this category, and this can be especially important when considering patients who live in the more remote areas with limited access to care.

A challenge that may be faced in the monitoring phase may be an example of a patient who is supposed to bring back their calendar blister pack to an office visit but forgets to bring it

back for the provider to check and see how many times they've needed to pop the blisters, to evaluate their pain control and make therapeutic adjustments accordingly.

Now that we have made our way completely through the medication use system, I would like to briefly step out and discuss self-care or over-the-counter care, which might not involve healthcare providers directly. It may be forseeable that, unlike the two fictional example products I have used in this presentation, some of these options might be stand-alone products for over-the-counter purchase, examples ranging from the drug disposal pouches or locking cabinets for the safe storage of medication. Potential technologies that could help the user here may be the mobile medical applications as I mentioned earlier or patients might be referred to these products by a healthcare provider outside.

In summary, the medication use system is a very complex process involving many stakeholders and technology. Although this system encompasses

the full spectrum of health care, the focus of this brief presentation has been on outpatient and inpatient pharmacies, which can feature different processes and technologies. As such, unique challenges and uptake of these new options may be based at various points in the medication use system, depending on the setting.

I would like to thank you for your attention for Session 4, our last session of the day, and for the opportunity to speak. I will now turn back to Dr. Chan to begin the panel discussion.

(Applause.)

Panel Discussion

DR. CHAN: Thank you very much. So we have developed questions to guide the panel discussion for this session on the integration of options into the medication use system. We have eight primary questions that we would like to discuss over the next 60 minutes. As mentioned previously, again, Paul is going to be sitting next to me and assisting to ensure we get everyone's name in order.

Let's begin with the first question. In this session, we walked through how these options might be integrated into an existing healthcare system using the medication use system as a model for illustrating this. One of the challenges that was raised in the presentation was the concept that providers will need to be informed that these options actually exist and that it may not always be clear what intended problem, or problems, is the target for any given packaging, storage, or disposal option.

What we'd like to better understand is how the labeling could be written effectively to distinguish the problems that are targeted by different packaging, storage, and disposal options. Who would like to start? Dr. Budnitz?

DR. BUDNITZ: Dan Budnitz from CDC. I'm thinking back on something that we did when we were working on preventing unsupervised ingestions in kids, and we had new packaging technology flow restrictors that we wanted to describe. One of the things that we came up with in the end, after using

a bunch of different terminologies, is worked with USP to have some standardize terms to describe. We ended up with some built like a flow restrictor and restrictive delivery systems.

So I think one thing that could be applied is for writing effective labeling, coming up with a rubric of standardized terms for what you are wanting to refer to, then both the prescribers and also payers, or whoever else might be using this, would have these key words, and everyone would be on the same page so to speak when they're done.

DR. CHAN: Ms. Cowan?

MS. COWAN: Penney Cowan, American Chronic Pain Association. Again, I'm going to go back to the ability for people to understand what's written in the label, that it needs to be written in a language -- a level that folks can easily read. But I also think on some of these things, it would be really helpful to have graphics to go along with it.

Pictures tell a thousand words. So while they may not understand certain terms, they can

understand pictures. And I understand it will be hard to get the right graphic, but we've done a lot of graphical pools. And if you work, you can get them. But I think language that's understandable, I would say at a fifth grade level, and then having a graphic or picture to help people understand what they're really using.

DR. HERTZ: I would just follow that up. We have a pretty good idea that the actual package insert doesn't get a lot of attention, and that's unfortunate since it's one of our primary modes of communication.

What I'd also like to know is not just how could labeling be written effectively, but how do we get that to the attention of pharmacists, prescriber, patient? Do you have any thoughts or tactics to try and improve that delivery?

DR. CHAN: Ms. Whalley Buono?

MS. WHALLEY BUONO: Liz Whalley Buono. The work that we've done in pharmacy, what we have seen is most of the major retail pharmacies actually print out new patient information, sometimes

branded.

DR. HERTZ: But clearly that's not often the material that we've written and tested.

MS. WHALLEY BUONO: Right. But then what we've seen is actually they've started to cease doing that and printed off of one of the databases online. The only reason I raise that is that I think there's an opportunity to be looking at the information that's available online, which right or wrong or indifferent, it's increasingly being used as the main source of retail data pharmacy patient information.

DR. HERTZ: Where does the data in that database come from, and how do we merge that with specifically trying to improve awareness here?

MS. WHALLEY BUONO: My understanding, although I'd need to dig a little deeper on it, is that those are somewhat privately maintained databases that licenses are --

DR. HERTZ: Wouldn't that just add another source of variability? What we're trying to do is figure how to consistently deliver messaging.

MS. WHALLEY BUONO: It's an opportunity perhaps to -- I think we have to work with what's going on. So if that's indeed what's going on, maybe there's an opportunity to work with those entities to standardize that and increase use of iconography.

DR. HERTZ: There's already standard language. It's called Medication Guide for Opioids, so there's no need for any kind of database, right?

MS. WHALLEY BUONO: I'm not advocating for it. I'm just telling you what we've seen in retail.

DR. HERTZ: I just would like to know how to do that, if that's going to be --

DR. CHAN: Dr. Walsh I think had a thought around this.

DR. WALSH: I'm just wondering whether or not there's been any discussion around smart technologies because we're using smartphones for all kinds of reminders in regular life, and people spend a tremendous amount of time on their phones,

but I'm not aware that there -- and in health as well. But I'm not aware that there's been any discussion around that for instruction sets, say, around specific packaging.

I know that not everybody has one, and I know there's is a couple of different platforms but I would guess that you could probably meet almost the majority of patients through that technology through apps.

DR. CHAN: Before I take the next comment, just so you are aware, Dr. Slatko spoke to the recent approval of a technology where in fact instructions are available electronically and accessed through, for example, the patient's smartphone. So I think that's kind of the direction you're going there in terms of access.

DR. WALSH: Yes. I must have missed that, and I apologize. Is it a passive? I mean, is it something that the patient has to do to get it, or is it something where they're poking you?

DR. HERTZ: Right now, it does require some cooperation from the patient. They have to wear

a --

DR. WALSH: You want to poke them.

DR. HERTZ: -- sensor patch.

DR. CHAN: I think Ms. Cowan had another comment to follow-up.

MS. COWAN: Well, we heard earlier that dispensing an opioid, instead of saying do you want a consult with the pharmacist to make it mandatory, and that would be where that conversation could go, where they pull out the medication guide and actually talk to them. If it were more appealing to look at color, a graphic, it wouldn't be as threatening to them, and they may actually catch on. And people would actually be more willing to look at something like that.

But to make the consultations mandatory instead of, no, I don't want to do it -- I mean, I don't want to talk to them either because there are other people around. But I think it would be really important for looking -- it's about saving lives here, and I think that is worth it.

DR. CHAN: Dr. Bosworth?

DR. BOSWORTH: Just building upon that, those of you who have children or even thinking about yourself, how do you learn? We all have different modes of learning, so whether it's reading or with oral, I just think that if you really want to move the dial with regards to education, I gather that you have your pamphlets, but that's just not really practical if you really want to.

There are a lot of companies out there producing things. Whether it's worth looking at it, that's up to you all. But I think that if you really want to address this issue regarding education and conveying that information, I would recommend looking out.

The other issue, too, is reinforcement, too. Just because you have one contact with a pharmacist doesn't mean that that's adequate, and oftentimes, most patients have questions further down the road. If they're at home, what are they going to do? Are they supposed to have that pamphlet? They're going to pull it out. That's going to answer the

question.

So just really thinking about the journey, that's what we talk about, the patient's journey, and thinking about alternative ways of communicating that and allowing them access could have a huge opportunity. So I get the legal aspects of it, but just thinking a little bit beyond what's available at the moment would help.

DR. CHAN: Thank you. Yes?

MS. WHALLEY BUONO: Liz Whalley Buono. You asked how do we get providers to recognize that there are these packaging variants out there, and how do we educate them. We have customers who have products out in adherence packaging with complicated dosing regimen or titrated dosing regimen and things like that. And we've worked with them to create educational campaigns for their sales reps.

So as part of the discussions the sales reps have with the physicians, they call the packaging type to the physician's attention and sort of help train the physician and the nurses on how to train

the patients on how to use the packaging. It's not magic. It's calling attention to the purpose of the package, and the blister layout, and that sort of thing.

One of the routes we might want to be considering is as the manufacturers are having conversations with their customers, the physicians, the packaging variant could be part of that.

DR. CHAN: Thank you. Dr. Bix?

DR. BIX: This is Laura Bix from Michigan State University. We've done several eye tracking studies with a variety of different products, and for a long time, it perplexed me immensely that the vast majority of consumers wouldn't turn to the drug facts label when they were making decisions. Then one day I was watching my 18-year-old take some aspirin, and it occurred to me he doesn't need to look at the drugs facts label. He has no allergies. He takes nothing. He has no conditions. He knows what he needs.

So enumerating the number of people that look at that information wasn't enough. And it

occurred to me that it's contextually dependent and patient dependent on what information is relevant, and that maybe we're in an era where we're looking at customized medicine. We're looking at it on the drug side of things; we're looking at it on the device side of things. Maybe it's time for customized packaging and labeling as well. And the use of artificial intelligence I think offers the opportunity to push the relevant information given the context and given the patient.

Now maybe at the consumer level we're not ready for it, but it seems to me that in the institutional markets and in the pharmacy there might be an opportunity to do that, where the extraneous information can fall away, and the important information rises to the top, depending on the patient and the context of use.

DR. CHAN: Yes, Dr. Cox?

DR. COX: I think I'll just follow up on that. That's a great idea. It reminds me of something we've done with the anticipatory guidance sheets in our pediatric practice. These were the

multiple sheets that we used to hand families about their 6-month old. Your baby's learning to crawl, or your baby will learn to babble. Here's your poison control information. Here's your information on [inaudible - coughing]. It got to be this whole thing.

We discovered if we presented them a menu of these are the things we could tell you about, which ones are relevant for you today, which ones would you like to defer you've seen, then we didn't have all these multicolored sheets scattered around our waiting room and throughout the hospital.

So I think this idea of contextualizing, both with the information we already have as a delivery system, but also allowing them to pick and choose; oh, we see you have children. You might be interested in this. There are ways to tier the information there.

DR. CHAN: I have a follow-up question to that because today we've been talking about the use of packaging to convey critical messaging, being able to use that extra space potentially, depending

on how the package is designed. So I guess when you ask a patient what is it that you need, it sort of goes back to the I don't know what I don't know sort of question. So we're talking about -- there have been earlier conversations about patients who may not perceive themselves to be part of the solution to the problem, and so on and so forth.

Okay, great. This is already generating some interest.

DR. BIX: I guess my response to that would be you're right, that they don't know, and they'll tell you a lot of different things than they actually do. So I would make it dependent on the EHR as opposed to the patient to drive it. So the artificial intelligence needs to be driven I think by the conditions, maybe by the patient history, by certain facts in their record, not what they think they need.

MS. MORGAN: And I'll just follow up and say I agree completely, but I think if they don't understand why it's relevant for them, they're not going to look at it, and they're going to stop

reading. So it's a mix of those two strategies.

DR. CHAN: Yes, Mr. Webb?

MR. WEBB: Kevin Webb, Mallinckrodt. I think it goes to the heart of the question of what exactly is it we're trying to solve for. If the question on the table is how do we prevent diversion as opposed to how do we prevent accidental exposure or conversely disposal, or accidental exposure with children -- if the question is how do we prevent diversion, I would tailor the messaging to that. But if we're trying to do everything with all the messaging, trying to address all of these, we're going to accomplish none of it.

Putting back on my old sales rep's hat, going back many, many years ago, it took an average of 8 to 12 calls in a physician to change their prescribing behavior. So just because you say it once, you're going to say this for a year before they change, and that's assuming you see this physician once a month.

So we have to make sure that the message is

simple, the message is succinct, something tangible, because the question always comes back from the physician, "So what do you want me to do?" And if I can tell the physician, "Doctor, this is what I need you to do help prevent diversion; it's required that every patient who comes through, you have to talk about X," that gives you a whole lot more running room to say you need to do all these things to prevent opioid misuse.

DR. CHAN: I think we've actually answered questions 1 and 2, so maybe we'll move on to 3 here, which is we've talked about how do we inform the providers, let them know these options exist, presumably methods of education there, but how do we get healthcare providers to then adopt?

This is the tricky part, right? Earlier in Session 3, obviously if we were to move towards a model -- I'm not saying that we would, but if you were to move to a model where it's uniformly adopted, everyone's creating this, then we don't have this question on the table. But in a scenario where you have some options out there and some

without, for example, how are providers going to be encouraged to adopt these?

Who'd like to start there? Dr. Budnitz?

DR. BUDNITZ: This Dan Budnitz, CDC. Conceptually, I think it's to make it easy, to order the products [inaudible -coughing] for the packaging. I'll tell you what we tried to do in one example to prevent child overdoses, and I don't know if it's worked yet, but that is trying to encourage use of milliliter prescribing instead of teaspoons.

To make it easy, we worked with the 2015 EHR certification standards for electronic health records, which I think there's been a delay in whether they'll be implemented or not. But the concept was that you would present -- and this got approved in the standard, that all prescriptions with milliliter dosing already embedded in it. So the prescriber would have to do something different if they did not want a liquid oral medication to be dosed in milliliters. So it made it harder for them to do otherwise.

The analogy here might be if a certain packaging was preferred, to have that as the default or higher up in the presentation of the EHR or have it indicated in some other way, like highlighted or something like that, again, to make things easier rather than harder so that prescribers don't have to do anything different or extra but have to do less.

DR. CHAN: Dr. Patel?

DR. PATEL: I'm Ashesh Patel, ACP. I would follow on with that. You can have an EMR prompt. A doctor prescribes a certain version of oxycodone, but then you can have a prompt from the EMR saying there's a safer version. Do you really want the old version or do you want this new safer version? That's kind of going back to what he was saying.

Also, many doctors probably will not prescribe a prescription if it's very costly to our patients. Our patients are very cost sensitive to co-pays and deductibles. So obviously if there's a cheaper version available, when the patient goes to a pharmacy with this new safer prescription, but

then they realize it's costly, they're just going to call the doctor back and say I know there's a cheaper version. I want the cheaper version.

DR. CHAN: Dr. Emmendorfer?

DR. EMMENDORFER: On the disposal, we have real-world experience with that piece. The way that we had the take-back program take off is remove the financial barriers. So we provide those envelopes and those on-site receptacles. Obviously, the envelopes are free of charge to the veterans. So that's one way to definitely engage not only the veteran but the healthcare providers.

It's the selling point, the marketing around it. Not only are you removing it from the medicine cabinet, and the accidental overdoses, and the potential diversion, but there's an environmental impact as well because they're destroyed. And the medicines that are returned are destroyed in an environmentally friendly way.

As far as packaging and storage, maybe just to feed off a little bit of what was just said, assuming cost neutral, it's probably not that big

of a deal when you can drive it through the electronic health record. Depending on the cost benefit analysis and the available evidence showing what the packaging is saying that it will do, I think that can come into play as well.

So there will need to be -- if it's going to be 10 times the cost, there's probably going to be some sort of discussion around what's the evidence of what the packaging is actually doing that it says it's going to do.

DR. HERTZ: Before we go on, a few folks on the panel have been very quiet, but I know for a fact that some of you have strong opinions about some of the things that we as an agency do. If you're holding back because you think it's critical, unless you're only holding back because you think someone else has said it, I would just like to encourage everyone to take the opportunity to let us know what you think.

DR. CHAN: Okay.

(Laughter.)

DR. CHAN: Ms. Morgan?

MS. MORGAN: A lot of this has to do with -- there are specific questions up here, and I certainly don't want to be not having those specific questions addressed. But you have allowed a door to be open to talk about general comments on everything that is being done this afternoon. Sharon Morgan, American Nurses Association.

So does building a better mousetrap lower the amount of mice in the room? That is my first question and my first take-away as we are dealing with this whole thing. Simply because we have a better mousetrap, have we addressed the problem that the better mousetrap is intending? And I think that's two big things. You can have a better mousetrap, but does it make it more effective? Do we minimize what we intended to do?

Have we now added a burden to the consumer in building this better mousetrap, and what is the financial stake for building the better mousetrap to the consumer? And will it prevent someone getting effective management through the use of opioids with this new mousetrap? Is it financially

not feasible now?

So these are nuances that as we're continuing these conversations, I'd like to make sure that we're sensitive to. And then when we are looking at things, not just packaging but storage and disposal, the human factor, is there a cost benefit analysis that could be done if we introduced someone interacting with the ultimate consumer of that medicine, two days later, to address effectiveness of the medication: how much is left, and how is the intent for disposal; whether this is done face to face, which allows access into a home environment where other issues could be raised, or via telemedicine approach, which allows for more outreach in a rural setting?

Then who is your consumer? An 85-year-old who has just had hip surgery is not going to have the same needs as a 25-year-old who just had knee surgery; so keeping all these in mind when we're talking about packaging and storage and disposal, just being sensitive to these other elements.

DR. CHAN: Thank you. Dr. Rao-Patel?

DR. RAO-PATEL: Just to sort of piggyback on that comment, I think that's a great analogy. I like the mousetrap analogy because I think creating a more expensive, fancier packaging solution or storage solution may not necessarily bring things down to the basics, which is educated judicious prescribing by providers, physicians, mid-levels, et cetera.

So it really boils down to whether physicians are making appropriate choices in the amounts of medications they're prescribing and the indications for which they're prescribing them, because again, the cost is important, and that translates not just to patients who are paying their monthly premiums who are on opioids, but to patients who are not on opioids as well. That translates into their bottom line and their monthly premium cost as well.

DR. HERTZ: So I think we all recognize that this is going to have to be multifactorial. Trying to address the prescribing side is being worked on in many spheres, but really here we're focusing on

another element. And cost has come up a few times, and I'm wondering while the packaging may have a finite cost associated with it that doesn't currently exist for products, how do you factor in the downstream costs of the accidental overdose, the sneaking of doses from the medicine cabinet by the -- I always call them stupid college kids.

(Laughter.)

DR. MENDELSON: Smart college kids do it, too.

DR. HERTZ: Isn't there a cost there, and shouldn't that also be factored in? There's the cost to the patient, but there's also the cost to the insurance company. And I think the insurance company is more of the limiting factor here -- payers, not the insurance company; I should say payers in general.

So how do you look at all of that information to figure out what the actual costs are?

DR. CHAN: Dr. Emmendorfer?

DR. EMMENDORFER: So being a healthcare

provider and not a law and order professional, I think part of the thing that I think maybe -- I don't know if others struggle with this, we call it third parties, and we'll call it diversion. But when you really get down to it, it's an illegal behavior that you want to study that you're trying to prevent.

I don't know how to design -- that's also part of the problem, too, because you have the real issue of accidental overdoses that you can prevent with the children, but when you start to look at the one realm that packaging may be able to help with, which is diversion, I don't know how a healthcare system to design that study to try to detect behavior that people are willingly -- or they're trying to hide it for a reason.

So I think that's part of the issue that maybe I don't know if others around the table struggle with. I don't know how you quantify that into the cost or how do you find that evidence.

DR. CHAN: Dr. Kelman?

DR. KELMAN: Doing a safety benefit analysis

is hard enough. Doing a cost benefit analysis on this is much harder. And the question is how much money, if any, you save downstream, and who does it accrue to? I don't think this enough data to make [inaudible].

DR. CHAN: Let's move on to question 4. With question 4, we want to discuss strategies to reduce barriers and encourage patient use of the packaging, storage, and disposal options to enhance opioid safety. We've talked a lot today and skirted around this issue of -- some of these aren't really necessarily directed to the patient or they may not recognize they have a role to play here.

When you consider that, what are going to be the strategies we need to think about to really get patient acceptance in use of these? We've heard a little bit about this. I think part of it is coming down to helping patients understand why they're getting it. That's part of the training perhaps initially or education that happens.

What other strategies or what other ideas do

we have to consider here? Who would like to begin? Yes, Ms. Whalley Buono?

MS. WHALLEY BUONO: Liz Whalley Buono. I'll just refer to the model that's already been rolled out to retain pharmacy, and that was the Walmart Adherence Program. And that program was started originally, really not focused on adherence but focused on leveraging large-count purchasing power to deliver a $4 generic market space to the industry.

It was only after the packages went into market that I think the retailers started to see an adherence improvement. And unfortunately, when the packages were first rolled out, they weren't accompanied by a patient or pharmacy education program, so you had that initial resistance to change. People were used to getting their vial, and they got something completely new, and they weren't sure how to open it, and they didn't refer to the calendar. And we learned a lot through engagement.

So fast forward a year. The retailer

launched a wholesome pharmacy and patient education program, which really amounted to a little more than a piece of paper that explained the packaging and some time for pharmacy counseling, and the acceptance rate skyrocketed. So now over a billion patients have received drugs in the adherence calendar blister packaging, and all the studies have been done to show that there's a clear ROI, and that patients learned how to use it. And once it wasn't, quote/unquote, "new and familiar," it was more broadly accepted.

From that case study, if you will, the patient engagement and the pharmacy engagement is really key to the acceptance of the packaging. Then of course, packaging evolved over time from what we learned from consumer feedback.

DR. CHAN: Yes, Mr. Webb?

MR. WEBB: Kevin Webb, Mallinckrodt. I think there are two things that I would like to advance as far as new strategies. Some of this is going to collaboration with your partners over the DEA, but we're learning this on the addiction

treatment front, that we cannot arrest our way out of an addiction problem, but we treat drug take-backs still as a law enforcement solution. The drug boxes, the take-back boxes are in the police stations. Some pharmacies have it. The very communities that we're trying to get drugs out of are often the individuals that don't want to go into a police station.

So how do we take the take-back initiative to where patients and families reside? Could we do fire stations? Can we do something else, whether it's a community-focused initiative -- drug take-backs, they don't happen often enough. They only happen twice a year. I applaud the DEA for doing it, but the challenge is they're not top of mind, but it's a concept people readily identify with. So if you could make them more frequent, but then also bring them further out into the community, I think that would be helpful.

The other thing I think we need to also look at is at milestones. Disposal of opioids is top of mind, meaning the death of someone in the family, a

college student coming to school or leaving to go home, someone selling their home. Like for example, an obituary, if it says make donations to the American Red Cross, as a drug seeker, I know that there are opioids in that home, and I'm going to visit that home when the viewing is taking place.

So if we work with realtors, if we work with the newspapers that do obituaries, if we work with the school programs to look at what is the point -- for example, college students, a high amount of diversion of opioids takes place, and it's even the ABC drugs. But if someone's now packing to go home for the summer, could that now be an intervention point where the school inserts themselves into -- if you're cleaning out your dorm room, there needs to be a message about drug disposal. If someone's selling their home, the realtors should be engaged.

So there can be leaders pulling together all of these different types of community organizations to really help become champions as far as getting

drugs out of the homes when there's thinking about it.

DR. CHAN: Dr. Rao-Patel?

DR. RAO-PATEL: Anu Rao-Patel, Blue Cross Blue Shield. Just to your point, I think Blue Cross Blue Shield Association, as well as our North Carolina plan and several of our sister plans, have partnered on a national level with Walgreens pharmacy for these drug take-back kiosks.

Within our North Carolina plan, recognizing that not everybody would want to go into a law enforcement office to drop off their unused prescriptions and opioids, and especially since North Carolina has four of the top cities in the nation to have opioid abuse problems, we have, again, partnered with Walgreens to co-brand drug take-back kiosk boxes and have located about 22 so far and are looking to do anywhere from an additional 20 to 50 boxes across the state, especially in high-risk areas and areas that have already been identified within the state for high use of opioids.

I think that's another possibility, is collaborative stakeholder partnerships such as that so that we can get the drugs off the street.

DR. CHAN: Ms. Cowan?

MS. COWAN: Get a hero. And the reason I say get a hero is that kids are going to listen to the people they really admire, whether it be on social media, on PSAs, or something, to give those messages, to distribute those messages. Even to adults, they have sport heroes, somebody that they're going to listen to. You could do the public service announcements. You can put them on Twitter and you can put them on their Facebook. That's how messages start.

So maybe we're looking at the wrong people to deliver these messages. They're not the wrong people, but they're not the ones they're going to listen to. They're going to listen to the people that they admire that they look on their Facebook. So I just think maybe we need to look at a different way of giving the message.

DR. CHAN: Dr. Bateman?

DR. BATEMAN: I think there's a real need to raise awareness of the alternatives for disposal of opioids. I think returning them to a police station or to the take-back box is perhaps the most environmentally consciousness way of disposing of excess opioids, but it requires a certain activation on the part of the patients.

I understand if the FDA says if you can't do that, then you can dispose of the opioids in the trash or with unpalatable substances, or even flush them. I don't think that is widely known by patients and even healthcare providers, so raising the awareness of those alternative practices I think could be quite effective.

I think there's also a need to have uniformity across the federal agencies. The EPA has opioids on the list of medications not to be flushed, and the FDA says they can be flushed, and I think there's some confusion.

DR. CHAN: I think we'll go ahead to the next question, which is, is there a way that we can implement these actions in a way that enhances

safety without adversely affecting patient access, and how might that be accomplished? We've talked a lot about the access issue today, that we need to make sure patients can still use their drugs. Multiple people have voiced these concerns, and yet we're talking about options that will be designed specifically, in some cases, to keep certain people out of the drugs.

So how do you balance that? Can they actually be implemented in a way that allows for that?

(No response.)

DR. CHAN: It's a tough question, yes. Mr. Webb?

MR. WEBB: Kevin Webb, Mallinckrodt. You have to allow patients an opportunity to opt out. It's counter to what we've been discussing, but it's not going to be the right option for all patients. There may be dexterity issues. There may be some just caregiving issues. But even the most basic format of a blister pack configuration, some people just can't do that, so we have to be

sensitive to that.

If we're creating fear in people, if we make it so difficult, they're not going to be able to get to their medication. We just have to make sure to ease that concern so that they know that they still have some options as well.

DR. CHAN: As a follow-up to that then, I'm going to bring this conversation back around because although we know that sometimes there are overlaps in these problems, we started the day walking through different problems and looking at them a little bit more distinctly.

When we think through, for example, the four problems that we teed up at the beginning of the day, within each of those problems, are there areas, for example, where you would say, you know what, in this particular case, it might be reasonable to consider going with an all or nothing option. In other words, we should do this across the board. And then in other areas for other problems, we might say, no, you really need to keep multiple options on the market, including what

currently exists as one option, and then have these additional options so that providers can choose and select the appropriate patients or circumstances for which they would fit.

So I'd like to throw that out there as a follow-up.

MR. WEBB: Yes. I think that if we're going to accomplish the results, which we obviously as a panel recognize there's an immediate need to do that, the going in proposition has to be that this is what we need to do. It's an all-in scenario. However, there are always mitigating factors to the situation.

So maybe it's a situation for a blister pack or a 7-day unit-of-use configuration, but there's also the availability, if it's the present judgment of the pharmacist, that they allow that patient to have an alternative packaging, but there's some other safeguard. At that point, then maybe it's you give them 7 days in a bottle, but this is required. You have to walk through the disposal initiatives, or you give them a pouch, or you give

something where there's some other safeguard that you're building into it so that you're still accomplishing the objective, but it's not a situation where you just have now an adherence issue or patients just won't take their medication.

DR. CHAN: Yes, Ms. Whalley Buono?

MS. WHALLEY BUONO: Liz Whalley Buono. I'll play devil's advocate, and I'll say that my initial inclination is to say no. I think that the real problem with this disease state, if you will, is that it doesn't have a face. It crosses every barrier within our society. So I would imagine that it would be virtually impossible for a physician to look at a patient and adjudicate whether that patient is someone who is going to be prone to having diversion in their house, or be prone to misusing the medication.

So I would say the trick here is to roll it out across the board, but make sure it's not so cumbersome that it harms patients; that it shouldn't.

DR. CHAN: Ms. Cowan?

MS. COWAN: I don't know that this is a solution, but I think one of the accesses to care is the cost of all of this that we're talking about, that we can't pass it on to the patient. We can't pass on new costs to them. So many people these days are on fixed incomes or whatever that that would be a real problem, working two and three jobs because they can't work a full-time job because of their pain. So I think we just have to be mindful of the cost, which is definitely going to impact the access to care for that person with pain.

DR. CHAN: Dr. Twillman?

DR. TWILLMAN: Bob Twillman, Academy of Integrative Pain Medicine. I'm thinking along the same lines. The economics of this is really I think what's a very important driver. And we're almost getting to the point where we're talking about a perverse situation where a patient has to have prior authorization to get a cheaper product, which would really stand things on their head a little bit.

I think that it stands even to the point of thinking that there are multiple options in the marketplace where some products are going to have these features and others are not. I think the reality from an economic standpoint is that it's more likely to be pretty much all or nothing. So I think you need to seriously think about the economics of all of this.

DR. CHAN: Let's go ahead and move forward to question 6. Let's go a little bit into practical workflow considerations because that was touched on in the presentation. If we're envisioning a future scenario where these are the options that are out there, potentially, or these are being approved, cleared, whatever, marketed, what are going to be those practical obstacles in terms of integrating into the healthcare system when it comes to the workflows that exist, and are they going to differ between open versus closed healthcare systems, and in what way?

I think Dr. Emmendorfer, you already had your hand up.

DR. EMMENDORFER: Just one, and actually it was brought up by you guys earlier. If you choose a packaging solution, what's the right number of quantity of tablets or pills? I think you're going to find a wide variable right now, especially if you started looking -- I know dentistry was used as an example or the emergency departments. I think that's going to be something that needs to be thought about and looked at pretty hard as to what that right number would be so you're promoting the most amount of prescribing to that quantity.

DR. CHAN: If I can just follow up, in this scenario, we've been talking a lot about certain indications may require a certain quantity or warrant certain quantities, but that could be a wide range. We've seen that already in the surgical studies, that even within the same procedures, those amounts have varied.

So when we think about that, it may not be realistic to assume any manufacturer is going to create 50 blister packages in different quantities; I mean, the enormity of even just shelving anything

like that, but also just everything that goes into that, then you have risks for medication errors, selection errors, and so on and so forth.

So as we're thinking about this, I'm curious then, is the thought -- again, this builds a little bit on the previous conversation with the idea that not everyone may not need a specific option. Then is it the idea that you need a couple of options with your standard, so to speak, that allows you that flexibility that we keep circling around here? But then, how do we marry that with the challenges that were just raised around this idea of the economic considerations and the fact that you don't want these prior authorizations to get the cheaper alternative, and the idea that it does need to be all or nothing.

We're sort of hearing two things here. All or nothing means you don't necessarily have that flexibility for all of these scenarios in terms of treatment of the patient that could arise. So I'd like to throw that back out. Yes, Ms. Morgan?

MS. MORGAN: It was something that was

raised earlier about the idea of doing the best risk assessment prior that may help drive. So maybe what it comes down to is an algorithm set-up where you go through a list of questions that talk to the patient's need for the medication, home environment, and other risks that may be involved, length of treatment, that will then drive to a set of packaging, storage, and disposal options of which it will at least provide the best scenario to minimize the risk because you're not going to be able to take the risk away.

So can we do the information gathering up front that will then allow this to be done in an algorithm setting, and to really minimize it for the providers as well because the burdens that are now being placed on providers to be able to get critical medicines included in this we need [inaudible]. So can this be done with an algorithm setting so we do as much of prevention ahead of time to minimize the risk?

DR. CHAN: I'm starting to hear a little bit of wandering into the creation of new tools,

collecting additional data up front, which I think we definitely need to keep some of those in mind for tomorrow's discussion.

I think as I hear you say that, what I'm hearing is the creation of a tool that allows you to identify who actually needs this option because it seems like what we're still revolving around is this concept that not everyone needs the option. So again, the idea of an all or nothing then creates this economic impact, if you will, potential economic impact of someone's paying for these even when they're not needed.

So again, there are these tensions that I'm hearing in the conversation. In what you just described then, what I'm hearing -- and I want to make sure I'm clear -- is that you're still saying we would need several options that include not having a particular packaging, storage, or disposal technology attached to it. Is that correct?

MS. MORGAN: Yes.

DR. CHAN: Any thoughts or opposing viewpoints around that?

(No response.)

DR. CHAN: So let's move on then to the next question. This is the sticky one. So someone will be paying for this. We've heard varying viewpoints on who that needs to be or who that doesn't need to be. But ultimately what's going to be -- okay. We've already got someone itching to go here.

DR. KELMAN: [Inaudible - off mic] decide how and when to pay under different systems, some regulatory, some scientific, some [inaudible] space. Evidence of efficacy is always a strong point that balances out [inaudible]. You can pay for a cheaper or more expensive product, you have reason -- it's a criteria for prior authorization. But we haven't addressed that.

I think having the tools is a very good idea, but it's not yet [inaudible]; it doesn't exist. So for payers to pay, it would be much more of a downstream than we are now. From a payer point of view, it's a lot simpler if there are only these products on the market. If you have mixed products on the market, and it's done in a pharmacy

box, the pharmacy, it may not be paid at all, depending on what the insurance is going to do.

So there are too many questions for you to answer this.

DR. CHAN: But I think that's extremely helpful to help us parse those questions down. We ask a very broad question, but help us understand what are all those considerations. What are all those sub-questions to help us think through this as we think about implementation? Dr. Emmendorfer?

DR. EMMENDORFER: In the VA, our formulary system is based off the safety and efficacy, and it runs through a national committee. I would just like to say one thing because it was kind of mentioned earlier on. I don't know that it's a formulary issue for us because if you look at 2016, we spent $1.2 billion on 2,286 drugs that are not listed on our formulary. So for us, it's about ensuring that our veterans have the drugs that are available to them based on their medical necessity.

Also, from a formulary perspective, we are dosage-form specific. We would not go down to

package specific. But it's safety and efficacy, and then I think there would be a pretty strong conversation -- it's an unknown right now, but you would start assuming that all the products are on the market are safe and effective, and then how much more value is this package adding to the overall system. We need to have a discussion within the committees.

DR. CHAN: So I guess as a follow-up to that then, if it were somehow reflected in the label, and the indication, for example, was for a particular scenario, because of the addition of this, whether it's a packaging, storage, or disposal option, looking at this where it might be a container closure or whatever else, then if that's reflected in the indication -- I guess I'm trying to understand where in the labeling does it potentially carry more weight, or does that make any difference.

DR. KELMAN: The indication may not be on the prescription. The FDA [inaudible - off mic] status is particularly some success. We assume

that every drug that gets on the market is safe and effective. Just because you say it's safe and effective [inaudible]. Unless you have relative safe and effective information on the label, [inaudible]. It gets complicated to argue that one drug is less effective or more effective than the other.

DR. CHAN: Any follow-up comments to that? Yes, Dr. Mendelson?

DR. MENDELSON: I think the good news is that there's consolidation of the pharmacy benefit management field, and the bad news is there's consolidation in that field. So you're basically going to deal with monopolies, two or three monopolies eventually. Every time one payer wins, someone else loses. So I think you have to be cognizant of those factors as you go forward.

Those of us who've been working with trying to get on insurance plans for various novel health treatments, it's quite a show. The word "payer" should be expanded to like about 300 or 400 different entities. Will these be behavioral

health payments or traditional medical health payments, Or will they be pharmacy? Who gets the benefit from the payment of insurance?

Doc Twillman [indiscernible] over there knows quite well. It's really a complicated area. You're wading into a very deep pool with a lot of currents in it.

DR. CHAN: So let's move on to our next question, question number 8, which is, could cost benefit analyses for packaging, storage, and disposal options to enhance opioid safety differ depending on the problems they're seeking to target?

Yes, go ahead, Dr. Ciccarone.

DR. CICCARONE: The answer to that one is easy. So the answer is yes. Dan Ciccarone, UCSF. At minimum, if you're thinking about problems, morbidity and mortality are going to cost differently. That's the first level. I do think we could do cost benefit analyses. I don't think they would take a long time either. These could be done based on models. That's just my quick answer.

DR. CHAN: Yes, Dr. Izem?

DR. IZEM: Can we follow up on that comment? We discussed earlier that the cost may not be to the person who is being prescribed the drug, but to the community. How would you cost that into a cost benefit analysis?

DR. CICCARONE: Societal cost benefit analysis is done all the time. The difference is, either from an academic point of view or a policy point of view, who's going to pay the cost. The insurance companies don't necessarily want to pay the cost.

If we're talking about at the FDA level considering a cost benefit analysis, what policies make the most sense. And then if the cost benefit analysis looks better -- when the safety option is brought in as a mandatory versus an optional, and what the uptake of the optional part would be, you just take a societal perspective, and then you impose upon the payers the answer.

I'm thinking sort of academically here. I'm not thinking in terms of the real world of who's

actually going to bear the cost. But that's why we do these things, is to try to help decide rationally, outside of any individual constituency, what is the benefit to society.

DR. CHAN: Dr. Bosworth?

DR. BOSWORTH: I can't pretend to be a health economist, but I know we've done a recent paper that was published in the American Journal of Managed Care where we did look at the cost benefit of blister packaging in the context of cholesterol within the VA population.

In doing this for 20 years, this is the first time I would actually say that this is something that seemed pretty cost beneficial in terms of -- now, what we didn't look at was what the cost would be to the manufacturer to re-change the whole process to do blister packaging, and we actually considered or put out there that the potential is when you transition from the vials to the blister packaging, you're talking pennies per month, relative.

I think that this is where research could be

beneficial. I think you could do simulation studies. I think that there are opportunities, but I think that the low-lying fruit in terms of some of these simple blister packagings could have some benefits. But I think that once you start putting the manufacturer costs, then you've got to work together because I don't know what those costs are going to be.

DR. CHAN: Dr. Staffa?

DR. STAFFA: Judy Staffa from FDA. A thought occurred to me, coming from what you were saying. It seems like there might be certain insurance that are bearing the cost for the patients, and they will also benefit from the benefit to those patients if they don't go on to misuse or have an issue with their opioids. But some of that benefit will be seen by the insurers of the family members, which may not be the same at all. For example, the family members won't be under VA or CMS or some of those payers.

So it's kind of an interesting model. You can see almost some bearing the costs and others

gaining the benefit.

DR. CHAN: We've got a couple here. Dr. Bateman first.

DR. BATEMAN: I'm just thinking that it's going to be extraordinarily difficult to do a robust cost benefit analysis in the absence of really any efficacy data for the types of approaches that we're contemplating. You have to think about what the impact of blister pack usage is going to be on the downstream risk to society of overdose. I mean, we have no idea what that industry's going to be. Any type of model you would come up with would be really very, very speculative.

DR. CHAN: Dr. Twillman?

DR. TWILLMAN: Bob Twillman, Academy of Integrative Pain Medicine. It strikes me that this discussion is very much like a discussion we have about abuse-deterrent opioids. The question is who is going to benefit primarily? Here we have evidence that the patient for whom these products are prescribed is going to benefit. If that's the

case, then we can make the case for charging that patient a little bit more [inaudible]. If it's society as a whole that's going to benefit, then the case is that that's something that really should be spread across everyone who's insured by that particular insurer. That cost should not be borne by the patient.

I don't know how that plays out in real life, but philosophically it seems to me that's the question that we're talking about.

DR. CHAN: Is there another comment?

(No response.)

Audience Participation

DR. CHAN: All right. Well, thank you very much. At this time I think we're going to move into our audience participation session. So if folks could go ahead and line up behind the microphone if you wish to say something.

Again, similar to earlier in the day, we're going to ask that you focus comments on the topic. And I am actually not seeing anyone lining up. Oh, wait. We've got a taker.

MR. SULLIVAN: [Inaudible - off mic].

DR. CHAN: Well, we allocated a fair amount of time for this session, so I think we're going to take some flexibility here.

MR. SULLIVAN: Thank you again. This is John Sullivan. The company is Marjo, and we're working on an electronic blister pack monitor with artificial intelligence, so it's small. Basically, we're playing chess with the patient so that the patient is always in check with this monitor from the standpoint that the minute you remove a pill, it automatically activates a down counter that tells you when you can have your next one.

As you start to look at the counter -- it's important for people with memory loss, too, because they can't remember when they took the last one, so it prevents an overdose in that situation.

I've been hearing a lot of things about, well, who should have it and who shouldn't have it. The problem is that we have 11.5 million Americans that are using these drugs that don't have a prescription, so they're getting it from the bulk

that people leave in their medicine cabinets. We have 2500 children a day that are taking this drug for the first time, and they don't have a prescription.

So the important part is, is to get the bulk prescriptions off the market. So after they're expired, they have to return, and there are a lot of different options to do that. We could provide a return box. You put it in a box, you send it back to the box, and it goes to the DEA certified diversion facility that will destroy them, or in some cases you can return them to the pharmacist and they can do it.

I know there was some discussion about -- in Howard County where I'm from, we have the police station. You take them to the police station. And every time I've been, the thing's been packed. I had to come back in a couple days because there are so many people using it.

So it is working, but the key is that if you don't know the date and time and the behavior patterns of the consumption -- because that's

really the key of this whole blister pack thing working, is that it tells you a consumption pattern. And once you know the consumption pattern, you know if they're getting narrower and narrower with the addiction, and the craving is starting to have them take more and more opioids. And if you don't know that, you don't know if they're getting addicted.

But I think the behavioral change is that anyone that's got a teenager, you know if you leave them in your house a month or a week, things are going to be a disaster when you get home. So automatically, people change their behavior when they know they're being monitored, and that's an important part of this monitoring program is that it does change.

In 1969, the seat belt laws came in. We all complained about we don't want to put seat belts on, but it changed our behavior pattern over time because we realized how important seat belts were. So I see this product, a blister pack monitor, as seat belts on opioids, and you would never put a

child in a car without a seat belt. Even today -- I grew up in the '60s. We'd all ride in the back of a pickup truck to go get ice cream. Nobody thought a thing about it. We would never do that now with our kids. They always have to be in a car with a seat belt.

So I think that over time, people will realize the benefit, the fact that 4.7 percent of the world's population were consuming 80 percent of the world's opiates, this cannot continue in this manner.

We're losing the top shelf. In my neighborhood, there were five [indiscernible] kids. They were children of attorneys, doctors, lawyers. This was the next generation of Americans that were going to replace us. They're gone, and this epidemic wiped them out. So thank you.

DR. CHAN: Thank you. We have another speaker. Please introduce yourself.

MS. HOBOY: Thank you. Hi. Selin Hoboy with Stericycle again. I just wanted to make a comment about this cost benefit and trying to

figure it out. I think that maybe parceling some of these issues out in terms of packaging or storage or disposal and coming up with ideas and understanding where the costs are for those might be a more palatable way to approach this.

I think right now, packaging is one aspect of it, and it's a pretty big aspect of it. You have storage where it's going to be within the pharmacies and you have all these different doses. And then you have the disposal aspect of it, which whether it's from the home or at the pharmacy, or at the reverse distributor facility -- but they all have their own issues.

I would recommend for the committee to look at those issues separately when you're looking at cost because if you lump them all together -- I think someone said this earlier -- you're trying to eat the elephant, so maybe you can take a bite at a time. That would be my recommendation. Thank you.

Summary and Closing Remarks

DR. CHAN: Thank you very much. It looks like that's it in terms of public comments. So

we're actually quite ahead of schedule today. I do want to thank the panel members and our audience for a really productive day today. We've covered a lot of ground. I know we've thrown some tough questions at people, and some of them were broad and intentionally so. Some of them were broad because sometimes when you have such a difficult problem, it's hard even to know what's the right question to ask.

So you've given FDA certainly a lot of valuable information to consider, a lot that we're going to have to go back and digest. I mentioned earlier that tomorrow we get to do that deep dive into the data, and I know a lot of people have already triggered some of those conversations here in various settings. So we're going to want to make sure that we don't lose sight of any of those key ideas and that we're able to probe that tomorrow.

So with that, I want to thank you very much for coming here and being a part of this discussion, and we'll see you promptly

tomorrow at 8:30 in the morning. Have a great evening. Thank you very much.

(Applause.)

(Whereupon, at 4:20 p.m., the meeting was adjourned.)