FOOD AND DRUG ADMINISTRATION (FDA)

Packaging, Storage, and Disposal Options to Enhance Opioid Safety

Exploring the Path Forward

Tuesday, December 12, 2017

8:32 a.m. to 4:39 p.m.

Sheraton Silver Spring

8777 Georgia Avenue

Silver Spring, Maryland

C O N T E N T S

C O N T E N T S (continued)

C O N T E N T S (continued)

PROCEEDINGS

(8:32 a.m.)

Welcome Back and Overview

DR. CHAN: Good morning, folks, and thank you for joining us today. For those who were unable to join us yesterday, my name is Irene Chan, and I'm the deputy director in the Division of Medication Error Prevention and Analysis within the Office of Surveillance and Epidemiology at the Center for Drugs in the FDA.

So again, on behalf of the Food and Drug Administration, I'd like to welcome everyone back for the second day of this very important discussion on Packaging, Storage, and Disposal Options to Enhance Opioid Safety.

So as people are continuing to settle in, I'm just going to review a few housekeeping items and ground rules. Again, the restrooms are located adjacent to the elevators down the hall to the left. The WiFi network information here is available at the registration desk. If you need shuttle service to the metro, please see the staff.

If there's an emergency, please see the staff at the registration desk.

Lunch options are available in the hotel as well as outside the hotel. You can see the registration desk for information. Please silence your cell phones, smartphones, and any other devices you might have if you haven't already done so. The workshop is being webcast and audio-taped. 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. Please note we will be sticking to the schedule, so please return from lunch and breaks promptly. Please do not interrupt the speakers. Public comment will only be taken during the audience participation periods, which follow each session.

Those audience participation periods are to allow for comments that pertain specifically to that 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.

For our panelists, as you speak, please make sure you're using the microphone, and they should be working today. So please make sure you're speaking into the microphone in front of you, and please also identify yourself when you speak.

So yesterday's discussion generated some thought-provoking questions and ideas. Today, we want to ensure that we continue the discussion around some of those key ideas, especially the ones on data that work their way into the conversation.

So as we do that, I think it's important that we carefully consider the limitations of the systems that are available to us, but think about how we can create better approaches to data or overcome some of those limitations.

We also have to recognize that having adequate data is not always going to mean having the best possible data, and that may be acceptable, especially in the face of this current public health crisis.

So I would like you to especially think about that as we're talking about proximal versus distal outcomes today and the challenges that surround looking at those distal outcomes.

So there's a lot that we've internally been considering, but frankly, there's also a lot that we don't know in this space and a lot that we're asking you to help us learn so that we can continue creating regulatory framework that supports and encourages the development and approval of these options to enhance opioid safety.

So I'm very much looking forward to today's discussion, where we get to dive deeper into the discussion on data both in the pre-market and the post-market settings and think about how that data is going to drive the labeling considerations moving forward.

Before we jump in, though, it's my honor to introduce the deputy director for regulatory programs in the Center for Drug Evaluation and Research at FDA, Dr. Doug Throckmorton, who will be providing some opening remarks.

As the deputy director for regulatory programs, Dr. Throckmorton shares the responsibility for overseeing the regulation of research, development, manufacture, and marketing of prescription, over-the-counter, and generic drugs in the United States. He is committed to ensuring that the benefits of approved drugs outweigh their known risks. Dr. Throckmorton?

Opening Remarks – Doug Throckmorton

DR. THROCKMORTON: Thanks, Irene, and welcome back to everyone. I think we may have added a couple of other people, too. Thank you.

Thank you very much for coming. Welcome to the panel, welcome to the audience, and welcome to this public meeting, the second day, to discuss packaging solutions in the ongoing opioid crisis.

I'm going to start with where Dr. Gottlieb started yesterday, reminding all of us that the scope of the opioid crisis is difficult to overstate and challenging all of us to do everything that we possibly can. He asked us to be creative and take advantage of every tool and every

opportunity that we have, including considering actions that we might not have considered not too long ago.

This takes us to this meeting and the important discussion we had yesterday. For me, this meeting and its focus on packaging solutions makes entire sense, given what he said and what we all know and is consistent with that charge.

It is also a logical extension of what the FDA has been doing over the last several years in the sphere of safe use of opioids. We have focused first on individual opioid molecules, trying to understand them as best as we can in the form of approvals of immediate-release opioids.

We have focused on opioid drug products and their best uses, on special opioid formulations like abuse-deterrent formulations, extended-release formulations, patch technologies, and we focused on labeling as a mechanism of educating prescribers and patients in the best uses of these opioids when they're appropriate for pain management.

Moving outward, we're now at packaging, and

that's the focus of today's meeting. Given this background and given the importance of both packaging and the need to take a look at all of our available tools, I hope we will continue to aim high as we have our discussion today.

Our goal has to be to identify innovative packaging solutions and decide how best to make use of them as a part of a successfully implemented healthcare response to the opioids crisis.

To the panel members, yesterday's meeting was tremendously helpful. I heard a lot in the discussion that I learned a great deal from, and I appreciated your candor. There was broad engagement around the table. There was also rapid consensus, I would say, in the frame of Willie Sutton that we should go where the money is.

For packaging, to you, I heard that meant focusing on actions with the greatest likelihood of having the largest impact in two areas, first prevention, reducing the supply, the unnecessary supply of opioids that are flooding the market, finding a way to reduce the amounts that are being

placed onto the market, focusing on acute pain and post-op pain potentially.

The second area was disposal, getting the unneeded opioids out of the market, out of the home, out of the lockbox wherever as soon as they possibly could. Those two actions, among the things that we identified yesterday, seemed to resonate with the people around the table, and this was very helpful advice to us as an agency as we figure out how to go forward.

We also had a lively discussion about the actions the agency could take to incentivize the development of meaningful and impactful packaging solutions.

Drawing on our experience with incentivizing abuse-deterrent formulations, we had laid out a couple of potential pathways, and there was a vigorous discussion about which of those you chose you thought would best suit.

So there was an incentivization pathway, incentivize industry to create and use the better mousetrap, to paraphrase one of the speakers

yesterday, or require industry to create and use the better mousetrap.

Put another way, we could either make mandatory the inclusion of packaging solutions or we could use market-driven solutions to try to incentivize their development. Obviously, I'm making it black and white and there are things in the middle, but those were the two general approaches that you discussed vigorously.

I didn't hear a single voice. I didn't hear a single vote there, lots of back and forth that was very useful to us. As we talk today, I hope you will continue to keep those two potential courses in mind, and to the extent other ideas comes up, I hope you'll share them with us.

You also were very good at talking about the challenges that would face us as we chose to use a packaging solution, and I am very grateful for that. First, it needs to be used and we need to consider the unintended consequences.

We all agree this is hard. We all agree, as Irene just said, that we cannot let the perfect be

the enemy of the possible or the necessary in this case. So we're going to have to strike a balance between challenge, and the need for data quality, and those things, and the need to get something done.

Many groups have equities. We understand that those groups all have different needs that we're going to need to try to understand to the extent we can. The incentives may be different for those different groups.

Success here is going to require change in human behavior, and I think none of us underestimate how hard that is. It is understandable to hold on to a few opioids in your medicine cabinet just in case something comes up. That's not something we want to encourage, but it's very hard to change that human behavior.

The various goals all have different solutions and the different ways to approach them, and we need to think about them carefully. The area is complex in a regulatory way.

We heard a discussion yesterday from Paul

Raulerson about how challenging it is about how the law here is complicated by the fact that there are drugs, devices, combination products, and other unregulated things that could be considered packaging solutions under some circumstances. That just makes it a challenge that we're going to have to take on.

Reimbursement was identified as something that is going to have to be thought about because it's going to help incentivize or detract from the development of these products, and then finally questions that came up that needed answers about cost, about data requirements, and standards, and how we might apply them.

The data requirements brings us to where we are today. I'm looking forward to the discussion about the specific development of products, in particular solutions, using packaging, understanding how storage products might be tested, for instance, understanding that more granular discussion about the data is going to help inform us as we try to decide where to go next.

I'll go back to where I started, though. We all agree something has to be done. We simply have to find a way to reverse the tragic trends related to opioid abuse that are ravaging the communities in the U.S.

We are considering solutions we would not have considered a few years ago, given the dramatic nature of the problem. As Dr. Gottlieb said, while we recognize that some of the ideas we are exploring are unprecedented, the tragic truth is that this crisis is so immense that we need to consider a range of more impactful solutions that we may not have considered before.

Today's session is a part of that, that discussion of things that we may not have fully considered in the past, to look for new opportunities. Ultimately, FDA believes it is our obligation to identify and explore every option available to us.

We're determined to make sure that, whatever we do has an impact and will yield meaningful public health results. Thank you for all that you

did yesterday. I'm really looking forward to today's discussion.

(Applause.)

Presentation – Iren Chan

DR. CHAN: Thank you, Dr. Throckmorton, great message to open the day and definitely great summary of the key things we heard about yesterday.

So with that, we're going to go ahead and begin today. Just a brief overview, we're going to have two general sessions, sort of give the 30,000-foot view here of what we're planning to talk about. And then after that, we're going to go ahead and proceed into the sessions that are going to follow that same arc in terms of walking through the accidental exposures, and the misuse, the third-party access, and then the excess supply, in that order.

I do need to note unfortunately Dr. Tamra Meyer is unable to be with us, so we have the lovely Dr. Judy Staffa stepping in. She is going to be in your agenda. Where you see Tamra, you'll see Dr. Judy Staffa stepping in, so thank you for

doing that. So with that, let's go ahead and get started.

So I'm going to talk about pre-market data and labeling considerations to get us started. Again, the views and opinions expressed here are my own, not those that represent an official FDA position. If there's any reference to any marketed products, it is for illustrative purposes only and not an endorsement by the organizations listed here. And any labeling statements in this presentation really reflect preliminary considerations and are included just to generate scientific discussion.

So for those who were with us yesterday, this should look familiar. We started the day by walking through the four high-level problems where FDA has identified a role for these packaging, storage, and disposal options. Again, these include the accidental exposure, the misuse, the third-party access, and the excess supply.

So as we revisit each of these in turn, we're going to be thinking about the data

considerations. And it's important to note that before we dive in, typically with evaluating products, we're focused on the outcomes for the patient, that individual patient that's taking the product.

Yesterday, we touched on this. Here, it's a little bit unique because in a lot of these areas, we're not just talking about what's happening to the patient, but we're talking about the outcomes that are occurring in others, outcomes occurring in the family members, and that can make studying these options quite challenging.

So let's start with the accidental exposure. Yesterday, we discussed the fact that despite the successes we've seen with the Poison Prevention Packaging Act of 1970, we do continue to see these exposures and these poisonings occurring in young children.

Again, there's no doubt that the Act has reduced morbidity and mortality in this population, but there are still failure modes that exist. Some of the ones we talked about was the fact that

adults are improperly using these caps in some cases. They're not engaging them, and the fact that there's this active need to reengage can present a challenge.

You also have the fact that they're not always required. They can be requested to be replaced with non-child-resistant caps at the pharmacy. You also have the quality control implications that can impact the caps themselves as well as violations of the law that may occur.

So I put this up on the slide here because, if you look -- and sorry the font is a little small here -- even back in 1982, which is where this comes from, we were already questioning what more we could be doing here, what more needed to be done in order to further reduce these unintended ingestions.

So given the failure modes that exist, if we want to make it more difficult to access the available supply that is out there, then we do want to consider packaging options that are going to carry through from the manufacturer directly into

the hands of the patient and not be repackaged at the pharmacy level.

So for example, we talked a lot yesterday about unit-dose blister packaging that may help to address this issue of continuing accidental exposures.

Now, with unit-dose packaging, you create that passive intervention. A user doesn't have to reengage the closure after removing that single unit dose, and the other benefit is you get that protection for each individual unit.

But the question is, how do you demonstrate this offers a benefit over your typical child-resistant closure like the child-resistant cap on the amber bottle you receive at the pharmacy?

The good thing is, we know others have actually looked at this question. This isn't a new question. There have been various investigation s that have attempted to look at this causal relationship between unit-dose packaging implementation and result in poisoning in children.

However, this has proven challenging when

considering there can be confounders that make it difficult to tease out the exact effect of the packaging. And Dr. Dan Budnitz is going to speak to this a little further today when he discusses a recent investigation that compared emergency department visits for pediatric buprenorphine/naloxone ingestions before and after product packaging and formulation changes.

So there have been interesting data seen in some of the investigations to date that suggests there could be promise around the use of unit-dose packaging to further reduce the risk for these accidental exposures.

Now, if I want to be a bit provocative, I might ask whether we need more data or whether we move forward, and then see what happens in the real world, collect that information.

But if that's too provocative, then the question is, what do we test next then? On the pre-market side, we might consider how we can advance existing trial designs or leverage testing protocols that are already utilized. Should we be

looking further at human performance testing that already exists to measure child resistance as a starting point, and Dr. Laura Bix will be speaking to that today.

With any other options we consider, the natural question is going to arise of whether an option does something better than the status quo, so we need to think about what exactly we're comparing to. Are we comparing that unit-dose blister to other options or are we comparing that to the amber vial that you get at the pharmacy?

If so, then we should consider that when we're talking about the vial and cap system, when properly engaged, the cap is in fact child resistant. So how does that change what we're studying or how we think about studying it?

So let's talk about misuse. Yesterday, I discussed that medication use is governed by complex behavioral interactions and beliefs, and it's important to understand there's a spectrum of misuse that we're dealing with here.

So some examples of factors that can

contribute to whether a patient misuses a prescribed medication, including a prescription opioid, include adverse events or fear of adverse events, lower health literacy, lack of understanding, forgetfulness, unwillingness to read information, access, and cost.

So today, we're also going to hear from Mr. Walt Berghahn from the Healthcare Compliance Packaging Council, who is going to share with us some existing data around the effects of packaging on medication adherence, as there have been numerous studies that have attempted to measure the impact of innovative packaging on adherence or compliance, and we did speak to this as well yesterday.

So I will say, though, one thing to keep in mind when we're looking at the existing data is to recognize that with a lot of the studies out there, there have been some methodological and other limitations. So moving forward, we are going to want to consider how these future studies should be designed to more robustly evaluate these options.

The other thing is, although adherence is certainly an area that naturally comes to mind, we really need to be thinking broader than just adherence. As discussed yesterday, these options really have the potential to do many things, including things like provide patient reminders; limit dosages only to those that are prescribed for; notify prescribers of aberrant dosing patterns; destroy unused supply even after completion of therapy; and provide critical messaging around the safe use of these products.

But if the options can be designed to allow for multiple features, then we need to consider when we're evaluating these, how do we tease out those effects? Are we looking at individual effects? Are we looking at combined effects? What's that approach going to look like?

As far as the data considerations go, we'll need to discuss the adequacy of adherence alone as an outcome. Does there need to be a link to some other clinically relevant health outcome when we're thinking about opioids?

We want to understand how best to study the impact of the critical information that's included with the packaging, and how do we then correlate comprehension to actual behavior? We'll need to consider patient preferences and qualitative and quantitative methodologies, including quantitative survey methodologies.

Again, the question of comparative studies will come up as we think about the potential for improvement in the design and development of these options, which may allow for the safer use of opioids.

Furthermore, human factor studies are going to be key when evaluating these options, whether we're talking about misuse or other target problems because we need to ensure -- and we heard this again and again yesterday -- that the user interfaces have to meet the user's needs at the end of the day and ensure that there's safe and effective use of the options.

As I've noted before, the data is ultimately going to drive the labeling claims that can be

made. So if manufacturers want to achieve specific labeling claims, then the studies should be designed in a manner that will produce the data that's necessary to support the claim.

As we discuss the data considerations in greater detail, it may provide some clarity to the labeling questions that we raised yesterday.

So let's talk about third-party access. Yesterday, I talked about how we're looking at both the outpatient settings and the inpatient settings. You've heard a lot of conversation about how one of the key problems we'd like to focus on is how to ensure that that prescription is used only by the patient that it's prescribed for?

We recognize this doesn't negate the possibility that the patient can abuse their own product, but we recognize that a patient determined to share their medication could likely remove that packaging, take it themselves. They could also give it to other people. And in that scenario, it's going to be very hard to capture that sharing event, so we need to think a little bit more about

that.

We think there is a potential for these options when the patient isn't even aware that someone else is accessing their medications, and we know this isn't uncommon. We hear stories. We see things like what you see on the screen, where you could have an adolescent in a household that's taking a parent's medication or a grandparent's medication, and they're not aware this is occurring.

So in designing options for this scenario and then evaluating their ability to deter this kind of access is one area that we also want to focus our conversation on. So perhaps an option intended for outpatient use could be designed to allow for things like patient notification of unauthorized access in real time; use of biometrics or other technology to limit that access only to the patient; GPS tracking, even, of some of these products; critical messages, again, that we hope could deter that kind of unauthorized access.

However, the same questions are going to

arise when evaluating the options that have multiple design features in terms of how to isolate their effects or whether we should be studying in that manner.

As far as the data considerations go, it'll be interesting to explore the idea, perhaps, of time-to-defeat studies. One might hypothesize that the longer it takes for a third party to get into a package, the lower the likelihood that he or she may attempt to do so, which sort of is some of the underpinning for what we think about with child resistance.

But if so, what does that mean more broadly on the likelihood of first time abuse and, as different options are developed, the same questions regarding the comparative effectiveness maybe raised and also may be tied to the labeling claims that are pursued.

If we consider the methodologies outlined in the category 3 studies for abuse-deterrent formulations, then similar approaches in terms of looking at subjective responses and leveraging

visual analog scales may potentially be explored.

One key question is going to be how the design of an option may impact the likelihood of that third party to attempt to thwart that packaging or technology, which in turn raises interesting questions around what is the right population to study here. Do we study individuals? Are we studying the family unit?

Furthermore, human factor studies are going to be key again because we still need to make sure that these options meet the needs of the patients that they would be dispensed to.

So human factors and other social science approaches are going to help us potentially to evaluate the key messaging around these options.

Again, the data is ultimately driving those labeling claims. If you want to be able to say something with regards to what your option can do, then we're going to need the appropriate pre-market data to give us the confidence to state that, and we'll need to understand what you think that pre-market data needs to look like today.

So when thinking about data and labeling considerations for the inpatient setting now, some of the same considerations as I just discussed for the outpatient setting are going to apply. As discussed yesterday, there have been various published reports of healthcare-associated outbreaks or infections attributed to diversion by healthcare professionals. And this is certainly an area where, again, we think these options could potentially make a difference.

As noted yesterday, one area that's been considered is the role, for example, of dual tamper-evident features here in products that are used in the inpatient setting.

Now, under current regulations, over-the-counter human drug products, with a few exceptions, must be packaged in tamper-resistant packaging, and the FDA has put out various guidance in this area.

But it's interesting to consider whether the addition of dual tamper-evident features could be impactful when trying to deter that third-party access in the inpatient or that ambulatory care

setting. And we discussed yesterday that while injectable vials do have caps where removal of the cap could be identifiable, there are still vulnerabilities when relying on that as a single tamper-evident feature.

So as we think further about evaluating that dual tamper-resistant design, we may need to consider methodologies that allow us to understand, for example, the detectability of entry, the time to entry, along the same vein of what I just discussed about time to defeat, along with other qualitative and quantitative methodologies.

So some of the outcomes that we're interested in are behaviors with intent behind them, which may be actually best captured using survey methodologies. So again, the data is going to drive the labeling claim and, depending on what the data shows us, that's going to determine what we can actually state in the labeling about any particular option.

Last but not least, certainly an area that really came up repeatedly yesterday as

Dr. Throckmorton mentioned is this issue of excess supply as a whole, the fact that this feeds back into every other problem we've discussed. It's really going to be important to think about how we evaluate this in the pre-market setting when thinking about the options that will come before us.

As we noted yesterday, there are numerous studies that have looked at excess supply. They've looked at the fact that surgical patients who are prescribed products for pain are frequently left with unused pills, and in some cases, these are being stored in unlocked locations such as the medicine cabinet.

So when we think about the goals of packaging and disposal options that are meant to address the excess supply, there are a couple of questions that come to mind, one being how do we actually drive that prescribing behavior towards lower pre-packaged quantities when appropriate, if these are on the market, and then how to ensure that the unused product that's no longer needed is

actually properly disposed of rather than retained.

So in thinking about options with these goals in options, with disposal options, we'll likely need to consider the extraction studies that help confirm leftover product is in fact properly found or made inert.

But confirming that that's the case still doesn't answer the more interesting question of whether the disposal option will be used in the first place, that active task that needs to be completed by the patient.

So there may be quantitative survey methods that are appropriate to consider when assessing the options, especially those that may be directed at the prescriber population here. And again, human factor studies will also need to be considered to ensure that the user interfaces for these options meet the intended users' needs at the end of the day.

So as I walk through each of the problems, hopefully you've been considering the research that you've been undertaking, thinking about the studies

you've conducted or the studies that your colleagues are conducting that may be useful to leverage here. No matter how obscure it may seem, I think we're looking for all the ideas that we can generate today when thinking about how to examine these options.

So this concludes my presentation. We've got Dr. Judy Staffa, who will now discuss the challenges and data needs in assessing the impact of these options after they're marketed.

(Applause.)

Presentation – Judy Staffa

DR. STAFFA: Good morning. So I am going to try to take you through just a brief overview of some of the issues that we think are going to be common when trying to study the impact of packaging, storage, and disposal solutions on any of the outcomes that we've talked about across these four areas.

My particular disclaimer is that I do have Dr. Meyer's notes, and I will do my best to read from them to make sure I cover all the topics, but

I'm not really renowned for my ability to stick to a script, so that is my disclaimer, that I will certainly do my best.

I'm going to try to frame some of the questions that we'd be trying to answer after a product is approved with one of these packaging solutions. I'll talk about what are some of the relevant populations because they differ across the different areas, and I think we touched on that a little bit yesterday.

For those of you who are not epidemiologists, talk about some of the basic designs just in general, talk about some of the data sources that we typically use in the area of drug safety and thinking about how applicable they might be in this space. And then talk about some of the unique problems and issues we deal with when trying to focus on packaging as the thing that we're going to study.

So, many of you had the pleasure of joining us for our meeting in July when we were trying to do this kind of same exercise with studying abuse-

deterrent formulations in the post-marketing space. And I'm unhappy to tell you that we think this is harder. So if you thought that was bad, this is even going to be a wilder ride.

A lot of those challenges, I can't possibly go through the two days of great discussion and ideas that we got, but I would encourage you, if you're interested, there's a transcript available on the website. And if you would like to look through and refresh your memory, please do so.

So I'm going to talk about what the questions are. We've got two main areas that we might be asking once a product is approved with the packaging or a storage or disposal solution to address any of these four issues.

The first would be descriptive studies, and I'll talk a little bit more about those. And the second would be analytical studies, which is really more of a comparison of trying to understand what the actual impact is. And those might be studies that are more formal in nature and where we really need to identify compared to what; what does this

solution do compared to something else?

So if I think through in these different areas, we started thinking about what are some of the relevant populations we'd want to think about.

So for accidental exposures, that's probably the most straightforward, that this would be children. We'd need to find data sources where we can look at the experience with children. For misuse, this would probably be mostly focused on patients, but remembering that there's many different kinds of patients, and there may well be preferential prescribing or use of these kinds of products in different patient subpopulations and how well are we able to define those, given the data sources we have.

Third-party access is a little more difficult because in drug safety, we're often looking for safety issues that occur in patients. Here, this would really be looking for safety issues that are happening, as we've talked about, in other people, so other household members, family members, community members, healthcare workers. It

can be a little more difficult to actually identify data where we'd be able to find those people who surround the patient who's been dispensed a particular product. And then excess supply of course kind of feeds back into these, as we've talked about.

So just as kind of an overview, we've got a couple of different basic epi designs. As I've mentioned, we can have descriptive or analytic studies, and there are varying degrees or different types of studies within that.

Within descriptive studies, we've got population-level studies, which I'll talk about a little bit, and then individual-level studies. And then in the analytical realm, we have both experimental as well as observational.

So just a few words in those different areas, descriptive studies is really what it sounds like. We would start out with studies that are either qualitative or quantitative in nature. Some folks call them ethnographic studies, where we really focus on trying to understand the details,

the things that big data can never tell us.

How are the products being used? Who is using them? What are the decisions being made around using them? Are there certain circumstances that they're being used? Why? How are they being used? Are folks circumventing them and trying to understand actually the barriers that exist and the dynamic of the person who's been dispensed this product and how they use it.

From this kind of work comes not just an understanding of the environment, but key variables, key definitions that we can then bring in to our hypothesis testing studies to make them actually more on target.

For ecologic studies, this is a type of descriptive study that we often use to assess opioid products. Ecologic studies describe aggregate measures of outcomes like abuse or accidental exposures in one geographic area or during a given time period.

These enumerator data are typically standardized or normalized by the number of people

living in the study coverage area or the number of people who are exposed to the product of interest. And you've seen this in the abuse-deterrent formulation world, as we call these abuse rates.

Sometimes analytical studies use the ecologic study design as well to compare aggregate events for different products or time periods, and Dr. Budnitz will be talking about the use of this design in some of his assessments of buprenorphine poisonings and packaging.

Then when testing hypotheses, we actually prefer to have individual-level studies, where we can actually assess both the exposure to the product as well as the outcome in the same person over time. And that way, we can try to control for characteristics that might bias or confound those results.

We use case control and cohort studies or just a couple of examples. In a cohort study, we would sample people based on who was exposed or who got the product, follow them along to see what their outcomes were. In a case control study, we

would sample people based on some kind of an outcome, of having that outcome or not, and then we'd go back in time to try to understand how they got there.

There's also pragmatic trials, which is more of an experimental design. These pragmatic trials are often done post-marketing on drug safety issues. They tend to be more practical and have less highly selected samples than the kinds of randomized trials you see pre-approval. We often use them when we worry about particular kinds of bias or confounding that might occur in an observational study.

We do these studies when we're very worried about confounding by indication, where we can't tease apart the decision-making that's made when a particular patient is prescribed one drug versus another. And so that's where we try to do something more pragmatic and look at a design like this, where there's a randomization to remove that kind of confounding.

I think some of the issues that came up

yesterday, the downside of trials is that they have to be rather large, they can be expensive, and they can take a long time to complete. So that's why we tend to use them sparingly. We also are concerned around the ethics of randomization when you're looking at populations such as young children or teenagers that are vulnerable, particularly in a space like thinking about opioids.

So let's turn to some of the data that we typically use in the area of studying drug safety issues and try to walk through where we see there might be some strengths or challenges to try to use these data to study these packaging issues.

So I'm going to go over very broadly electronic healthcare data, some other kinds of utilization data, touch a little bit on surveys and interviews, and then hit on some other data sources.

So when I say electronic health data, I mean electronic health records, the kind that are generated in the process of taking care of patients. Also medical or prescription

administrative claims data, these are usually generated by an insurer in the process of payment. And then inpatient health records, same thing, electronic records, but in the inpatient setting. But remember, they're often not linked to what happens in the outpatient world.

So with regard to electronic health records, when we look at whether they have utility in trying to study packaging, there can be some limitations because a prescriber may record in an electronic medical record, an order, or a suggestion, the intent to actually give a patient or prescribe a patient a particular kind of packaging. But oftentimes, electronic health records are not linked to what is actually dispensed, and that may change when a patient gets to the pharmacy depending on insurance coverage or generic substitution policies in their state.

So there may be a lot of wealth of understanding of prescriber's thinking, which in this space could help us a lot, but perhaps less information on a lot of the details of the outcome

of what ends up happening along the process.

These records also capture the diagnosis codes and the free text, as often a lot of valuable information of how a prescriber is approaching a patient is here. But free-text data, as we all know who analyze data, can be very challenging to actually try to group together and analyze, so that's a challenge on that front.

Again, in the United States, at least, oftentimes electronic health records are specific to only one physician or one group of providers. So for example, you may be accessing a patient's experience with their primary care provider, but be missing their care that's provided by other specialties, such as an allergist or OB-GYN.

Integrated care systems like Kaiser can overcome that, but then of course we worry about representativeness of those systems and whether those findings would apply to other settings.

Administrative claims data actually provide different challenges. These contain data typically on dispensed prescriptions. They will contain

diagnosis codes and procedure codes for care that's provided and paid for. So the advantage here is that we'd actually get the product that was dispensed. So I'll talk a little bit more about the way we capture that in the next slide.

But there's some value here that, if a packaging solution is linked to product, and dispensed in that way, and identifiable in data, claims data, we might actually be able to capture it in these kinds of data. Unfortunately, there's not going to be a lot of detailed information on why that selection was made in these kinds of data.

The other limitation here is that many times, particularly for inexpensive generic products such as many opioid analgesics, their cost will typically fall below the patients' co-pay, so they'll end up paying cash for those prescriptions, so those will not be captured. So it's not always clear what piece of that person's experience we're capturing.

Then finally, many times, since diagnosis codes are actually used for payment, we often in

drug safety require proof or validation that the code actually means that the patient had whatever that disease state was or that event was. So we typically require medical record access to verify that until we get comfortable that a code is being used in the way we think it's being used, because, for example, many times codes can be used to rule something out.

So just to go a little bit deeper, the National Drug Code, for those of you who are not familiar, is one way to capture detailed product information, and this is how prescription claims are typically paid for.

So there's a 10-digit number, and the first four to five digits typically include the manufacturer, repackaging, or distributing firm. The second three to four digits actually include information about the actual moiety and the product formulation details.

Then the final two digits in the code are typically for package size and form. So there may be an ability -- if these solutions are actually

built into the product and actually coming from the manufacturer, there may be a way to capture those prescription claims codes through the NDC code.

Turning to inpatient health records, we have less experience with this. We do use aggregated data from a number of, like, hundreds of hospitals pulled together to look at drug use in various hospitals, but to get those hospitals to put all their data into one bucket, what happens is that since they all have different systems for recording drugs that are purchased and administered, there's often a company that will do what's called mapping. So they'll be mapping all the different heparins to one code that basically says heparin.

So the good news about that is that we can look across a large sample of hospitals and understand how much heparin is used. We can't always see, though, what specific manufacturer or brand of heparin that is. So again, one could imagine going to individual hospitals or smaller groups of hospitals that might use the same method and actually being able to identify that.

We're not really clear on whether there are data systems governing the supply chain side in hospitals or the automatic dispenser cabinets, but that could be something that could be tapped into, and some of you today may actually have experience that might be relevant there.

Then for other utilization data, we regularly look at data captured from pharmacies rather than insurers, which means we capture across all payers, including cash payers, to look at dispensings out of retail pharmacies. Also, the growth of the prescription drug monitoring programs in each state allows looking at that, those kind of features across the state for controlled substances.

Now, some states are talking to each other. We're hearing that, that there's more talking across and checking across states. But whether those data can be aggregated in any way, any meaningful way across states to be able to look at some of these issues, and whether packaging could be included as one of the features picked up in

PDMPs remains to be seen.

Then finally, we also have sales data, which sales data to us is what's going in the back door of the pharmacy, so it's what's coming out of the manufacturer to the backdoor. That's often the way we look at over-the-counter products. And again, since some of these packaging solutions may actually be sold as an over-the-counter product for a patient to purchase, it's not clear whether we'd be able to capture that.

Some companies do capture these data, but it typically is associated with some kind of a loyalty card, which might tag it to a household, which could be helpful, but not necessarily to an individual patient. So again, we have less experience with that, but these are sources that could be explored.

Now, turning to surveys and interviews, this may be a valuable way to gather some information since we might want to craft some individual questions around packaging solutions. And again, as we talked about in July, there are big national

surveys that are probability samples designed to represent the U.S. population. But there are also enriched populations and some newer internet-based surveys.

So some of the selected national surveys, again, the National Survey on Drug Use and Health and Monitoring the Future are two that we look at a lot. Monitoring the Future focuses on adolescents, and I know we have folks here today who actually have a lot of experience with some of these surveys.

In our July meeting, we learned that it might be very challenging to add individual questions on to these surveys because of the length of the survey and the need to balance that with getting information and getting people to agree to participate.

There's also a considerable lag time in getting questions added, so it may not be the quickest way to do things if we were to try to ask questions about packaging on these surveys. But we thought that Monitoring the Future being an

adolescent-based survey, focusing on one of the subgroups that's of great interest, may actually prove to be a helpful vehicle for moving ahead. And we'd love to talk more about that with you.

With regard to some of the enriched populations, we use a lot of surveys that actually focus on individuals who are either entering or being evaluated for entering treatment for substance-use disorder, including opioid-use disorder.

We've used these or seen these used a lot in trying to understand the impact of these deterrent formulations, because those formulations are designed to prevent behaviors that might occur perhaps more advanced down the spectrum of opioid-use disorder, where someone is actually altering a product to be able to snort it or to inject it. So for that purpose, that may be just exactly the right population to be asking questions about those products.

Here, we weren't really sure whether perhaps, by the time an individual who is that

advanced in their substance use might actually -- the package may have long been separated from the product for that individual.

So we throw that out there to see if there's anything that could be done with this population, and if we could, whether we'd be able to generalize those results to some of the other populations, again having talked about some of the experimentation that might go on in the household as opposed to folks who are well advanced.

In newer survey methodologies, we talked about these some in July as well. There are new opportunities for internet-based surveys, which can be very valuable because everybody is on their phone, and we talked about that. So it's a great way to access people you might not be able to access in other ways.

The problem is it's always difficult to define that sampling frame and to really understand who you're accessing and who they represent, and to actually ensure the quality of that information. But these might be survey methodologies that lend

themselves to flexibility in terms of adding questions as products are approved.

Then finally, again, we could mount various provider, pharmacist, and patient surveys. This may be the only way to capture some of the outcomes we're interested in. Big data may not help us with some of the details around the behaviors that we're really interested in exploring and understanding. But if we do that, we may need to do that in local or pocket levels because we may not be able to do this on a national level, so we need to be thinking about how to be strategic so that we'd be able to generalize those results maximally.

Then again, other data sources we thought about are poison control centers. They collect a lot of detailed information on whatever is available when someone calls for assistance, and they often have information on dose and route. It's not clear that they would have information down to the packaging level. It might depend on exactly how the call was made.

With regard to mortality data, clearly,

there's not going to be any information in there about packaging unless there might be something around a death scene investigation, but again, that doesn't make its way to the death certificate.

Then again, with emerging technologies, some of these options that have the RFID options to them, where we might be able to track how a patient is opening or someone is opening a package and that gets recorded, that might be very useful. But we would have to be sure to be validating and making sure that technology performed the way we expected it to before we used it for outcomes.

So this is kind of an overview slide. Let me see if I can walk through this as well as Tamra would have been able to, to kind of summarize all of this in one slide.

We start with the prescription order from the prescriber, which is recorded in an electronic health record. Then that goes to the pharmacy, at which point a particular kind of packaging, a unit-dose blister pack, may be dispensed, and that might be picked up in a prescription claim.

Again, if it's more of a cap that is added on that isn't manufactured with the original product, it's not clear how well we would be able to capture that, but that would probably happen at the pharmacy level.

Then the prescription goes to the patient, and this is where it gets even more difficult because, then, again, the patient can purchase things over the counter, can order things on television that they've seen, family members may buy them, particular aids, which we may or may not know about and data may not capture.

Then of course it gets even more complicated when we try to think about the family members or the other people trying to ascertain the use of a product, a packaging solution as it works its way through the system, and then tie that to the outcomes in those individuals.

Then just a note, third-party access with regard to the inpatient, we're not really sure how well these systems will work, but again, it's something we'd really like to learn from folks'

experience and to understand in a hospital system how these data might be collected to be able to detect third-party access to an opioid product that is stored and whether a package solution could prevent that, and how that information might actually be picked up, and whether that information could be made available to researchers.

Excess supply, as we've mentioned, we almost could think about in a way as an effect modifier, for those of you who are epidemiologists, because these behaviors may be happening anyway, but the more supply that's around it may actually enhance the behavior, and how did we think about that to be able to study that.

This is just a graphic, a kind of way to think about this. Each row, if we think about accidental exposure, unintentional misuse, intentional misuse, third-party access by a teenager, for example, or third-party access by a healthcare worker, this is just a hypothetical scenario of the different events that could happen along a chain that could result in a very bad

outcome such as death, or hospitalization, or an infection. But there are different behaviors and events that happen along the way.

You can imagine that you might want to be studying events that are very close to a product being implemented toward the left-hand side of the graph, if you were going to be trying to evaluate the impact of that intervention.

However, if I overlay that with some of the data sources that are available, you can see that many of our data sources that are available actually detect things that are not very proximal to the package solution, but are much more distal, things like overdose and death or hospitalization.

Even though we might capture those, the further we go toward the right of the slide, the harder it is to relate that back to the intervention that's way over on the left, because there's a whole lot of other factors that impact how that product is used, the circumstances in the home, for example, even things that impact whether someone who overdoses ends up dying or receives

care and is able to recover.

So there are a lot of other things that affect that, so one of our challenges here is to figure out how do we get data closer to the outcome or the proximal data, but also how do we best use the data at hand. We have to be practical. Even though they're distal outcomes, are there ways that we can use them in ways that will help us to at least have a feel for what these solutions might do?

So the main messages here are really that designing studies to do this is going to be really hard. It's going to be even harder than it is, I think, to evaluate abuse-deterrent formulations and we haven't exactly figured that out yet.

The existing data systems may capture exposure in particular relevant populations, but we'll have to explore that further, and we'd love to hear your thoughts.

We may not have data sources that link exposure and outcome in the same person, so we may need to be thinking about how to link data sources

together or how to build new data sources, creating them perhaps, like, through surveys.

Some of the problems we're targeting like intentional misuse are hard to operationalize, and define, and measure. It's one of those things that we know when we see it, but we really need to do that if we're going to be able to assess how these things perform.

Again, we may need to be thinking about more proximal outcomes or surrogate markers that may make us feel that we are comfortable that these are doing something even if we don't wait all the way until we can measure a distal outcome. And again, we may need to be generating new data in that space.

So with that overall introduction, we're going to move into Session 5, where we're going to be focusing specifically on accidental exposures. So we're going to start this session with a couple of presenters who are going to talk to us about some specific work that they or their colleagues have done in this area.

We're going to hear from Dr. Laura Bix first, and then we're going to hear from Dr. Dan Budnitz. So I'll turn it over to Dr. Bix.

(Applause.)

Session 5 Presentation – Laura Bix

DR. BIX: Good morning, everybody. As was mentioned, my name is Laura Bix, and I was asked to talk to you today about the history preceding the Poison Prevention Packaging Act, the Act itself; the subsequent regulatory details that dictate child-resistant protocol; insights that we've garnered in the course of using the protocol a bit; and the promise that it holds with regard to the current epidemic that we're facing in 10 minutes or less. So I am going to do my best to deliver on that promise.

Recent history or modern history of childhood ingestions or unintentional exposures to medication and household chemicals dates back to 1943. I remember personally how incredible delicious children's flavored aspirin was.

I don't know if anybody else remembers that.

But apparently, there are several cohorts that came before me, that also thought that it was quite delicious. And after that product was introduced, there was a significant uptick in exposures, and a lot of subsequent activity followed.

We had the establishment of U.S. Poison Control Centers and poison clearinghouses, which were intended to serve as a source of information for treatment as well as collect data.

By 1959, researchers had recommended the use of what was termed in that era safety closures or special closures, largely due to the ubiquitous nature of packaging sort of being present with the drug or the offending substance at the point of use.

By 1970, the Poison Prevention Packaging Act was enacted, which required special packaging for select drugs and chemicals. In 1972, the Consumer Product Safety Act transferred the regulatory authority from the FDA to the Consumer Product Safety Commission, who continues to administer that test jointly with the EPA.

The Poison Prevention Packaging Act does define special packaging and it defines it as packaging that was designed or constructed to be significantly difficult for children under 5 years of age to open or obtain a toxic or harmful amount of the substance contained therein within a reasonable time, and not difficult for normal adults. And I have added emphasis there to use properly. I think this definition is important in the way we operationalize things, so I'll come back to that later.

It has been, I think, largely due to the reason that it was started, because of the ubiquity of the package with the product throughout its life, as long as it's used appropriately. It has been very, very effective.

This is data from the National Center for Health Statistics that shows pediatric poisonings from 1972 to 2013, and you can see that they've leveled off. Unfortunately, the CDC also predicted or detected an early signal regarding opiates, and Dr. Budnitz is going to talk to you about his

recognition of that early signal and enlisting the help of Protect and Protect RX to try to do something about it.

This is an article that appeared in the New York Times on September 20th of this year that states from the CDC data opiate ingestions. Poisonings because of opiates were at 16 in this population in 1999compared to 87 by 2015. So it's unfortunately going in a direction that we don't like to see.

It's happening all over the country, and you'll see here, in the Times article, in Salt Lake City, they interviewed an emergency room doc that had to revive 4 toddlers in a single shift all due to opiate ingestion. So it's really an alarming new trend.

With regard to the protocol requirements, what we do is we test panels of children in groups of 50 blocks, blocks of 50. So at the end of 50, we evaluate, is there such a clear signal that this is a great child-resistant product and we can stop testing? Do we need to continue on with another

panel of 50, or is this package doing so poorly in terms of testing that we don't even bother testing anymore?

We do that with up to 4 panels, so up to 200 children. Those children are between the ages of 42 and 51 months of age, which is actually older than those that are generally at risk. The reason for that is they presumably are a more robust test of the system because they're more physically capable, probably getting to the point where they're able to read.

They are tested in pairs in a familiar location. And the reason that they're tested in pairs is if you take them back by themselves, they become shrinking violets, and they just are not very robust in their approach, where a pair will feed off of each other. There's generally kind of a lead and a follow.

In terms of the test, we give each child a package for a period of 5 minutes. If they open it, that particular test, that particular package is recorded as a fail. If they do not open it, we

give them a demo and we say, "Watch me," and we do that for them, the idea being there are people in their home that will model that behavior, so we want to model it, too.

Another thing that we do in the United States that's not largely done in the rest of the world is we encourage the use of teeth, which have been shown to be an effective means to enter packages. I didn't write the protocol.

We then give them a second 5-minute period and encourage them again to try to open. If they open, that package is recorded as a fail. If they fail to open, that package is recorded as a pass. There are certain requirements in terms of a proportion of children that can come from certain test facilities and the number of testers that must be used, et cetera.

One thing that we touched on yesterday that is important to note, when you're dealing with a multi-dose container like a bottle or a vial, a single breach is considered an opening, where with a blister or unit-dose package, it is dependent on

the drug's toxicity, so basically, the manufacturer has to determine the toxicity to determine the number of breaches that's considered a failure, up to 8; 8 is the maximum number.

If they don't want to go to that hassle, then the default would be one blister being a failure, and that's called an F1. So you'll hear F1, F2, F3. That's what that deals with.

Now, this is some of the data that we've collected over the years. I apologize. These are daycares. They're kind of noisy. But I think one of the challenges that we face is my mother threw me out the back door. She may be watching, so she may be insulted. But she'd throw me out the back door and say, "Come back at lunch time," where today's kids are on tablets and iPads, and they're doing very fine motor things.

Many of the children that we work with can even read. And if you listen to this little boy in this particular test, you'll see him. I really think he's reading. He'll say, "You push down and turn."

(Video playing.)

DR. BIX: So this little girl on the left is in before the tester even notices. She is so quick. She's in right now.

(Video playing.)

DR. BIX: On this particular day, this is a peel-push blister that you have to separate the laminate layers and then push the pills through the back of the blister. I could not get my fingers into this space to separate the laminates on these particular blisters, but she was able to find a little crevice and work her way in.

(Video playing.)

DR. BIX: Another thing that happens with children -- with adults, if they fail, we see them try the same thing over, and over, and over again. They keep going back to, well, and they try the same thing.

(Video playing.)

DR. BIX: Children start using different strategies; okay, that didn't work; I'll use something else. This boy on the left is going to

actually pull that cap straight off of there, ramping over.

(Video playing.)

(Laughter.)

DR. BIX: So in terms of the senior tests, we do eliminate children with overt or obvious disabilities from the test prior to their entry, but we do the same thing with adults. So that interpretation of normal adult, what the regulators interpreted that to be, was basically if you have an overt or obvious disability that would preclude you from interacting with the packaging, you will be screened out.

We test seniors from the ages of 50 to 70, and we test 100 of them. We give them a package for a period of 5 minutes, and if they open and, in the case of reclosable package, successfully reclose it, we'll give them a second package to open and reclose in a period of one minute.

If that package is opened, it will be a pass. If they fail to open and reclose the second package, it will be a fail. If they fail to open

the first package, we go back to this normal adult definition again. And we'll give them two non-child-resistant packages, so one that just twists off, another that's a snap cap. And we'll give them a minute each on each of those non-child-resistant packages and ask them to try to open it.

If they open each of those, they're considered sort of capable, so their CR result is considered a fail. If they fail to open those, they are excluded from testing.

So these seniors would actually not be eligible because we work with people in my lab a lot that have overt and obvious disabilities, so probably most of these people would not be eligible under the protocol testing. But we see a lot of issues such as --

(Video playing.)

DR. BIX: This is a tremor, so when somebody will go to purposefully use their muscles, they actually go into tremor, which can cause a lot of problems when you're trying to work with fine motor types of development. We also see people with

stroke who have had the dominant sides of their body paralyzed.

(Video playing.)

DR. BIX: A lot of times, they will internalize the failure and actually think less of themselves because of their inability.

(Video playing.)

DR. BIX: So with that, I will turn it over to Dr. Budnitz, who is the second of our panel.

(Applause.)

Session 5 Presentation – Daniel Budnitz

DR. BUDNITZ: Thank you, Laura.

So I was asked to give a little bit of real-world examples of using post-marketing data, basically using the data that we have in hand, as Judy said, to try to address the issue of accidental ingestions by young children.

Similar to my FDA colleagues, I have the same disclaimers, that the findings and conclusions of this presentation do not necessarily represent the official position of the CDC.

So I'm going to start this brief

presentation by giving a brief background on the post-marketing data and data systems that CDC used to identify pediatric medication ingestions as a public health problem, why we thought that packaging innovation could make a difference for prevention.

Then we'll get into some of the post-market data used to assess the impact of packaging, and finally some lessons that apply to this, but other types of opioid overdoses as well.

This is just a general slide about this overall CDC approach to preventing opioid overdoses that includes conducting surveillance and research, building state and local capacity, supporting providers, partnering with a public safety system, and empowering consumers.

Now I'm going to focus on this first circle, conducting surveillance and research, because I sometimes joke that CDC stands for the Center for Disease Counting because that is a lot of what we do. But it is significant to try to translate public health, to try to quantify data and turn

this data into information to improve public health and safety.

So what is the data source that we predominantly use? This one is called NEISS, the National Electronic Injury Surveillance System. And I think it's actually a good example of collaboration across federal agencies. It's a system that's administered actually just down the road in Bethesda, Maryland by the U.S. Consumer Product Safety Commission.

What CDC and FDA did together a little bit over a decade ago was to work with the Consumer Product Safety Commission to expand the system to include medications as well as other consumer products.

Although electronic the term is in its name, this is not big data. This is not EHR data collection or administrative data. This is electronic from the 1970s, meaning there was chart abstraction going on with real people looking at paper charts, but they had computers, about the size of a suitcase, to type in their findings and

send them electronically to the U.S. Consumer Product Safety Commission.

So this is kind of the old-fashioned data collection, but the secret sauce is in how it's constructed. It's a national probability sample. Instead of trying to collect data on all ED visits across the country, these are 60 representative hospitals, large and small, academic and non-academic, children's hospitals, that can be extrapolated to represent the nation.

Another thing that we think is important at CDC are case definitions. I think that's really the first step in counting. What we were counting with this system was injury from use of a drug.

Now, what we considered injury was basically the ED visit, and from use of the drug is actually the explicit documentation by the treating clinician that this drug caused the ED visit. It's not a statistical association or it's not a possible causality like might be reported to the FDA FAERS system.

This was the case definition for the first

years of the system, but with the opioid abuse epidemic, we expanded our case definition to include not just therapeutic use, but abuse, misuse, self-harm, and recognize the reality that there can be unknown intent of taking a medication as well, and up to four drugs, initially just two drugs were able to be implicated, now up to four, starting in 2016.

Here's some of the first data that we saw from the system, looking at the rates or population rates of emergency visits for adverse drug events. Something that struck me at this time was that the rates were as high for children less than 5 for ED visits for adverse drug events as adults 70 to 75.

I was trained as a general internist, so this was surprising to me, but I did have two children at the time under 5, so this kind of piqued my interest. And maybe if I had more training in pediatrics, I would have known this, but about 60 percent of these visits were overdoses. And not only that, almost all of them, on the order of 95 percent, were due to

unsupervised medication ingestions, kids getting into the products, not adults making administrative errors or errors in administration.

As Laura mentioned, the folks most at risk are actually 2-year-olds. And it works out that about 1 out of every 150 2-year-olds ends up in the emergency department for getting into a medication or a medication exposure overdose.

We tried to look a little bit about what were the products kids were getting into, and I'm going to focus first on solid dose-form medications and prescriptions. That's the majority of these ED visits. And it turns out that the most common class of medications leading to ED visits is opioids, leading to about 4600 ED visits a year and about 14 percent of these prescription-solid ingestions.

But still, there are a whole host of products. We tried to look a little bit more specifically at what products might be implicated and which ones might be implicated in the most serious events, the ones that lead to

hospitalization.

What we found is that in children less than 5, actually, one drug, buprenorphine, buprenorphine-containing products cause more ED visits than any other product. Up to almost 8 percent of the hospitalizations were due to buprenorphine-containing products.

Again, this is a kind of absolute number each year, similar to the number who ingested clonidine, so we tried to look at rates. It turns out, at this time, between 2007 and 2011, for every 500 adults that were treated with buprenorphine in a year, 1 child was hospitalized, and this far exceeded the rates of hospitalizations for ingestion from any other product. And as you see at the time, buprenorphine was packaged in the traditional child-resistant bottles.

So I think folks have heard this a few times, so I'll just be very brief. We thought about, are there packaging innovations that might address this issue, ones that provide automatic protection, where the unit-dose packaging, for

example, might remain in place for every dose, after 1 dose is opened. With unit-dose packaging, the concept might be that a little or a smaller dose might be less harmful than a lot.

Here's the data that we're getting to. We had a natural experiment. During the subsequent years, after 2011, as you can see in the dark black dotted line, there's a change in the market. Buprenorphine began to be marketed in a new formulation that required unit-dose packaging. Folks are quite familiar with this with the change in the Suboxone formulation. And also, new products were coming on the market that also were needed as packaging.

By 2013 to 2015, 80 to 90 percent of the products sold were packaged in unit-dose packaging. What we found was that the ingestion rates declined by 65 percent by the time 80 percent of the products were in unit-dose packaging.

This is ecologic data. There is not direct cause and effect here. We do have association, not causation. And we also note that this was a change

in formulation as well as packaging.

I think we try to triangulate some more data sources. For example, we also have data on another type of packaging change to try to reduce ingestions of liquid products. That's adding something like flow restrictors, basically changing the large orifice of a bottle neck to a small orifice, or even an orifice with a valve or reclosable seal.

What we found from poison center data that Dr. Green was involved in putting together was that there was a reduction in the numbers of ED visits after this packaging change as well as a decrease or twofold higher odds of ingesting a toxic dose in old packaging versus the new packaging.

Finally, this was some information that was presented this summer at a conference in Switzerland. I wish I could have gone on the government's dime to Switzerland this summer to see this in person, but I'm left to reading the abstract. But the key point here is this is another data source, again using Poison Center

data, but another situation over in the Netherlands where there was repackaging of thyroid hormone, thyroxine, from bottles to unit-dose packaging. And again, they saw 50 percent reduction in calls to poison centers and a 65 percent reduction in patients that ingested toxic doses.

What are some considerations when we look at post-marketing data to try to assess impact of a change in packaging? I think there are a couple things that hopefully we'll get into in the discussion. One is you have to have a case definition and what is your definition of harm? Are they exposures, physics [indiscernible], toxicity?

What about the attribution of harm? Are there symptoms truly due to this drug that you can determine from your data source or are there multiple substances involved? It turns out, for this buprenorphine example, typically these are single-dose ingestions, but that may not be the case for other types of misuse or abuse.

You also have the intention for

administration. You've have heard and Dr. Chan really highlighted these four types of problems that we are trying to address, but it might be kind of difficult from the documentation to tease out exactly which of those buckets any event might occur, might fall into.

There's finally data limitations also in the categorization of products. We've heard a little bit about those this morning, but by active ingredient, brand formulation packaging, data sources can be limited in identifying those characteristics.

We also need to think about the denominator. I guess this is the use. As we heard again this morning, the unit of exposure, prescriptions written, dispensed, days supplied, dose supplied, or patient-days used, or patients, can all be an appropriate denominators depending on the question.

There's the time period you're looking at. We are talking about a problem of shelf life, maybe not so much in the pharmacy, but in the patient's home; how long did these products remain there.

And if you do make a change, how long will it take before the new packaging permeates the shelf and the old leaves the shelf at home?

As I mentioned before, this intention of administration, there's the intention by the consumer to take or patient to take. Those are the intentions for the prescriber. We heard Dr. Gottlieb talk about he wanted indication-based dosing, how do you get that indication from the data sources? That could be a challenge.

Finally, the same challenges of categorization for use of the products that we heard about this morning, and maybe you can get NDC codes that include information on the brand formulation packaging and maybe you cannot.

Finally, if you're using post-market data to assess impact, we do have to think about time trends. This is ecologic data, so correlation is really not causation, and we have to do something to assess secular effects. Doing that quantitatively can be challenging. Are there appropriate approaches to triangulate using

different data sources where we can do this qualitatively?

Any monitoring system may not be stable over time. There can be changes to systems that are new, like new case definitions that are added can mature, and the operating characteristics can change. You can have drift of both the numerator and denominator estimates.

Finally, there's the timing requirements. If we want to assess a change, we have to start with the baseline. So you have to start thinking about what is your baseline before you implement your packaging change.

Finally, there's the issues of statistical testing. There's a number of ways to test time trends, with different data sources, one testing method may be more or less applicable.

Finally, I'll end with this, "unknowns over time". It's great to characterize the types of intents of abuse, misuse, and accidental ingestions. I think we're fortunate a little bit where accidental ingestions has an age cut-off.

That's pretty concrete. But other types of intents can be hard to describe, and there is often unknown intents that one has to factor in as well.

With that, I think I'll start the open discussions. Thank you.

(Applause.)

Panel Discussion

DR. LOSTRITTO: Good morning. Dr. Staffa and I are going to moderate this session -- this is a discussion session -- but before we get into the questions, we're a little bit short on time, so we'll have about seven minutes or so for each of five questions.

Just a couple quick summary points. We've seen several very good presentations this morning. We've seen the value of proximal intervention and outcomes discussed. We've seen testing strategies for both children, and seniors, and adults. And we've seen some targeted case studies just now with buprenorphine, acetaminophen, and so on. And as was pointed out by Dr. Staffa in her discussion, a lot of this is ecological data, very qualitative.

I'm going to exercise my right of privilege here and cause a little bit of controversy on the floor to stimulate some discussion. What do we need -- or do we need more data? What data do we need and how can we take this from a theoretical or ideal discussion to something practical and pragmatic?

So with that, we'll start with the first question. Remember you have a little less time than usual, so we're going to have seven minutes per question. What types of pre- and post-market studies might be useful for supporting a claim that a packaging solution is expected to reduce pre-market or post-market accidental exposure?

DR. IZEM: Sorry, if I may, I know we don't have that much time. I would like to ask a clarifying question to Dr. Bix before we maybe start the conversation. In terms of the studies that you collect for child-resistant tampering packages, what type of assessment do you make before making a decision? Is it mostly qualitative or is it quantitative? Do you have benchmarks?

DR. BIX: Do you mean in terms of bringing the package up?

DR. IZEM: No. After you collect the data on your 50 children to see how they're doing with the packaging.

DR. BIX: Its very binary, so it's a breach where you can obtain a portion of the dose or access to the entire content.

DR. IZEM: I see. So one breach would mean failure for the packaging.

DR. BIX: Well, it would be dependent. Like if you're on a unit dose, it would be dependent on the toxicity of the drug. If you required three -- what is it, a 24-month-oldcertain kilogram weight of child, what would be a toxic or lethal dose for them? So if it's three pills and they're in unit dose, it would be three breaches where they have access to the content.

DR. IZEM: I see. So out of the 50 children, if one of them succeeds, then it's that packaging's failure.

DR. BIX: That particular trial is recorded

as a fail. It's 80 percent of children can't access during the first 5 minutes and 85 percent during the second 5 minutes.

DR. IZEM: Thank you.

MS. WHALLEY BUONO: So I am shocked. I have a couple of things to say, but I think they're relative, so I'll try and say them quickly. I think it's critically important, since the testing protocol is kind of the backbone of where we start from when we're looking at child-resistant packaging, it's critically important to understand that blister packaging is not blister packaging.

So there are two types of blister packaging. There's a foil-backed and a paper backed. For the paper-backed blisters, those are the ones that are difficult to get into by design, and we know that adults tend to use things like scissors and knives, and they're really very difficult to get into. And the usability preference for those are very low, borne out of that preference to not have the paper on back, which the good part of that is that it's non-reclosable, so it stays with it.

To Dan's point, it's always there, which is a great aspect to it. The difficulty is that we know that, because people like them very little, they'll expel multiple pills at a time because they simply find it hard to get into.

The foil-backed blisters are the ones where you push it and the pill pops out. The CR feature is on some sort of external cover to that that's integrally attached. So the blister slides out, slides back, and there are a bunch of different products related to that.

I'll also say that the CPSC testing protocol is absolutely drafted, because of when it was drafted, for cap and vial closures. So it unfortunately gives a bunch of discretion as to how you design these testing protocols for non-cap and vial.

There's conduct in the marketplace that's very concerning. For example, some packaging manufacturers will test a white pack, which is a package that doesn't have the opening instructions printed on it. And they use their discretion to

interpret that regulation. And that is clearly not the intent of the regulation, but because there isn't guidance associated for non-cap and vial, it gives that room.

So things like they'll test a package with white placebo pills instead of pink, and if the pills in market will be pink, the pink color of the pills can incent the child to try harder to get to them.

So things like that, I really feel very strongly that there needs to be a guidance document or some sort of amendment to the CPSC testing protocol that provides more clarity that these tests really need to fulfill the intent of that testing protocol, or else we're going to have packages in market that technically have passed, but will pose risk to children.

So that's the first thing I wanted to say. The second thing is -- and we filed these comments in the context of the child-resistant notice and comment that was put out earlier this year. Right now, I think there's insufficient reclosing

instructions on a lot of these packages.

Now, obviously, with the cap and vial, it's imprinted on there oftentimes. But for some of these newer packaging concepts, where there's ample space for patient information, I think it should be made very clear that reclosing is an important aspect of this.

A third thing I wanted to say is we are in a conundrum here when we're talking about conducting studies on packaging because until the packaging is in the market, obviously you can't collect post-market information on it. And really, that's the best way for real-world setting evaluations.

We were in a very unique position where we had retail pharmacy putting these packages in the market, so we had a wealth of data to look at. But I think FDA needs to think about perhaps a staged approach to data collection, where there's a sufficient amount of information that you can collect in a very timely manner on safety. Perhaps that's enough to launch the product and then evaluate it post-market for some of the ancillary

benefits that you hope you'll see.

The last thing is that very excellent slide on capturing outcomes, where we had the bar graphs that spoke a little bit more than the circle diagram to the intent and behavioral issues, I don't know if we have the information, but I'd really love it if we could take that slide and put a relative percentage to those various behaviors so as we're thinking about what issues do we try and address in the market, it would just be so helpful to understand, relative to tragedy, where do each of those lines sit relative to each other.

So as we're thinking about designing packaging, we can start with having, from a quantitative perspective, the most impact.

DR. STAFFA: Dr. Green?

DR. GREEN: I can appreciate all the details that Elizabeth went into. I think we also started at the beginning saying don't let the perfect be the -- whatever the saying is. And I think we have very strong data that show unit-dose packaging has made -- at least it has a relational impact in

emergency data that Dr. Budnitz presented.

We also have a paper coming out that shows similar results in poison center data, so it was a nice validation of that intervention as well. And we didn't really go into -- we know what the impact was with iron, like, decades ago. So we don't just have data with opioids. We have data in other areas as well.

So unit-dose packaging, I think, whatever the mechanisms are, doesn't have to be that difficult. There are many packaging options today. And then we have ways to evaluate that. We've evaluated it here.

Also, mentioning the flow restrictors for acetaminophen, at Rocky Mountain, we did callback surveys to the caregivers for those specific accidental unsupervised ingestions to get more product information, to confirm what the product looked like, what flow restrictor was on the packaging, and had a great participation rate in terms of being able to confirm what that packaging was.

So I think there is a way to evaluate that in the real world by getting back to those individuals who have had the experience and the exposure with those specific products.

The question is do we have evidence. I think we have great evidence that the unit-dose packaging can make a big impact with the pediatric exposures.

Then, of course, with that requirement, we'll influence the implementation or what the details are. But I would encourage us not to get caught up in the details of what it exactly has to be other than should this be a requirement for the opioids that are leaving the pharmacy.

DR. LOSTRITTO: I'll just add something to that. Because blister packaging is used for multiple purposes, I think it will be important to capture whether it is the backed or the push-through type when you look at these studies either retrospectively or prospectively.

DR. GREEN: That's why we have the testing standards and the ratings for the F1 and the F2,

and maybe it's that it has to be a minimum of an F2 or whatever that minimum criteria could be, and then the application of that is really up to the manufacturer to make sure that they're meeting those requirements. But there's plenty of information out there on what works and what doesn't in terms of current packaging.

DR. LOSTRITTO: Anything else on question 1?

(No response.)

DR. STAFFA: Before we move on, I just wanted to acknowledge we do have an additional panel member today who wasn't able to join us yesterday. Dr. Spitznas, would you just like to introduce yourself?

DR. SPITZNAS: Hi. I am CeCe Spitznas. I am a senior science policy advisor at the Office of National Drug Control Policy and have been working on the opioid issue since 2011. And prior to that, I was from NIDA, where I did extramural research administration on addiction treatment and provider training. Thanks for having me.

DR. STAFFA: Thank you very much for joining

us today.

DR. LOSTRITTO: Before we move on to 2, is there any more input on the notion of looking at these types of studies that were just discussed by Dr. Green and others? Yes?

MS. MORGAN: Thank you, Sharon Morgan, ANA. Just as part of this, I also am a big strong component of not reinventing the wheel, so can we tease out existing data to better determine if there is a specific packaging that is working now, that we would want to test?

As part of the testing, would we consider the collection of unused meds in a very prompt manner to see if that is the determining value of the indicator of accidental poisonings, that it's not so much the packaging, but the fact that there are unused medicines being left in a home situation. And then does it matter whether it's an acute versus chronic pain management situation?

So just other aspects as we're collecting on the packaging.

DR. CHAN: Can I ask a clarifier to that?

When you say, are there unused meds, are you saying you're envisioning this as occurring only in the scenarios where leftover meds are being --

MS. MORGAN: Well, wouldn't that be interesting if that is really the issue at hand, not so much the packaging, but that there are unused medicines being left in the home. And it is that medicine over time in an area that is a greater determinant of accidental poisonings than the actual packaging and access into the packaging

DR. CHAN: So I would be interested to hear the panel's thoughts on this. And this is not an area for which I have expertise, but I'd like to understand, while I certainly could see that the excess supply and what's being left is part of what's being accessed, but I think even when someone is actively utilizing a prescription, these vulnerabilities, I would imagine, likely still exist.

So I guess the question I would throw back to you is, even if you really dig to a root cause of the excess supply, does that change the question

before us in terms of, should we still be doing something about the packaging here?

So what I heard before was essentially -- what I heard was I like the provocative thought; let's go ahead and implement here. We probably have enough data, which is I think what you're saying. Leverage the data we have; there seems to be enough of a signal here to say we could move forward, and then let the real-world data collection begin so that we can really measure this.

I'm seeing a lot of head-nodding in here. I'd like to get more panel discussion on that and sort of be able to close it out.

DR. GREEN: So if I can just comment on the other root causes because we actually did publish another paper that wasn't presented on the buprenorphine accidental unsupervised ingestions from both poison centers and the manufacturer safety database and looked at root cause. And a majority of them were active users that had maybe set out their medication for themselves or their

others on the table, on high chairs, on just ridiculous things that just make you want to cringe because of just irresponsible placement.

It's always the uncle that came to visit and lost his pill in the couch or fell out of a tissue, the same individual pills being put in the plastic wrapping around cigarette boxes; a bottle of the product given to a child to use as a rattle.

So these I think are more active users, and it's the active product that's being laid out that is accessible to the kids rather than a 2-year-old is not -- well, they do sometimes. But they're not going to climb into the medicine cabinet, and pick up the bottle, and try to bust into it. It's usually those free-floating tablets that the kids get their hands on. So hopefully that's useful in answering your question.

DR. STAFFA: Ms. Cowan, did you have a comment?

MS. COWAN: Yes. I was just thinking about the use of the teeth by the children, and if they could put some kind of a taste on the packaging.

So if you put it in your mouth, whether it's the lid or the little blister pack, if they're trying to open it with their teeth, they immediately stop because it's very bitter or not sour.

They like sour. For some reason, kids like sour. I don't get it. But bitter, I think, would be a better one to do just as a deterrent. I mean, it might help.

DR. SCHARMAN: Dr. Scharman, West Virginia Poison Center. So a couple of things. The National Poison Data System database that our poison center uses actually has a whole scenario page that covers what type of packaging the product was in and what the child was doing or the parent was doing with the package before the exposure occurred, because we actually obtain that information as part of the call in trying to verify what the dose was, and they usually tell us. I know it's one because it was in a blister pack.

It's just that particular subset of information is voluntary, just extra questions to ask. So if there was incentive for poison centers

to take the time to ask those questions, that database was already put in, and that could be changed in very quickly.

DR. STAFFA: Can I just ask a clarifying question about that? So is that common to all poison control centers, not just your state?

DR. SCHARMAN: That's every poison center. It comes in under the scenario code, so that data can be captured. And some centers currently do, but most do not.

DR. LOSTRITTO: I just have a clarifying question. When you capture blisters, do you capture type of blister?

DR. SCHARMAN: It doesn't capture type right now, not to say that can't in the future, but it does just generally categorize that.

I think the other comment, if you look at the slide of the number of hospitalizations in those children going to emergency departments that was posted, if you look at almost all but two at the bottom, those are all medications where it just takes one.

So I think part of looking at all the data that we have on what is a toxic dose in children, not from the manufacturer, but what we already know post-marketing, and look at do we need special considerations for those products where it does just take one as opposed to the other types of products.

DR. LOSTRITTO: So for clarity, what would it take to get this done more consistently in a form, F1, F2, F8?

DR. SCHARMAN: To do what more consistently?

DR. LOSTRITTO: To capture the amounts that are reached consistently actively for a given drug.

DR. SCHARMAN: So what would it take for the poison centers to capture that data?

DR. LOSTRITTO: Yes, more consistently and accurately.

DR. SCHARMAN: I think, with any industry, you've got fewer and fewer resources and more and more things asking for those resources. So there is some sort of incentive to capture that data. I think universally, if you look at the pharmacy

realm and the poison center realm, you kind of see unit-dose packaging as such a no-brainer for decreasing poisonings that we don't even think to look at it.

I think part of getting more research is letting the people on the ground, schools of pharmacy, pharmacy organizations, to know that this is a question that people are interested in because I think the reason you don't see tons of publication with the data that we have is because no one knows that anybody cares, because we just consider it such a, well, of course it is. So I think letting people know that kind of data is needed is important.

DR. GREEN: Dr. Jody Green. Just to add to Elizabeth's point about consistency, because it is such a no-brainer, I think that the callback surveys do provide a little bit more systematic review of those types of exposures to get at the more targeted questions, because keeping in mind that the calls to poison centers are really intended for medical management of the situation

and helping to secure the best outcomes for the patient. So that secondary data collection can be done more systematically with a callback system or a follow-up survey.

DR. STAFFA: Dr. Spitznas?

DR. SPITZNAS: One of my questions got answered, but just for clarification, I'm thinking about the unfortunate situations where children have gotten a hold of these patches, fentanyl patches, and if there's any data on joint storage and disposal types of things or packaging that includes some sort of disposal mechanism it for those -- I think Canada, some provinces, have a program where you have to return your actual patches, but I don't know if you have to return your used ones.

But I am not seeing necessarily the unit-dose packaging making that much of a difference for those exposures, and I don't know if there's information about how many of those -- if those are just high-profile things that I've heard of a lot or if those are really happening more

frequently than they ought to.

DR. STAFFA: Does anybody have a specific comment about that? Ms. Whalley Buono?

MS. WHALLEY BUONO: Liz Whalley Buono. So my understanding is that the patches do come in child-resistant foil patches, which are pretty difficult to get into without a scissor or something like that, and that the poisonings occur when they are taken off and they no longer have therapeutic value, but they're placed, let's say, in the garbage. And then the child puts it in their mouth, there's enough residual product that it gets absorbed.

DR. LOSTRITTO: At least in one presentation yesterday, the concept of a disposal pouch was mentioned.

DR. CHAN: So I think one thing just to clarify -- and perhaps Dr. Bix can speak to the fact that we're not looking at transdermal systems when we're talking about the testing under CPSC, but absolutely understood.

I think -- and this gets to what Ms. Whalley

Buono was just saying, though. Yes, when they are coming in a package, like have not been used yet, often they are these unit packages for each individual pouch. But then what happens is, once you are worn, we have to think about the adhesion issues, and you have to think about -- even if the adhesion is staying for the duration of wear, which may not always be occurring, then on top of that, you have to think about how people are disposing them and who's getting into them after that point, so certainly a different set of considerations there.

DR. STAFFA: I believe, Dr. Bosworth, we'll take one more comment, and then we're going to move to the next question.

DR. BOSWORTH: So this is a little different. I guess I heard post-marketing, and I'm not hearing a lot of discussion regarding that. So when I think as a researcher, I think we talked about the pre-market issues. And then I think of the post-market, and I think of the retrospective and then the prospective.

But I also think that, living in my ivory tower, if someone came out with an RFA, a research funding announcement, I could really get a bunch of different investigators to really think about these topics and actually look at very diverse datasets that I haven't heard and also partnering with industry to look at some of these issues.

What also is an important part is the cost, the cost from the societal perspective, from the individual perspective, really understanding these things, which is also then the third party that's evaluating this outside of the industry or the company themselves.

So there's a lot more -- perhaps I'm biased -- that could come to that. But if there's a possibility of really thinking about it, if these products are moving into the market to really think about the post-market, I think of these large healthcare systems where you have merging of CVS and Aetna, where you have databases that weren't available, the VA as a possibility -- so there are a lot of options there to consider as you think

about if you really want to do the post-marketing prospective evaluation.

Frankly, we work for a very little amount of money, so for small amounts of research funding announcements, you would see the market really developing some really interesting protocols and projects that could be answering some of these things that we don't even know yet.

So to whatever capacity you could consider, those are some things on the table.

I just want to argue, too, one other thing, these pragmatic trials. So we're working in these PCORnets and these other databases where we have 40, 50 clinics, and merging these datasets. And they're just growing exponentially and the opportunity to take advantage of some of these things, where you are also looking at different rural urban, all these other environments, and particularly areas in the Appalachia where we haven't even discussed geographic areas.

So there's a lot of databases that we in the academic world are playing with that could be

potentially created or adopted very easily. But I want to emphasize that pragmatic trials, we're not talking RCTs.

One thing for everybody to struggle through is we use the RCT as the standard, gold standard, and frankly, we know that that really reduces the generalizability. Yes, we can address issues of confounding because we have that randomization, but these pragmatic trials are really powerful, can be done in a short period of time, and frankly could be potentially done in a much more cost-effective way.

We never can talk about causality. You can try to argue with an RCT about causality. It's still not there. So the issue is you don't want to wait five years for trial or do you think about doing something where you could do step-wise, where you're doing 3, 6, 9, and start getting some evidence much quicker and effectively. So other things to think about.

DR. STAFFA: Thank you. Let's move to question 2. Again, this one focuses more on

designs. And, again, folks have raised the fact that blister package is not a blister package is not a blister package. There are different kinds as well as other kinds of packaging and other solutions.

Are there particular designs that you would consider most useful, either pre- or post-marketing, for trying to compare? Because that will certainly come up if we allow innovation in the area. If we want people to be coming up with innovative solutions, eventually there will be a need to understand the comparative performance.

MS. WHALLEY BUONO: Liz Whalley Buono. I guess I would just say we have a very effective process for testing these packages for child resistance, and it's been in place for quite a long time. And in my mind, I question why we don't simply rely upon those testing protocols as sufficient evidence of child resistance.

I mean, unless we're calling into question protocol parameters, which I don't think we should because they've been very effective, I think the

question is -- and I'm sorry if I was inarticulate the last time I spoke about the details. My intent on that was, I think we have to be very clear on how the protocol is applied to the next-generation types of products. And the next-generation types of products have been designed for very purposeful reasons because people are misusing the early-generation blister packs.

So I think the important thing is that we make sure the protocol is being applied appropriately, either through guidance or amendment, and then we rely on the testing results.

Now, we know that it's the misuse of some of these packaging types that is causing the child ingestions, the non-reclosure, so that's a whole other thing that I think we have to rely on the CPSC testing protocol as sufficient evidence of child resistance and then evaluate misuse as a separate topic. This would be my suggestion.

DR. STAFFA: Dr. Mendelson?

DR. MENDELSON: I was going to ask this clarifying question before, but it applies to this

section as well. I notice that people aren't testing the behavior of the children around the medicine once they get it. In other words, do they like it; does it taste good?

Now, naloxone is one of the most bitter substances known to man, and we did a study years ago where we had to try it and it really was foul. And I gave a little to Alan Leshner at a meeting, and he took away all my grants.

(Laughter.)

DR. MENDELSON: It was that bad. It really was just an awful flavor. But apparently, it doesn't deter children from taking Suboxone. So if that's a true statement -- and I would like you guys, if you could, to break out the buprenorphine alone versus buprenorphine-naloxone combinations if you have that data on those 500 of those overdoses, because that would be really important. That would tell us -- because naloxone should have been a 2 for 1. It should have prevented IV administration. It should have prevented pediatric exposure, too. But maybe make this stuff taste

like broccoli or legumes.

DR. GREEN: They're all combo. Dan studies that.

DR. MENDELSON: They're all combo? That's amazing. That's amazing because it's really unpleasant, naloxone. But I still think, if people are going to take them out of the packaging and put them someplace else and other, capsaicin, something else that's aversive, maybe -- I recognize in some cases, a single dose is toxic, but get the kids to expel it from their mouths.

I would add behavioral testing of excipients that are designed to actually make it less desirable for children. And I'm surprised that naloxone failed that test because I don't think any adult would keep naloxone in their mouth unless they really needed to.

DR. GREEN: It's sublingual.

DR. STAFFA: Dr. Bix, did you want to respond to that?

DR. MENDELSON: I know that, but if you don't need the medication, you'd rather do this.

DR. BIX: We get them off of the drug as soon as that opening occurs --

DR. GREEN: Yes.

DR. BIX: -- and debrief them thoroughly afterward.

(Laughter.)

DR. BIX: I'm not a toxicologist, so maybe I'm the wrong person for your study. But I do think you raise an interesting point. I think there are a lot of opportunities to think more creatively about how we defeat one population and enable another that statistically can't be segregated.

DR. MENDELSON: Well, Bitrex is an approved additive.

DR. BIX: So that's one possible solution, but I think there are other things. We tend to look at the physical, keeping them out from a physical standpoint or a cognitive standpoint by coupling dissimilar simultaneous motions.

We've looked a little bit, but I haven't seen strategies that are dramatically different

employed, like can we have them chase a red herring like bubble wrap or something like that in a non-working portion to prolong the time to opening? Then the question becomes, does that become an attractive nuisance or things like that.

But I think there are a lot of ways that we can integrate things from an interdisciplinary perspective, child development specialist, biomechanist, get a lot of people involved to look at it differently than we have traditionally.

We did a study where we tried to segregate people with disabilities from a group of young children statistically along multiple measurable metrics. And the only place that we could find statistical significance was the size of the hand and the grip strength. In terms of dexterity, in terms of all kinds of pinch grips, we couldn't statistically segregate them.

So I think we have an opportunity to use data to design more effective systems in creative ways, like you're saying.

DR. MENDELSON: Yes. Taste, I think would

be a good one. Can I borrow your kids? I have a bank or two, and I'd like to borrow your children. And I have some things I'd like to check out.

DR. BIX: Have them taste your drugs?

DR. MENDELSON: To open things, to open things.

DR. LOSTRITTO: Just to get us back on track, I think the question is focusing on comparative claims of drugs, so this one or that one is better. We normally don't have that right now, child resistant. So I'd like to point it at that, what studies have the most for assessing comparative claims of child resistance.

DR. STAFFA: Dr. Scharman, did you have a comment about the actual question?

DR. SCHARMAN: So I'm interested in the packaging, where we look at one particular manufacturer's packaging, whether 80 or 85 percent of the people can get into those packages.

Has that industry ever looked at one particular -- using that method in a different form and looking at one type of blister pack versus

another? The kind where you have to take the cardboard off, and then it's the foils, or the ones where you have to peel it, and it's the thin paper versus the ones that are almost like cardboard?

So there are multiple different types of blister packs. And have we ever looked at studying different types within that same cohort of children?

DR. BIX: The data is available. The problem is, it's very frequently proprietary, so the company will pay the testing organization, and it will be held in confidence and not published.

We in my lab haven't done a side-by-side comparison like that, but it would be out there to make that comparison if you could get people to divulge their data.

DR. LOSTRITTO: I'm going to jump in right there because I've actually worked with that before in other areas not related to this topic at the agency. There are ways for proprietary data and groups that have that proprietary data to work with the stakeholders involved and either present it in

a blinded fashion or in some manner that doesn't create a proprietary problem, but still allows for the scientific veracity of the data that they made available.

So if that data is there and it's helpful, it would be useful to find pathways to get around that particular block.

MS. WHALLEY BUONO: So just on that issue, I think it's important to consider things that are tested as F equals 1 or container, where once you open it, you assume failure. And then anything other than F equals 1 is pill in hand. So if it's F equals 3, the child's got to expel 3 pills.

The problem with that is that children tend to lose interest, so it's really not the best evaluation when you start F writing. So we test all of our packages at F equals 1 as containers because the child may open the blister, it's foil-backed, and they just simply lose interest after they expel one pill, which really doesn't get to the meaning of the protocol.

So as far as the proprietary data, what

happens is it's iterative. So the package goes in. If it fails, the designers take it back and design the package such that it won't fail. So I'm not sure you could try and do a head-to-head based on those iterative proposals because they become moot once the package is redesigned.

I think the only way you could do this is, really, what we're talking about as package misuse. So we're talking about a package that has passed CPSC protocol, then goes into the home, and it's misused. It's either left open or it's left with a child unattended for a protracted period of time.

When you think about how to design a head-to-head trial for packaging based upon misuse, I can't think of an ethical way that you could possibly get that done.

DR. STAFFA: Dr. Budnitz, did you have a comment?

DR. BUDNITZ: Dan Budnitz, CDC. I think my only comment is I don't want to get lost in the forest for the trees. If we had a medication that reduced hospitalization by 65 percent, I think

that'd be impressive, and I probably would be able to retire and fly myself to Switzerland every weekend. I think we're getting a little bit lost in the details.

DR. STAFFA: So what I'm hearing is when we talk about unit-dose packaging, there seems to be a connection. Again, this is just the way I think because I'm in the post-marketing world. There's a connection between what we know about the testing that goes on pre-marketing with the performance of these things in the real world. We've seen data to actually show that.

So my question is, do we have that link with other kinds of packaging or disposal solutions? Because again, I'm just not familiar with that, because, again, that could also be low-hanging fruit in this area if there are other solutions that are out there, like for example some of the disposal solutions. I'm just not sure.

Do we have any kind of data in both settings, again, as starting places that then serve as models for other products? Dr. Green?

DR. GREEN: Namely just the flow restrictors. There was a study done in daycare with the flow restrictors as well for the acetaminophen stuff that Dr. Geller did at the Georgia Poison Center, so I'm just throwing that out there. Methadone is another product that has a higher rate of the pediatric exposures, and there's a lot of liquid products in there. So that will be another consideration.

That's why maybe the unit-dose packaging is a better way to go than, say, a blister pack, because you are going to have to consider some of the liquid medications as well.

DR. STAFFA: Dr. Twillman?

DR. TWILLMAN: This is more of a, I guess, philosophical question, but is there a good enough level of child resistance? If we're already at 80 to 85 percent, how much more incremental improvement can we expect to see? How long are we going to chase the perfect and not allow ourselves to do something that's already pretty effective?

So is it possible to, a priori, say that a

certain level is adequate, and beyond that, the comparisons really don't matter?

DR. STAFFA: We are actually routinely asked to set those kinds of thresholds.

DR. LOSTRITTO: We only have about 5 minutes left of this particular portion of the session, and I'm being advised we should move on to question 4, if that's okay.

Question 4, this touches on some of the things that came up, but maybe we'll extract more clarity and detail in controversy.

Are there existing post-marketing data sources that could be modified or linked together to capture packaging exposures in children and outcome claims, accidental exposure, accidental poisoning, deaths due to overdose and accidental poisoning, et cetera?

DR. STAFFA: Dr. Bateman?

DR. BATEMAN: So I think this is an area where healthcare utilization data or claims data could be quite useful. There are family IDs that allow linkage between parents and children, and I

could imagine constructing cohort studies where you would compare within families or between families that are dispensed and opioid that comes in the newly packaged form and the traditional packaging, and then subsequent rates of hospitalization for some of these outcomes in the children. I think those would be relatively straightforward to conduct.

DR. STAFFA: Other thoughts? Dr. Cox?

DR. COX: Yes. This is back to question 4. This may be a little bit out there, but one of the things that we've used in investigating child deaths is photographs of the scene.

Thinking about the issue with poison control trying to collect data about what exactly happened in the moment when you are trying to treat a child as opposed to having the parent take some photographs later of the package, the scene around that package, many times what we'll find with the child death investigations is that there are just so many other things in the scene that are informative about what really happened here.

So a little out there, but it is very interesting qualitative data.

DR. STAFFA: Ms. Whalley Buono?

MS. WHALLEY BUONO: I will just add one thing, is that stigma is a big part of this reporting process. So if you envision being a parent whose child unfortunately gets access to your medication, you might be reluctant to confess to the healthcare providers, especially if you don't see a particular benefit in doing so.

So I think from a behavioral perspective, we have to think about the fact that it's not a particularly attractive thing to tell someone that you left your child alone with your medication, particularly if it was unsecured.

DR. STAFFA: That is a great point. Dr. Spitznas?

DR. SPITZNAS: The other thing along those lines is, frequently, people are criminally investigated for these kinds of things. And I think that there is a great deal of variability between what the coroners and the mental examiners

do, what ends up getting written on the death certificate information, and what kinds of information they collect.

So I would be more inclined to be looking at something like the hospital setting and the accidental non-fatal overdose situation as opposed to the fatalities, because I just think that's a really difficult path to be going down.

DR. STAFFA: Dr. Budnitz?

DR. BUDNITZ: So Dan Budnitz, CDC. I was thinking about these connecting administrative databases for this purpose, and I would like for something like this to work.

I think one of the things that we're challenged by is administrative diagnostic ICD codes that just do not define very well the product or the other products we're interested in.

For example, there's no ICD code for buprenorphine poisoning. There's general opioid overdoses, which actually also include heroin. So when you make these studies, it's going to be very complicated to try to tease out. You're going to

have to go back to the charts if you really want to do any of these studies. I think the administrative data can be screening data, but it goes back to chart review [indiscernible] to really understand what's happening.

Audience Participation

DR. STAFFA: That's a great point.

Now we're going to move to the audience participation portion, so if any audience members wish to speak, just like yesterday, please line up behind the microphone. There's a staff member to help you. We ask, again, that you focus your comments on the topic of the session.

You'll be given up to 3 minutes to provide comments. The light system that you see in front of you will keep time and notify you when your time is complete. It works just like a traffic light, so if it's green, you can just keep talking. If it's yellow, you need to be finishing up because you've only got a minute left. And when it's red, you should immediately return to your seat.

(Laughter.)

DR. STAFFA: So with that, the first speaker, could you introduce yourself?

DR. HOLADAY: Good morning. I'm Dr. John Holaday. I really appreciate the contributions of each of you to this very important question. One of the things that's been amply reviewed is that drug overdoses and deaths often begin at the medicine cabinet, where the leftover drugs are not properly disposed.

One finds in looking at the different regulatory agencies that there are different recommendations. For instance, the FDA has said to flush the drugs and get rid of them that way. And of course, the Environmental Protection Agency says no way. The DEA says get in your car and drive to the nearest collection facility and turn the drugs in there.

There's an alternative solution, one which enables the permanent destruction of the drug in the vial in which it is dispensed so they cannot be extracted for abuse and will not leech into landfills. And my question I guess is, is there a

singular agency that has control over getting rid of leftover drugs that can help stop the overdoses and deaths from these products such as opioids? Thank you.

DR. STAFFA: Thank you for your comments. The next speaker, please, please introduce yourself.

MR. SU: Hi. My name is Hoong Su. I'm with Shire Pharmaceuticals. I'm a packaging engineer and have some questions.

We talked about, of course, correlation doesn't equal causation. We all know that, and there's a lot of data out there on that, and I heard about teasing out of some more studies. So based on the picture that was shown on the 65 percent reduction of the incident, the ED -- I don't know what ED stands for, but it must be bad.

DR. STAFFA: Emergency department visits.

MR. SU: Thank you. And there is a drop on that; very interesting. But I also saw the picture in that diagram that shows a bottle, and that's typically a pharmaceutical bottle that goes through

a supply chain, and it goes through the pharmacy, and the pharmacy would typically dispense it in a different vial. Usually, the patient doesn't get that whole bottle.

So the question on that is -- and one of the reasons why is that it typically comes in a 100 count or 120 counts, and you don't usually dispense that in a whole bottle. That's why I make that statement there.

Regarding the data, more data on that, I guess it's more important to find out a little bit more. Is the unit dosage the one that is reducing it, as Liz mentioned, or is it the re-closure of the container, closure from the pharmacy bottle?

That's the first point, get more data on that part of it. The second point I want to make is in the European markets, they tend to do a lot of blister packs. And the reason I know that is because they sell a lot of blister machines in Europe for the oral solid dosage. In the U.S., it's typically a bottle.

So if we want to get additional data, one of

the studies that we want to consider is looking to the comparator between the geographic comparison, see what kind of data they have and what kind of data we have related to ED.

So that's a supply chain kind of question and also additional data that the panel can look into that would help us to drive to a better conclusion.

DR. STAFFA: Thank you very much for your comments. Next speaker, please?

MR. SANER: Thank you. Good morning. I'm Bob Saner. I'm here appearing on behalf of the American Academy of Pain Medicine, the recognized physician specialty in pain medicine.

The academy is very supportive of what you're all trying to do here today, but at the same time, I think we're concerned as all of you are about unintended consequences. The point was driven home for me when Dr. Bix said they couldn't come up with a childproof packaging that didn't also defeat access to the product by people with physical and cognitive impairments. And a very

significant percentage of both chronic and acute pain patients suffer from comorbidities that involve physical and mental impairments.

So I know you're all very sensitive to this. I just want to put the academy's two cents in here to say be very, very careful that whatever you do to defeat inappropriate access to this product doesn't at the same time prevent people who are properly prescribed these medications from getting to them.

I will throw in one personal example of that. I'm a reasonably healthy old guy, but in the past 15 years, I've had surgeries on both hands, a total of four surgeries. And at the end of those, for a period of weeks, and in one case a couple of months, I couldn't even move my fingers on one hand. And I was prescribed pain medications, fortunately which I didn't have to use in most cases.

I was prescribed pain medications in each of those four surgeries. And if my wife hadn't been there, I wouldn't have been able to get into any of

those packages of the type you're using now, much less ones that have enhanced characteristics that will prevent inappropriate access to them.

So as physicians say, first do no harm. Thank you.

DR. HERTZ: Wait. Hello? Just one moment. This is Sharon Hertz from FDA. So we are always concerned about unintended consequences. What do you suggest as an answer? I mean, we're aware that there are pluses and minuses to many of these, but when we're dealing with a concept of accidental exposure, particularly when it comes to kids, how do we strike the balance?

MR. SANER: Yes. I don't have the answer, although the academy would be happy to try to engage with you and give you their best thinking on it. In other contexts, the academy has advocated for what I will call in laymen's terms, escape-valve solutions.

For example, many states and the federal government have been dealing with this question of limited number of pills in each prescription or a

limited dosage in each prescription. The academy has consistently advocated for some sort of exception mechanism so that certain types of patients would not be subject to the same limit that might work appropriately for the large majority of patients, but not for every patient.

Perhaps in this context, the prescriber could have some flexibility with respect to prescribing a packaging that might be more appropriate for the particular patient as opposed to the packaging that might be most protective in the context of large numbers of patients.

That's just kind of an example of how you might approach it.

DR. HERTZ: Just another follow-up, if I may. In the context of having that sort of escape-valve mechanism, if a finding supported a more general approach, but there were some allowances for that, would you advocate for having more protection with the escape or some other combination? I just want to make sure I understand the position.

MR. SANER: I think it's hard to respond in the abstract. You need to know what exact proposal is on the table. I think the general principle is you need to maintain access to the product by the patients to whom the product is appropriately prescribed. You have to weight that heavily because, after all, the physicians I'm here to represent today are in the business of treating people who legitimately need these medications.

DR. STAFFA: Thank you. Just in the interests of time, just because we all have biological needs, I'm going to ask if you have thoughts, please we are very interested in ideas. And I've pulled up question 3 that we didn't exactly get to. But if folks have ideas, and if you're like me, they come to you at 3:00 in the morning, please submit them to the docket. We'd really love to hear more and to be able to follow up and chat with you. So thank you. Next speaker?

MR. STRASSBURGER: Thank you and good morning. I'm Phil Strassburger with Purdue Pharma, and there was a question raised this morning about

disposal systems for opioid patches. And I wanted to point out that there is a disposal system that's currently available, and it's on the market. It's a disposal system that's currently being used by Purdue for buprenorphine patches. It's being used both for the name-brand product and for authorized generics.

It's a relatively low cost disposal system. It's off patent, but it's not without issues. Larger boxes are required. But it does seem to have been accepted by the distribution system, at least with the buprenorphine patch.

I think this relates to the fundamental question that Dr. Throckmorton raised this morning about whether we should rely on incentives or requirements in order to implement certain types of packaging or disposal systems.

When you look at the fentanyl patches, which I don't believe are currently using a disposal system, despite the fact that it's been available for a number of years and the fentanyl patches have been available for a number of years, but it has

been picked up by the fentanyl patches, I think it leads to really a legitimate question as to whether or not it will be used for these types of products unless it's a requirement. Thank you.

DR. HERTZ: Excuse me, a follow-up. This is Sharon Hertz. Do you have any data on the extent to which patients actually use that with patches that have it accompanying it in the packaging?

MR. STRASSBURGER: Dr. Hertz, as I stand here, I don't know whether we have that data or not, but we'd be happy to submit it on the docket afterwards.

DR. STAFFA: If you find it when you go back home, we'd love to have it submitted to the docket, yes.

MR. STRASSBURGER: Yes. We'll look into it right away and submit what we have.

DR. STAFFA: Thank you.

MR. STRASSBURGER: Thank you very much.

DR. STAFFA: Thanks for sharing your comments. And next speaker, please?

MR. LANGLEY: My name is Nathan Langley with

Safer Lock, and I have some data that you guys might be interested in when considering the different options and then also a recommendation that might inspire people to innovate in the packaging.

So again, I'm with Safer Lock, which is the combination locking cap, which was shown in a couple of the slides there, and it is used for dispensing at this time on a very small scale, and then also given away through a pharma company with their specific medication or at least made available to them.

You brought up the CPSC -- great presentations by the way. The CPSC type product, we are CPSC certified, so I brought up our results, and I was kind of curious on what that came out with. After demonstration, zero children got into the cap. The adult test, 100 percent of adults were able to get into it.

Then I also noticed that there was an ease code on there, on how easy it was for them. And 97 out of 100 found it easy or very easy to get into

the locking cap, which was ages up to 70, I believe it is.

Then something that I think might inspire innovation in the industry and have a potential for a larger impact on this opioid epidemic is, for us, it was a personal experience, but there's the accidental exposure, age 5, which is what the current requirements are, but maybe adding another population, which is maybe 12- to 17-year olds, which has a high rate of diversion.

I don't know how you would measure that, but consider maybe making that some other sort of certification for that because I know that's another population, which I think would bring other players into the market in great innovation and packaging. So that's my comment.

DR. STAFFA: Thank you for sharing that. And again, if you could share the details of that to the docket, we'd be very interested in learning more about that.

MR. LANGLEY: Yes. I can post it.

DR. STAFFA: Thank you. So I'll remind

everyone the docket will remain open until February 12th, and we would love to hear anything you didn't get a chance to bring up today in that way.

Irene, I'm assuming we're going to take a break. I'm going to beg you for a break.

(Laughter.)

DR. STAFFA: And what time would you like everyone back?

DR. CHAN: So if everyone could please be back in the room at 11:05, we'll start promptly. Thank you very much.

(Whereupon, at 10:53 a.m., a brief recess was taken.)

DR. TRAN: Please start to take your seats. We will restart session number 6.

DR. CHAN: Hi, folks. If I could have everyone please sit down, we're going to get started here. Thank you very much.

The discussion this morning, definitely very lively and very engaging, so we really appreciate that and hope to continue that momentum for the rest of today.

Coming into the next session, we're now going to shift topics. We spent the morning talking about accidental exposures. We're now focusing on the next circle, if you will, in the wheel we've been looking at, which is looking at misuse. And to get this teed off, I'm very excited to have Mr. Walt Whitman here with us as part of the -- what did I just say? Walt Whitman?

(Laughter.)

DR. CHAN: Wow, a slip. I'm sorry. That would be something quite miraculous, and I cannot produce that for you. I'm sorry.

Walt Berghahn, who I am equally very excited to have with us here today, who is from the Healthcare Compliance Packaging Council, as one of the hats that he wears, and is going to be talking to us. Really, he's done a lot of work with companies and looking at the data that is out there, especially because medication adherence has come up quite a bit.

So with that, I'm going to turn it over to Walt. Thank you very much.

Session 6 Presentation – Walter Berghahn

MR. BERGHAHN: Good morning. It was funny yesterday because a few folks kept referring to me as Dr. Berghahn. I was thinking, I love the field promotion, but it's a little bit much. It's really mister. But I got the ultimate promotion this morning –

(Laughter.)

MR. BERGHAHN: -- when I was elevated to Whitman. Wow. That's really classic.

The HCPC, the Healthcare Compliance Packaging Council, is a trade association that's made up of companies that make packages, machinery, and contract packaging, but it's all focused on improving medication adherence, improving product safety.

From that work, it actually morphed into an opportunity for me to work at Rutgers and create some classes around pharmaceutical packaging, so it's been a really good experience and a really good symbiotic relationship between the two, so I've been enjoying that.

The mission of the organization is quite simple, to advance the use of compliance-prompting packaging, to improve medication adherence, patient safety, and health outcomes. I mean, this is as basic as it gets. We fully recognize that pharmaceutical packaging is a lot more than simply storage. It's about creating a safe effective outcome for the patient.

So before jumping into the data, I just wanted to do a little history lesson. Everybody's got a little caffeine and sugar in them right now. You can probably tolerate a history lesson, so we'll do it really quick.

If you can imagine 1955, and looking around this room, most of you have to imagine it, but some people may remember it. I don't remember it, but I can imagine it.

So if you're sitting at home, and you're watching your television, maybe a little bit of Elvis or maybe a little bit of President Eisenhower, and your phone rings, and on the other end of your phone is your pharmacist, Sven Swedberg

from Swedberg Drugs. He says, "Walt, I've got your prescription ready."

So you jump in your car, and you head over, and Sven is really excited because he's got this brand new package to present to you, and he just can't wait to put it into your hands, and here comes this little plastic amber vial from 1955 when it first came out of the market.

So obviously, we've got a very different world today, where your doctor's going to get on CPOE and put in your prescription. You jump in your Prius, immediately pick up your cell phone, maybe check some emails or stocks as you drive over to the pharmacy, using GPS because we can't find anything without GPS anymore. And you get there to find out that your pharmacy has a drive-through Dunkin' Donuts, which is really nice because you can pick up something healthy while you get your prescription of lovastatin, which comes in a little amber vial. And that's 62 years of evolution in America.

So we're here to talk about opioid

packaging, but we've got a much broader issue to deal with at some point in time. So the question that's been asked over the last day and a half is, can packaging help with the opioid epidemic? And the answer is yes, but there's so many different facets of the problem. You have to decide which problem you're going to target, and there's different tools and solutions, which will help address those individual problems.

From my perspective, I think that when you talk about calendarized blister packaging, the most effective point is tracking of dosing times, the visibility of somebody trying to take or taking an unintentional dose, which may not be necessarily captured by the patient, but by a caregiver, creating a communication tool between the patient and caregiver.

There's visible evidence of doses taken. It's not in a bottle. It's not, gee, how many are left in this bottle? And when you talk about then tracking when doses go missing, it's the same point, visible evidence of doses missing.

There's really no way to get that. I haven't seen any capped closures that can count doses that come out of a container. Maybe there could well be that technology, but I personally haven't seen it.

So these are the key points. We're quite accustomed to evolution in packaging to meet the end user requirement. In every other market, we see changes over time to deal with facilitating proper use of a product. It's all around us.

It's not that it's unusual for pharmaceuticals. We use it in many places. When you talk about transdermal, this is the ultimate combination of a package and drug delivery system. I mean, a patch is effectively a pressure-sensitive label. It's just a very smart pressure-sensitive label.

You deal with epipens and the injectors. This is a multi-component package, but at the end of the day, it's still just a very, very well designed effective package for delivering the proper dose of a drug, even into inhalers. It's

all the same things. These are just complex, well thought out, well designed packages to present the proper use of a drug.

So why is it missed, solid-dose pharmaceuticals, and what can be done to change it? We've been discussing this for the last day and a half, so I'm not going to go through this in individual detail. But you can see the idea of presenting doses in a way that a patient and a caregiver can understand what's there, what hasn't been taken.

The nature of the beast, the nature of these packages when you start dealing with an F1 CR package is that you're going to present billboard space. And that billboard space can be effectively used to help teach the patient, help the caregiver understand what's there, a communication tool between the two. There's a lot of real estate, and it can be used to help.

So going back, gosh, 11 years now, almost 12 years, even the IoM, when they released this report, which was a huge thick report, buried

somewhere in the middle of page 250, they made this statement that, yes, they even then in 2006, saw the benefit of using a calendar blister pack to help people reliably and safely take their medication.

That might lead you to believe that maybe this is something new, but the reality is that the idea of a compliance-prompting blister pack goes back to 1960, when the first birth control compact was released. So this is 57 years old, this technology, this concept of helping people take doses in a regimented fashion.

So what's out there? What kind of data is out there? This is a very broad paper that was done, and I'll get into some specific instances. But this one looked at 17 studies and showed that any variety of packaging interventions was having a positive impact on the medication adherence.

In this case, it covered 22,000 different patients over 17 studies, 52 different reports, and everything showed that there was an effective increase in adherence.

Now, again, in this situation, we're doing something a little bit different than adherence, but adherence is there at the base. You want people to be taking their drugs properly. We're also trying to accomplish some other goals along the way.

So let's get into some specifics. The thing that I find interesting about this is that there's some good ancient history here. This is 33 years old, this study, and here it was.

What they looked at was this particular product and two groups of women who were tested, and there was a dramatic difference between the compliance in the research group using a calendarized blister and the control group just using a normal amber vial; 82 percent versus 30 percent, just dramatic.

Another study not quite as ancient history, coming forward about eight years, the thing that I found interesting about this one and the data -- as you look at the compliance rates at 10 days, 1 month, and 3 months as you go down and, yes,

there's a dramatic difference between the control group and the research group, but it bothers me that at 3 months, we were down to 48.9 percent compliance, and yet that looked good compared to the control group using a cap and vial.

More recent -- and this one actually, the HCPC had involvement in this through one of our member companies. PCI and Cardinal Health had organized and helped get this study performed by Ohio State, looking at a blood pressure medication.

This one, the thing that's interesting about it is that they took it to the next step and looked at not just the performance of the package and whether or not there was improvement in adherence, but they were looking at the actual performance in blood pressure.

So if you look at the bottom there, the folks using the compliance package, 50 percent of those using it had an improvement in the diastolic blood pressure versus the control group. Only 17 percent had any improvement in the diastolic blood pressure.

That's a scary, scary statement, that people using a cap and vial, that 83 percent of them had no change in their diastolic blood pressure. And then on the systolic, it was a little different. You had 57 versus 40 in the study group versus the control, but there's still a pretty dramatic difference in any improvement and any benefit from this drug, which we as a country are paying a tremendous amount of money to have patients taking.

The thing that you look at on the top there is that in the study group where you had an 80 percent accuracy on refill rate versus 66, that's not a big difference. Statistically, it's a big difference. It's 14 percent. But when you look at the difference on the bottom of the percentage of patients seeing improvement, the spread is much further, meaning that somewhere between 66 percent and 80 percent accuracy, you actually saw the benefit of the drug starting to take place.

This one I liked because if you start with a control group where there's absolutely no

intervention with patients and you go to a reminder card simply just to try to get information, messaging in front of the patients, you go up 7 points, a compliance-prompting package, up another 4 points, and then put the reminder together with the package, you jump 12 points and up to 87 percent.

That to me is, the big messaging for this group is that we're not looking at any one solution. There's no one solution that's going to solve this problem. It's going to be a combination of different features and actions, which are going to, at the end of the day, improve performance for people across the board.

A more recent study, this goes back to about 2012, this one had a very wide base of use, again looking at a compliance format, looking at a package which had good messaging front and back, and fairly significant improvements in performance from one to the other.

Most recent -- Dr. Bosworth is sitting over there. This was actually his work. The use of

graphics on this package were fantastic. Look at the messaging. Look at the warnings. What's good for your cholesterol; what's bad for your cholesterol. Good instruction on the bottom of the pack.

This was referenced earlier that in this case, the CR function is on the external package, so when you slide that blister out, you're dealing with a simple push-through foil, which requires very minimal dexterity to accomplish. And getting the outer pack open requires a squeezing mechanism on the outside.

So it's a great example that, yes, you can use blisters and, no, it doesn't have to be this horrendous blister that requires a pair of scissors to gain access. The interior blister is a simple push-through foil, but the exterior package is providing the child resistance in this case, more messaging able to be accomplished on the back of the blister, including the calendar labeling on the blister card itself. The data results from that study as well were very impressive.

So there's been discussion about, well, what's next step? What else can you do with the packaging? And there are companies out there who have integrated electronics via RFID and/or near-field communication. And the way it's done is that you have basically a printed circuit, if you will, behind the blister package, and when you punch a dose through, you're breaking that circuit. And you're either capturing the dispense event on a chip that's embedded in the package, or if you're using near-field communication, then you have the opportunity to communicate with the device.

So that dispense event can be either communicated to your cell phone, to a computer, to some other device that's managing it, and then you can get some real-time data sent to the patient, the caregiver, a pharmacist, the physician.

The importance of that concept is that if you're trying to prevent pilferage, you're trying to prevent people from taking doses that should not be in that pack, there is a way to do it. There's a solution. You can do this. This can be live. I

guarantee you, it's the most expensive way to do it.

But the point that I've been trying to make in talking to folks in the last few days is that all of the tools are out there. There are fantastic tools. We can do a lot with packaging. We need to understand which problem we're attacking, and then we can say here's the solution that fits that need.

But there's very little that hasn't been developed, meaning that all of the problems that have been discussed in this room, packaging can take care of it. We've got solutions. Can we afford it or do we want to afford it? Those are really the two biggest questions.

So when we talk about it in a broad sense, visibility, visibility I think is the biggest thing that the packaging can do. It can provide visibility for the patient, for the caregiver. It has the ability to help educate about risks. You can create the opportunity for self-recording of dispense events, or visual recording of dispense

events, or electronic recording of dispense events, any of the three.

The ability to visually capture pilferage, what's happening, there's doses missing, what happened, where did they go, these are areas where I think packaging can do the most good. There's no way you can stand here and say, well, packaging is going to help reduce somebody who's already addicted to the product. I don't see the opportunity, personally, that packaging is going to help them.

We're talking about prevention. Certainly, we talked enough this morning about protecting children. That's the most basic simplest function we can accomplish, the packaging, hands down, it can be done. This is a little more complicated, but it's there. The tools are there.

So different concepts that are out there, these are just designs that were done by some companies. We ask people to give us some different concepts and ideas. You can see it's about short regimen. We talked about having shorter initial

regimen delivered to patients.

Even in this case, doing something as simple as giving a patient the space to record when they took the dose, manual recording. That's about as basic as you can get. It still can help the caregiver understand what has or has not happened.

But beyond the fact that we're trying to solve a very focused problem, I think we need to consider what is the package doing in the broader supply chain, because we talked yesterday very briefly about the Drug Supply Chain Security Act and the fact that it's about preventing the introduction of counterfeit and gray market drugs in the market and also the fact that we're just trying to protect drugs basically.

So if you consider our current methods, I think there's a lot of room for improvement. And I think the conversations in this room are taking us in a good direction, but I can guarantee you it's not going to stop at opioids.

Somebody made a very good point this morning about one of Dan Budnitz's slides, that every other

drug on that page was toxic at dose 1.So we'll have a conversation about opioids, but we're going to have to have a conversation about other products very soon. So thank you.

(Applause.)

Panel Discussion

DR. AIKIN: Thank you, Mr. Berghahn. So I'm pleased to help Dr. Staffa moderate this session on pre- and post-market data and labeling considerations for misuse. I think if we could start with the first question we have for the panel. I assume we're going to put that up. Here we go. Great. It's already up. Thank you.

So our first question is -- and we're going to focus first on pre-market. Are there existing methodologies, for example human factors or randomized trials -- this is not a complete list -- that can be utilized to study whether packaging, storage, and disposal options can minimize misuse of prescription opioids in the pre-market setting? Who would like to start us off?

MS. WHALLEY BUONO: So if I understand how

we're defining misuse, there's unintentional misuse, non-adherence, and then there's intentional misuse, which could be the patient, could be a third party.

There's proven ways to study unintentional misuse, non-adherence. And those are out there, and that's everything from human factors to panel engagement, to pharmacy claims data analysis, to prospective clinical trials.

So that's all out there. I think, in my mind, I can't envision away -- and it's not my area, but I think it would be very difficult to design studies around intentional misuse, other than barriers to entry perhaps.

DR. AIKIN: As a reminder, can you state your name before you speak? Thank you.

MS. WHALLEY BUONO: Apologies, Liz Whalley Buono.

DR. CHIAPPERINO: I would just like to clarify, you wanted to bring misuse by a third party into that. And I think, in our context, we want to differentiate between third-party access,

which is more abuse, and we think of misuse as for therapeutic use.

DR. AIKIN: Ms. Cowan?

MS. COWAN: Penney Cowan, American Chronic Pain Association. Just coming from the space of people living with pain, there's a lot of people that are dependent on opioids as part of their treatment plan, and pain is never consistent.

So there are times when they may have to go do something or have an engagement, and they may take more than prescribed only because of the fear of, if I get there and my pain medication wears off, I need to take more.

So when we're looking at this broader scope of misuse, keep in mind that people living with pain, there's different reasons for why they may use different doses at different times, and a lot of it is just the fear of the pain itself.

DR. AIKIN: So to clarify, it sounds like what I'm hearing is that it's very important for us to keep in mind intentional versus unintentional misuse.

DR. SPITZNAS: Correct, yes.

DR. STAFFA: Also to get the kind of feedback from these more ethnographic type studies before we program in something that would not allow you to do that if it was something that was needed.

DR. AIKIN: Dr. Twillman?

DR. TWILLMAN: Bob Twillman. Just adding to the last discussion, intentional misuse, you also have to take into account what is the motive for that intentional misuse, whether it's to keep your pain under control as Penney was talking about, or whether it's to achieve some other state of being.

DR. AIKIN: So with that in mind, are there certain methodologies that lend themselves to this?

DR. SPITZNAS: I think EMA, ecological momentary assessment, paired with diaries is something that can commonly be used to look at the rationale for what people are doing and when people are using.

Another thing that we haven't talked about but that I'm familiar with is Ed Boyer, who is at Harvard now and was an ER physician, has a

technology to tell if a pill has been taken by the patient that uses RFID. So it's not just a matter of pulling it out. There's something around activating the RFID battery via stomach acid. And he was able to look at adherence and found very poor adherence in a number of people that he was examining who were on opioids.

So that's just another thing I haven't heard of today that I just wanted to throw out, just taking it further. You could have a dual step, including the packaging, letting you know when it was open and then letting you know when the patient actually took it.

DR. CHAN: Yes. So I just want to make sure to kind of prompt the conversation a little bit, because we've asked a very broad question. Right? We're like what are any methodologies that might be out there? And we've sort of listed a couple here, and I know that they've been echoed.

So let's take an example. Someone has developed a product that they claim can actually address misuse here. And because we're raising

this unintentional versus the intentional, where there may be different considerations, let's start with perhaps what some may view as perhaps the slightly less complicated approach, and we'll look at that unintentional misuse.

This is where we talked a lot about there is already data in the adherence space, but we've also talked about, we need to look broader than just the adherence question alone because there's also other things we need to consider around critical messaging for things that provide warnings for what can this impact, you and household members and things along that line.

So thinking about that example in mind, does that help for people to start thinking about, okay, what do I want to see if this was coming to me, and someone is claiming to me that this actually helps in unintentional misuse. Let's start there. Then what is the data I want to look at, and what methodologies that already exist can I leverage here, that I think is important to leverage here to start testing that and looking at that?

So let's get that conversation going.

DR. AIKIN: I think we also had a comment.

DR. STAFFA: Yes. I think Dr. Bosworth wanted to comment here.

DR. BOSWORTH: So I'll try to answer Dr. Chan's question just recently, but I also add a little bit more to it. Most of my work has been more in chronic disease, which does include sickle cell. So it's not dichotomous between intentional and unintentional. In fact, we have published data demonstrating that there's actually pretty good overlap.

Frankly, when we think of intentional, the unintentional tends to be the forgetfulness or something along those lines. The intentional could be, as somebody just mentioned, where I am out and I may take an extra pill or something along those lines. So it varies from day to day, moment to moment. So some of the devices that are available do allow us to track the frequency.

There was a presentation at the White House that I was asked to attend, and one of the speakers

actually had a device that was also related to geospatial, and they could track when somebody was -- actually, this was in substance abuse. When they were going to that area to get the drug, they could track what was going on. And I know your colleague, Rob Califf, works for Verily, and Verily can tell you exactly where we all are at any moment.

So there are these mechanisms out there and companies that are developing these opportunities that allow us to track what's going on.

I just want to point out that when we think of intentional, we have 40 percent of our population when we look in chronic disease, that they actually will report that. So you can go from the level of all these complex devices, but frankly, when you're asking somebody how are you using your medication, the word "intentional" has a lot of derogatory value to that.

If you ask them how they're using the medication on a day-by-day, you'd see that there's a lot more. We would define it as intentional

misuse. They may not.

So I think there's a lot. We simply start off with self-report. If someone is telling us they're not using it the way that it was supposed to, that's a starting point, before we get into all these expensive devices. And what we would do is actually target and entail our interventions based upon those responses.

So depending upon what they're telling us, then we can convey information. So whether we use pharmacists, we use case managers, we work in Medicaid, the VA, we have infrastructure that we use to script content so that we can then have a person communicating the information to them.

So there's obviously variations with regards to opioid, where there is purposely misuse and something different than with the hypertension, cholesterol, but there are still some overlaps that I would say could be useful to consider.

DR. STAFFA: Dr. Green?

DR. GREEN: Dr. Bosworth, I completely agree, and my comments are going to be in that

regard in terms of the root cause analysis of therapeutic intention. So whether it's intentional or unintentional, I'm not sure those are the right words, but for therapeutic intent.

That I think is a much easier way to get to the patient experience. There are very different issues, but we have done some work in over-the-counter analgesics of getting at why have you taken too much. And generally, you can find those root causes, which are they forgot or it wasn't working. They might have grabbed the wrong med.

But knowing those root causes, I agree we need to know those before we can design the interventions and the devices, and letting that data dictate the technology instead of the other way around, because technology is very cool and it's exciting to get into a lot of things. But I can see, for instance, the calendar working very well for a medication that has a consistent dosing regimen, but not for PRN, which we know, to Penney's point, is really how a lot of these medications are being used.

DR. STAFFA: I just want to complicate it a little bit more, because what I'm hearing is that there's going to be distinct differences between those prescribed these medications for acute pain and what we think of as intentional or unintentional. Those are probably not the best words, but use and patterns of use we may want to be aware of versus the patient with chronic pain, that these may be very different pictures.

So I'm going to suggest, if people have ideas of ways to differentiate that in the way that these are evaluated, maybe that's another element here we need to be considering, although it can be difficult to know when one leads into the other, right?

DR. GREEN: I think the diary study might have already been mentioned, but that behavioral health-type of surveillance has been done, certainly with over-the-counter pain medications, and a similar model may be able to use it.

You can set up anonymous online real time, so they're entering into their smartphone or

tablets as they go. That real-time data capture that allows for some confidentiality, anonymity seems to be a pretty good blend.

DR. STAFFA: Dr. Mendelson?

DR. MENDELSON: Yes. I'm going to try to answer the part are there existing methodologies. And there's a lot of methodologies out there, but most of them are actually kind of ancient and don't take advantage of modern technology well.

In this meeting, we don't have anyone -- I'm a tech developer these days, but other than me -- I'm not a very good tech developer. Other than me, you don't have anyone.

So I think, actually, you're going to want to reach out to the engineering community and actually find out what they can do, and try to focus them because they'll do everything, and none of it will have any meaning to you when you are finished if you don't focus. They have no idea.

I have worked with a lot of engineers now, wonderful, smart people, a lot smarter than I am, but they don't know the questions to ask. So I

think that's essential that you reach out to the engineering community. And there's a robust one that participates through NIDA and other groups that actually understand something about addiction.

Amongst the human factor side, a lot of us now talk about this really weird word called "gamification." That means that you can really think of it more as the user experience, something that they actually like doing, that patients enjoy, that people enjoy, and will do for you repeatedly because they like it.

I think that's going to be a huge part. It should be a huge part of the discussion of improving adherence and tracking systems, that they should be things people want to do, and you can build those. You can actually build those. There are people out there who really are interested in that question.

Like for medications, we've been talking for our products about cadence, the cadence of use. That's an interesting word. Can you get a score? If you have your little Apple watch, you have your

little activity monitor on it, those little three donuts. Those are very carefully thought out, interesting ways to express adherence. They're adherence to physical activity regimens, but they could be medication adherence regimens and outcome regimens.

So you can do this, but I would start fresh with actually engineering, and if you want to really do this nice, you can be in a panel with the engineers, spend a few days, maybe even a hackathon, bring some engineers in, some clinicians, some researchers, and then build. And probably in four days you'll have a workable prototype.

DR. STAFFA: Interesting. Ms. Whalley Buono?

MS. WHALLEY BUONO: So we have electronic monitoring and back-end data analytics arm, and we know from the work that Bernhard Renz has done in, I guess, over 500 clinical trials, that generally people tend to over-report their adherence in diaries and in counseling.

Then when they are confronted, if you will, with their actual adherence patterns, you start to unearth things around day of week, habit, behavioral causation, that sort of thing.

So we know that there's incredible value in these adherence pattern analyses, and we know that 80 percent, let's say, adherence, can look very different. It can look like long drug holidays. So the 80 percent number really doesn't capture adherence behavior.

The first point I want to make is I think there would be a lot of value in the electronic monitoring space here, but you have to think about how that gets implemented pre- versus post-market, and what is it specifically about the opioid epidemic challenges that would play into that, because that's really only been studied in unintentional non-adherence.

Then the second thing is when you talk about head to head, Bernard has also done some very interesting studies looking at the SmartPill versus the MEMSCAP and electronic fitted monitoring, and

looking at how closely is that proxy event of opening the bottle correlated with actual pill-taking versus ingestion of the SmartPill.

They did that by doing the electronic monitoring, but then also correlating with blood draws. So that's sort of on the other end of the spectrum as far as invasive research, but you can do head-to-heads in the pre-market setting, and they can be very accurate as far as determining how effective is that proxy event.

DR. STAFFA: Ms. Cassidy?

MS. CASSIDY: Hi. Theresa Cassidy from Inflexxion. I just might be skipping ahead a little bit to the post-market or sort of combining some of the conversation in the two as it relates to pre-market setting and trying to identify if there's ways or methodologies to evaluate whether people can break into the particular packaging.

I guess I'm just wondering if there are any parallels to what's done on the abuse-deterrent side and looking at that guidance as it relates to the extraction studies and looking at mapping that

back to the populations of interest.

So we're also mixing the unintentional versus the intentional misuse, so this might come into play as it relates more to people who were in that intentional misuse area with use for illicit purposes or beyond pain relief to get high. You're possibly looking at ways to deal with the packaging extraction, trying to tamper with -- among experienced users as are done in those extraction studies, pre-market might be a model to use.

DR. STAFFA: Actually, that's going to be the topic of one of our sessions. Which one is it, Irene?

DR. CHAN: So our next session is exactly going to be looking at the parallels between the ADF and studies being done there. I think where this gets tricky, and I think even what we see happening now amongst the panel, because of the terms we're using, the unintentional, the intentional, I think there's a little bit of a lack of clarity here.

So I'm just going to refocus that within

this session, our focus is on people who are using this for a therapeutic use. So we're not talking about people who are trying to gain some sort of specific physiological effect outside of trying to treat whatever the indication is, for example, pain. So keeping that in mind, of course, that does I think change the focus.

So what I am hearing, though, is I'm hearing a little bit of this recurrent theme amongst different people about this idea of needing to take advantage of tracking technologies, perhaps, which then open the gateway to the conversations that allow you to tailor what you need to for the individual patients. That's what I'm hearing, and do we have a comment related to that?

MR. WEBB: Kevin Webb, Mallinckrodt Pharmaceuticals. I'm glad you brought that up, Dr. Chan, because I would like to make a comment as we think about recurrent use.

As we look at the data, most prescriptions are for immediate release, but they're also going to opioid-naive patients. For immediate-release,

acute pain, it's episodic. It's going to be short duration, your dentist extraction, et cetera.

So if we put up too complicated of a package for a patient who may use their medication for two or three days, that patient experience can be terrible if they know they're being tracked and monitored, and we're putting a lot of bells and whistles on this.

If we focus on how are we eliminating or bringing down the supply -- we've kind of addressed the fact that this is a significant supply issue. So if we're able to put out a unit of use in only no more than a 3-, 4-, or 7-day package, that by itself is going to have a significant impact on reducing the amount of availability of a product.

But then, if we overcomplicate it, where you now put out a package where it becomes burdensome to get into, you've created another problem on the back end, which has patients either just taking their medication or they're just not going to use it. It's going to be very difficult.

So I don't want to overcomplicate and think

that every patient is going to need some type of advice, especially since we're only talking about patients that are opioid-naïve and this is the first time. What are we trying to do to solve for that problem?

DR. STAFFA: This is Judy Staffa. I really appreciate your comment. I think that that's something we have to tackle, but I also think, though, we have to think about it from the perspective that many, many -- in fact, I think we have a paper coming out that 90-some percent of patients who take long-term opioid therapy, meaning more than 90 days, are actually taking immediate-release products.

MR. WEBB: I agree. So to Penney's point, they can titrate up and down.

DR. STAFFA: Exactly. That's right. The line is kind of blurry, so I think we're going to have to tackle it. And it's going to be very hard to tease out, again remembering that indication is not always on these. So again, if there's ways to think about packaging differently for intended

acute use versus intended chronic use, maybe that's a way to separate, but it will still be challenging.

MR. WEBB: And maybe part of the thought is, instead of trying to attack it from a chronic long-term use/acute use, we approach it from a therapeutic approach, indications, for dental procedures. And we start to kind of ease our way into the process, where a certain type of procedure is limited to certain medications, because generally those types of procedures are episodic or short term. And then it gets us away from the long-term use of chronic back pain, et cetera, because we know that that's more of a chronic condition.

DR. STAFFA: I think the metrics or the patterns one might be looking for that signify that a conversation needs to take place would be very different in those two different groups.

DR. STAFFA: Dr. Izem, do you remember your comment?

DR. IZEM: Yes. Rima Izem, FDA. I wanted

to just go back to a comment that was made about the diaries. I just had a clarification question for the diaries, for over-the-counter. Dr. Green had in mind the actual use studies that are used for over-the-counter drug as a model on top of the sort of examples that are presented in this question or whether there were other studies that she had in mind.

DR. STAFFA: Dr. Green?

DR. GREEN: Dr. Green from Inflexxion. There was a behavioral study done by some colleagues at, I believe, Pinney Associates, where they did behavioral whole surveillance, both an online module, but then they recognized that there were more vulnerable populations they weren't getting to, so they actually hung out in the mall, and enrolled people, and wanted to get at their use of primarily acetaminophen, over-the-counter acetaminophen. I can send you some citations and whatnot and engage them, too, to see if they have any submissions for the docket.

Then also, similar to the pediatric

surveillance, at Rocky Mountain, we did callback surveys from the poison center of adults who had reported therapeutic intent, whether it was intentional or unintentional misuse.

The success rate of the surveys we had with the pediatrics, to Elizabeth's point earlier, the parents were very engaged because they wanted to help other parents avoid having to go through the trauma of your kid getting into stuff and all of that. So our participation rate was very high.

Participation rate for the adult survey was very low. So adults are not as willing to share with you one on one in an identifiable situation of the bad decisions that they've made that led to an acute event that they had call a poison center for.

So I think there might be a little less utility in the callback surveys from poison centers, but I think the online daily tracking and diary can work.

A separate study that we did, we are developing an app that's a medication history assessment tool, MedHAT. So it's an app on iPad

that collects medication histories from patients in different clinical settings. In that app, we did a diary study where they prospectively captured in their diary for 30 days what they took, and then we did an interview style and did the app at the end of the 30 days.

So that's another example of a diary study that you can use to also validate some of these other data collection tools, whether it be real time or trying to get historical data. Real time is obviously better, but I'm happy to talk offline about more details of those methodologies if it's helpful.

DR. AIKIN: I think we are going to move to question 2 at this point, which now we're going to talk about the post-market setting. So are there existing methodologies, for example qualitative/ethnographic, or traditional epidemiologic study designs that can be utilized to evaluate whether packaging, storage, and disposal options are effective in minimizing misuse of prescription opioids in the post-market setting?

So let's now switch to post-marketing.

DR. STAFFA: So I know we had some comments already about post-market, but are there any lingering comments in post-marketing specifically? Dr. Ciccarone, was that a hand or were you just waving to me?

DR. CICCARONE: Yes. So building off of Kevin Webb's comment in the last round, in addition to burden -- I'm interested in the unintended consequence of some of these. I'll just pick on the electronic monitoring thing.

One's going to be the idea of burden. I guess I'm mixing my metaphors now. If we're looking at blister packs, we find that the people do funny things when they have to interface with a package that they don't like, like take a scissor and cut them all out, and put them in another jar, a familiar jar.

The same thing might happen with electronic methods. There is a segment of the American population that's not going to want to be surveyed. They're just not going to like that. And that's a

hypothesis, and I would explore that qualitatively. I'm not sure how I would explore it other than qualitatively, but since I'm a qualitative expert, that's what I'll say.

DR. STAFFA: Dr. Bateman?

DR. BATEMAN: If we're thinking about packaging as a way of rationalizing prescribing around certain acute indications to address the problem of excess supply, that's certainly something that could probably be tracked in using claims data or in a pragmatic trial-type of setting, where the endpoint would be the amount of leftover medication, whether the patient disposed of the leftover medication, whether the patient reported that their pain was adequately treated, the need for refills as well.

DR. STAFFA: So you are suggesting electronic healthcare data? How would you get at those outcomes? Like linking it to specific questions to patients after you see them getting dispensed prescriptions?

DR. BATEMAN: Yes. So if we saw the

introduction of, say, set quantities tied to particular indications, you could look at prescribing following those indications over time and see whether there was a reduction in excessive prescribing, so say with dental procedures or certain surgical procedures.

DR. STAFFA: Things we know to be acute.

DR. BATEMAN: Yes, exactly. And that could be coupled with surveys where you would perhaps call patients and ask them whether the supply was adequate, whether their pain was appropriately controlled, and what they did with the leftover medication.

DR. CHAN: So can I ask a follow-up? Is part of what you're getting at this idea that if these things were put out on the market and doing what we hoped they were doing, and that providers were seeing a benefit from that, that by tracking the prescribing patterns, that's another way of looking at how effective these are? Is that what I'm sort of hearing here?

DR. BATEMAN: Yes. I think so. So if the

studies that have been published to date show that the amount of opioids that are prescribed following certain acute indications, say dental procedures, is often greatly in excess of what clinicians expect patients to use. So the question would be, with the introduction of these packages that include a set amount as tied to a particular procedure, do we see reductions in those very large quantities that are sometimes dispensed?

I think, coupled with that, you could look at rates of refill to see whether the supply that's going out appears to be adequate for most patients.

Does that address the question?

DR. STAFFA: Thank you. Dr. Lostritto?

DR. LOSTRITTO: Yes. So I think I am seeing two things conflated here in terms of novel packaging that could be used to prevent misuse, and as we're seeing the capability of the package versus the complexity of the package being conflated. I think the two are interfering with each other.

If we separate out capability for a moment

and assume we don't have to take scissors or a hammer to it to get it to work the way it's supposed to, the issue of complexity is being raised at patients who won't like it.

I'm going to challenge that in a sense by saying, how well do we really know that and how can we assess that? A patient is always going to prefer an easier package. Any one of us would. But in an area where this is such a well-recognized problem nationally, would patients or could patients perceive one or two slight steps in complexity for capable packaging as being some sort of assurance that misuse or accidental use or exposure are going to be mitigated?

I think many patients would see that as a benefit, even if it was a little more complex, provided it was a capable package.

MS. WHALLEY BUONO: Liz Whalley Buono. I'll just say that's exactly what we saw with the Wal-Mart program.

So I think there's an awful lot of noise and resistance to change any time you make a change,

just by human nature. But when you take the time to explain to the individuals the purpose of the change and explain how to use it correctly, we saw a dramatic upsweep in the usability and acceptability from the patients.

So that I think is a critical aspect of it. And as you're looking at the data, just keep in mind that any time you make a change, there's going to be that initial noise if it's a significant enough change to have it and things like that.

DR. STAFFA: Dr. Miech?

DR. MIECH: This is Richard Miech, University of Michigan. And going back to the question about existing methodologies, I want to point out that the surveys I think are pretty effective here.

Some people have said before that it would be very hard to study illegal behavior or a stigmatized behavior like intentional or unintentional misuse. But actually, people are happy to tell you about it, and that's our experience, particularly if this survey is

anonymous. If you don't ask them their name, then there's no need for them to hold back.

So if you ask people if they had misused opioids and you also ask them about their packaging, that would be one way to get at if there's lower levels of misuse post-market with some packaging as compared to others. And questions like that could be adopted on national surveys.

DR. STAFFA: Thank you. Ms. Cassidy?

MS. CASSIDY: Yes. I wanted to just follow up on the idea of patients don't like it and would they use it. And I guess one of the questions that comes to mind for me is what type of patient are we talking about that maybe needs to benefit from something like this.

So in relating that to existing methodologies, in the post-marketing setting, we have developed a tool called -- it's for pain patients to evaluate individuals' pain levels and outcomes as it relates to pain, but embedded within that system is screeners for determining opioid

misuse, risk, and for people or pain patients who have been prescribed opioids, risk assessments that determine whether they are now misusing their medication.

So these might be identifying high-risk populations and being able to track in a post-market setting who is misusing a particular opioid medication. And they might benefit from having one of these types of packagings prescribed to them, and then being able to track further as they're moving forward, interacting with their healthcare provider, understanding whether they are continuing to use in an aberrant way or in an atypical manner for that particular product.

Also, as a little sidebar on that, it doesn't exist yet, but also thinking incorporating outside of that, maybe extending that to understanding diversion risk for particular patients and maybe adapting some type of scale to incorporate into that setting.

But this is data that is early. We don't have widespread adoption across all pain clinics

and practices, but it is a way that we could collect that data in real time, and it does collect medication-specific information.

DR. STAFFA: So are these risk assessment tools validated? Because what I hear you saying is these are tools that could be used to perhaps identify patients who might be most in need of this kind of solution.

MS. CASSIDY: Yes, they are. There's the SOAP, the screener for opioid abuse for patients with pain, and the COMM, the Current Opioid Misuse Measure, so they have been used widely already just out in practice.

DR. STAFFA: Thank you. Ms. Cowan?

MS. COWAN: Excuse me, Penney Cowan, American Chronic Pain Association. Getting back to the tracking, I think most people wouldn't like it, but I think there's a population of people who are on chronic opioid therapy that are losing access to care. And if that would improve that, I think they'd be more than willing to do it just to have the access to ensure that they have continued

access to care.

DR. AIKIN: Mr. Webb?

MR. WEBB: Kevin Webb, Mallinckrodt Pharmaceuticals. I appreciate the question of are there certain patients that would accept a different type of packaging if it would help perceive patient safety or family safety.

When we've looked at this, the other question that we also have to ask -- and I don't want to lose sight of the fact -- are you willing to pay for it? Ninety-nine percent of immediate-release opioids are generics.

So while someone may say yes, this is nice and I accept the fact that this is an acceptable change for me to use the medication, as long as I don't have to pay for it, I don't want that to be lost in the discussion.

If we get too far down the path of looking at what new technology could do, we always have to kind of temper that with what can we do. I think that just needs to be balanced with that.

DR. AIKIN: So let's move on to question 3.

That's a good point. We're going to change this up just a little bit based on what we've been hearing here, and that's within the spectrum of misuse from unintentional to intentional behaviors.

How would study methods differ for these two populations or would they?

DR. STAFFA: Dr. Spitznas?

DR. SPITZNAS: So I was prepared to answer the question the way it was written. I just want to say something about that if I can. One is just that I think we need to think about what we're trying to do ultimately.

One thing we're trying to do is we're trying to prevent fatalities in situations where these drugs, if combined with something else or even if taken accidentally, too much of, are going to cause real problems.

I was thinking -- we were talking earlier today about methadone and dose escalations, and how that period is really critical. When a dose escalation happens, that would be a place where reminders, and packaging, and yes, you better

adhere to this, don't take more, should really be driven home and could be driven home potentially with packaging.

I think this whole idea that patients can just kind of take a little more here and there is something that we should really be combating as much as possible, because so many times, patients aren't on just one thing or providers don't know all the things that the patient is taking. So a patient makes up their own mind to take a little bit more, and they're on something else, and then they're in trouble. So I think that that's something that we want all of this to guard against.

Then the other two patient populations where I think this could be really valuable is when we're trying to determine if somebody is going to develop an addiction or in the process of starting to take these things more rapidly than they ought to. Something having to do with timing or something having to do with increasing of their dose on their own, I think it's very important when we're trying

to look at additional liability with these.

The final thing is really with people who are on addiction treatment medication and if they may be showing a sign of relapse. They're a group that, among opioid takers, we probably don't want to have stop adhering suddenly.

So I think that anything that is going to give you a good idea about the date and time and immediate notice when, for some reason, they're not taking that medication, I think it could be really valuable because either they're not taking it because they're holding onto it, selling it, it's going somewhere else, or they're gone off and they're using heroin or something.

I guess I question the value of applying some of these things in populations or two populations that are maybe less likely to have problems with it. But I think that some of these populations like methadone users, for example, were really in a good place to do something with this packaging that somehow is timed or somehow gives us notification when people stop using.

Just adherence for adherence's sake to opioids, I think, is less of a priority for the pain patients unless you're looking at addiction development.

DR. STAFFA: Dr. Emmendorfer?

DR. EMMENDORFER: So underneath storage to get to the point of that's great, we can survey, and find those patients that are willing to report how they're going to steal the meds, I think that brings us to storage.

To me, it's education to the patient, that if you have an age group that may be at risk, lock and key. If you really want to get down to it, when maybe the analogy is the gun safes, right, that's a high-risk area for children as well, and the promotion there is lock and key.

So I don't know that packaging is going to necessarily prevent those individuals that are willingly going to want to steal a medication. And even in the pharmacy departments, you look at that, like in the VA pharmacy, we far exceed the Controlled Substance Act requirements.

All of our C2s through C5s are in a big, large bank vault, restricted access, dual authentication to get into it. When you go into a retail pharmacy, the lower schedules are dispersed through the inventory.

So I think when we're looking at this issue, I think part of the discussion needs to be around education of storage for patients that have folks inside the house that may be a higher risk group for diverting the drug.

DR. AIKIN: I want to make sure that we focus our conversation on the data, the data that either exists or the data that we can develop. So I just want to keep that in mind as we discuss here.

DR. STAFFA: Ms. Morgan?

MS. MORGAN: So in light of this very specific question -- Sharon Morgan, ANA -- I am driven back to what Dr. Green was saying earlier about some of the areas where the accidental poisoning occurred, the cap not being put back on, the dosing that is sitting on a table and then

being accessed unintentionally by the wrong individual.

Within the spectrum of misuse, whatever should be appropriately focused, I think this is a great opportunity to take a look at existing packaging, storage options, and disposal options, and frame a very cohesive education campaign around the appropriate recapping, the appropriate storage, the appropriate and prompt disposal, and to use that education venue across a variety of mediums, social media, being able to use opportunities to educate not only the individual, but the community at large, and to have the message as very succinct and uniform across the platforms.

DR. CHAN: So thank you for that. If I can just jump in. So tying this back and thinking about that in the context of the data discussion now, we've talked a lot about the idea that we need to leverage these platforms, whatever the packaging may look like, to drive educational messages, drive critical warnings, whatever it may be. And we've talked a little bit. We've skirted around these

methodologies in terms of surveys and other things you can do, human factor studies, to look at that.

So how would you want that studied? That's really the question here before the panel. How do you actually want to carry out that study? You've got your research grant, and you've now got this question before you. How would you begin this? That is where we'd like this conversation to really focus on.

DR. AIKIN: So let's go on to question 4. In the post-market setting, are there existing or modifiable data sources that could allow for detection of the packaging, storage, and disposal option as well as third-party access.

Dr. Bosworth, did you want to say something?

DR. BOSWORTH: Unfortunately, I wonder -- I mean, there are people that are researchers here, so I don't want to be the token one. But I think it all comes down to the stakeholder and the question that they're asking, because the payer, the product -- I could just imagine all different ways of questions and then formulating that study

design, what I would be doing.

I think they're all readily available data sources, as I mentioned before. I think you could start from everything from qualitative data all the way up to these pragmatic trials, to try to stay away from the RCTs. But I think, in the end, it comes back to who the stakeholder is and what they're trying to answer, and who's going to want that information.

So in some ways, I would turn it back to you all. If this is something where you are regulating and making the decisions on what goes forward to set what those guidelines are to say, okay, this is the criteria that we need.

The case control studies are great, but that's not the level of quality that we're looking for. Are pragmatic trials acceptable? If not, then we have to shift it up to an RCT.

So I think, understanding with all these new types of research designs, what is acceptable at this point and then determining that would then tell me what the stakeholders are and then what the

research questions are.

So I can give you all different study designs and different methodology if you want, but I think it keeps coming back to who is a stakeholder and what is the level of acceptability of what you would take and use.

If we're going to keep coming back to RCTs, then this is a moot point and we'll come back and just focus on RCTs, and just try to figure out how to do this more effectively, and efficiently, and cheaper.

DR. STAFFA: So this is Judy Staffa. I just want to ask a question because the different ideas I heard you suggest all involve primary data collection as opposed to using existing data, which is often where people go first.

DR. BOSWORTH: So let me just preface it. Yes. I tried to explain before.

DR. STAFFA: Can you talk about that a little more?

DR. BOSWORTH: I think there are a lot of datasets that I haven't heard or have been

mentioned that I would encourage people to look at. And that's why I mentioned the FOA. So that's one bucket over there.

Also, it sounds like what you were talking about was primary data collection and looking at things like cost analysis, which haven't come up in a conversation yet. So if we're talking about those things, we're in primary data collection, then we're trying to answer who is a stakeholder. Is it the payer? Is it you? Is it the patient? Is it the healthcare system? All of those are going to require different questions and different methodology.

Anyway, yes, it's very important to differentiate between available datasets and going that way. And then I think there's also the post-market primary data collection and what do you want to achieve.

DR. STAFFA: Ms. Cowan?

MS. COWAN: Penney Cowan, American Chronic Pain Association. I already talked to Dr. Hertz about doing a survey of our members, who are people

living with pain, and hopefully working with the FDA to make sure those questions are framed right, so that we can really understand how people use, store, and dispose of their medications.

We've never done that of all the surveys we've done. And then hopefully -- I hate to always just do a survey -- do some kind of educational video or something after that. But hopefully, we can work with you to ensure that the questions are appropriate and get the right information. But this would be one population. These are the people who are living with pain.

DR. STAFFA: Dr. Miech?

DR. MIECH: This is Richard Miech, University of Michigan, and I have a clarification question and then a comment.

So question 4, I'm not quite sure what it means that could allow detection of the packaging, storage, and disposal option. I'm not sure what that means.

DR. STAFFA: Again, the talk that I gave this morning talks about different kinds of data

sources might not capture something. It depends on how it's distributed. So for example, if a product is dispensed from a pharmacy with --

DR. MIECH: Oh, I see.

DR. STAFFA: -- a particular package or device attached to it and there's an NDC code identifiable for that, then we can see it; whereas if it's something that, at the pharmacy counter, the patient can purchase it separately at a low cost, whatever, to then use at home, that's not something that might be picked up.

I think that's kind of what we're thinking, of how to get visibility of these across the board.

DR. MIECH: I got you. I'm just in my survey mode, where it's just really easy to ask them.

DR. STAFFA: You just ask, right.

DR. MIECH: Yes, right. And along those lines, I just want to throw out there, since we're kind of brainstorming, if you use the existing National Survey on Drug Use and Health or Monitoring the Future, they ask about what drugs

people are using. They ask if they are misusing them.

What's real nice is that you might have a natural experiment in terms of your controls, where some of these opioids are coming out with new packaging, but other drugs aren't, you could look at the levels of misuse and you could compare.

Particularly drugs that are similar to opioids, but are not, like barbiturates, you could see if the levels of misuse go down among those drugs that have the new packaging compared to the ones that don't. Because it sounds like you're not going to do all the drugs at once in terms of the packaging. They're just going to focus on particular classes of drugs.

DR. STAFFA: Dr. Spitznas?

DR. SPITZNAS: Just going with that suggestion, I thought there was a state -- I feel like it's Virginia -- and there may be a few others that were mandating individual dose-unit packaging that we heard about back in June or either that or there was legislation that was in progress.

Somebody who was at that meeting from FDA was tracking all of those state laws, and I don't remember who that was. But has that passed? Because that would be just a neat little place to look and to pare it up with the NSDA data, for example, or even with IMS health data or possibly PDMP data if they're participating in that PRSS.

DR. STAFFA: PBSS, I think you mean.

DR. SPITZNAS: That one of the PDMPs. I think that's something that you could be looking at.

DR. STAFFA: Yes. I'm not sure which states might collect those data in their PDMP. That's something we can learn more about. But I'm not sure about -- with specific states, there is an effort going on, and we're going to be having a public meeting in a few months
about -- Duke-Margolis is doing a landscape.

Look for us to be identifying a lot of what's happening out there in the different states and health plans. And it's kind of around all different interventions, and I would assume we

might learn more about some packaging interventions at the local level.

DR. SPITZNAS: But I think the measure of an early refill would be important, as would concurrent providers, cash payments. I think you might be in the position to look at those things in a closed health system like VA or DoD.

DR. CHAN: So following up on that, I heard one comment before about the claims data, and then a comment just now also looking at the early refill pattern to capture. And I'm wondering if we can marry those concepts.

I've been told that there may be limitations into how much we can get on rejected claims, for example, and I'm wondering if people who have more experience on this panel, having tried to probe that, can give us a little more insight, because when we think about whether we're talking about misuse or third-party access in both of these spaces, perhaps we need to think about alternate ideas for getting at that.

So if this shows up as a pattern of someone

going back to their pharmacy early, how do we capture that? So I'd be interested to hear thoughts from the panel.

DR. MENDELSON: John Mendelson. Just a quick caution of unintended consequences. If you decrease the amount you prescribe, they're going to go back sooner, if you cut your prescription. If you go down to a 4-day supply, people will show up sooner for meds. Early refills, you could be counting success in the near future, not failure.

DR. STAFFA: Ms. Whalley Buono?

MS. WHALLEY BUONO: Liz Whalley Buono. You mentioned the state work, and I think that's the low-hanging fruit. I think there are certain states that are way out in front on collecting and communicating databases together, so slightly different twist.

In the State of Virginia, we received financing from the White House to look at social innovation funding, and we specifically looked at home visiting, which is unrelated to this. But it's relevant because the data issues were the

challenge.

Virginia has established an all-payer claims database, which is helpful and ahead of where a lot of the states are. But they've recently passed a bill to develop the electronic infrastructure to then make that database communicate effectively with the judicial system, with birth records, with several other relevant databases so that you can look at things in the social innovation arena that make sense, and you can look at statistics that will help you interpret the effectiveness of some of these innovations long term.

So I think there's an opportunity to look at which states are out ahead of these things. And Virginia specifically because there is a centralized all-payer claims database, managed care was more willing to work with us because the data-use agreements were already in place, and there were certain assurances that were we to access rather sensitive claims information, the risk would somewhat be mitigated as far as mucking around in that very sensitive information.

DR. BATEMAN: Massachusetts has created a similar database with a focus on opioids, where there's a linkage between PDMP data, all-payer claims data, death certificate data, birth certificate data, that allows some of these questions to be looked at.

DR. STAFFA: And we're funding something similar in Connecticut as well. Dr. Bosworth?

DR. BOSWORTH: So just to make sure I understand the question, you're trying to understand that point where a prescription is made, the patient has a prescription and they are going back to try to refill it, and that timeline is too early, and where is that data, and can you capture that data.

DR. CHAN: Right. So that is one of my questions. Sometimes, with the challenges we're facing with the different data systems we're looking at, are there other data streams we look at that are an appropriate surrogate for something else we want to really understand?

DR. BOSWORTH: Yes.

DR. CHAN: So in that setting, yes, exactly as you described it, if someone is going back early, how do we capture that?

DR. BOSWORTH: So you'd have to partner with industry partner. CoverMyMeds has that data, as one entity, it's just to put it out there. I know we're not supposed to name names. This is also what CVS and Aetna -- one of the issues with CVS. And if you looked, we call this primary non-adherence, but this is an area that's really gotten a lot of attention because we always throw out 50 percent are non-adherent, but that's not including what you're describing as a denominator.

So there are sources of data where you can see where the prescription has been made. The patient picks it up or doesn't pick it up, as well as when they are supposed to pick it up and when they come in. But that's on a commercial level and maybe on the VA side as well. I haven't looked to it, but that may be something as well.

DR. BATEMAN: I was going to say there are algorithms that have been defined in the literature

to potentially capture opioid misuse based on early filling, filling for multiple pharmacies, things of that nature.

DR. STAFFA: That was Dr. Bateman for the transcriptionist

Brian, are there validated metrics? Because we run into the issue of, again, big data tells you what is happening, but it doesn't really tell you why it's happening. And I can imagine many reasons people would come in early for a refill, some of which have to do with concerning behavior and some perhaps not.

DR. BATEMAN: Yes. There have been efforts to sort of cross-validate within claims, so look at the association between those types of behaviors and ICD-9 diagnosis claims for opioid misuse, or abuse, or overdose. So some of that work has been done. I'm not sure that there have been validation efforts that have taken those algorithms and then gone to medical records to validate.

DR. STAFFA: Because we have actually asked the industry group that makes extended-release and

long-acting opioids to actually be doing some validation metrics on doctor and pharmacy shopping because we haven't really seen -- again, people use lots of different definitions for those, but we've not really seen the data that show you when you see someone going to X number of doctors, what percentage of people above that level are actually engaging in a problem behavior as opposed to seeking care that they're not able to get.

I want to get to Dr. Emmendorfer?

DR. EMMENDORFER: In VA, with our prescription data, we have what we call the release date, and that tells us if the prescription was dispensed physically to the veteran. So we have that. The limitation that we would have is if the veteran would choose to go outside our healthcare system and use a non-VA pharmacy, and obtain healthcare from somebody else, and pay cash for that prescription. That prescription would not be visible to us, so that's why we rely on the PDMPs as well.

Just to give you an example of how much we

rely on them, we have over 2 million documented queries to the PDMPs by VA providers. But yes, we would have that within our healthcare system.

DR. CHAN: Are you also then able to track them when someone is coming back earlier or are you even doing so?

DR. EMMENDORFER: So that's a whole big discussion. When you start getting into trying -- there's a lot of different variables that can contribute to that. One of the things just a little bit related is when we're developing one of our metrics on the greater than or equal to 100 morphine equivalent daily dose.

We originally wanted to report out the most recent MEDD for that quarter, and what we found is when we went in and did the chart validation to see if that methodology made sense, it didn't work. We actually had to report out the highest MEDD for that quarter for that patient. And then that way, we're able to trend what the peak MEDD is for that quarter over time down using the business rule of big data.

So I know that doesn't get directly to the question of the early refills, but there's a lot of different variables that can influence when you're looking at early refills and release date.

DR. STAFFA: Mr. Webb?

MR. WEBB: Kevin Webb, Mallinckrodt Pharmaceuticals. As far as we consider terminology, since all opioid prescriptions are considered new prescriptions, trying to track a refill as you get into the data might be very difficult because, in essence, refills don't exist anymore, so you're going to be looking at new scripts.

But part of the challenge is that you look at what sometimes gets caught up in the whole drug-seeking behavior. If certain retail pharmacies may put a cap on how many prescriptions can be filled in a certain month, if a patient comes in and presents a valid, legitimate prescription, they may be turned away.

Now, if they try to go to another pharmacy, they're now tagged as a drug seeker, drug-seeking

behavior. So just trying to get a legitimate prescription filled, the system now has locked up and they cannot get the prescription that they're looking for. But just through no fault on their own, they're just trying to get their pain medication.

DR. CHAN: So as we start to connect these ideas, taking into account what you just stated, if there are systems that exist in some of these retail settings -- and I'm looking to my NACDS panel members here -- that are looking at there may be limits to how many times a person comes back, if we connect that then to what they filled and their history of filling, which I assume is also captured in that system, what do we shake out of that?

Where might there be may be something -- I guess my question to the panel, is there something interesting to look at connecting those two?

DR. EMMENDORFER: One other thing I'd like to hear from the retail side --

DR. STAFFA: This is Dr. Emmendorfer speaking.

DR. EMMENDORFER: Sorry. Tom Emmendorfer. It would be interesting to see what retail has to say as well. But one of the things I think is that -- whenever you can, to leverage it, that helps the VA healthcare system is our VA pharmacists have access to the electronic health record.

So when there's some sort of issue going around where it may appear to be an early refill, being able to get into electronic health record and to start looking at the progress notes, indication for use, and what's going on can really help investigate and help the pharmacist, the VA pharmacist be an advocate for the patient and for the VA provider to try to figure out what's going on.

I don't know what the experience is in the retail pharmacy change as far as getting access to some of the electronic health records or labs here and drug screens, that type of stuff.

DR. SMITH: This is Chris Smith from NACDS. I'm not sure I could speak to that. Can you repeat

what your specific question was, what are the two things you're trying to connect?

DR. CHAN: Yes. So in connecting some of the disparate concepts we're talking here, my question is just, in thinking in these settings, at a pharmacy store, for example, that might have a way of looking at how many times a patient attempted to fill any particular drug with specific cutoffs that Mr. Webb just spoke to, if that's being looked at, and you also have a database that's collecting what they've been filling.

How do we now combine those and think about how we get at some of this?

MR. SMITH: I'm not sure about the second part of what you're saying, but that sounds like the PDMP, what you're talking about to some extent. No?

MR. WEBB: This is Kevin Webb, Mallinckrodt. The PDMP will obviously get to what is being prescribed. So you have to go deeper into the data, assuming that the PDMP is tracking to that level of granularity.

But the other option that you may want to consider about is that several of the states are obviously moving forward with partial-fill legislation. Again, it kind of goes back to what the AMA was trying to do with their legislation, that the prescription is written for the month, but that it's only filled for the two weeks. If that patient then comes back, it's still under the one script, but yet you now can see whether a refill is needed and you can probably get to it through something like that.

I'm not aware of any states yet, though, that are allowing that type of legislation. Either through a PBM or even the retail pharmacy under the CDC guidelines, they're trying to keep it within that MME threshold. So many of them are keeping within that 3 to 5 days under a certain dosage strength.

DR. STAFFA: Dr. Bosworth, would you like to make the last comment before lunch? No pressure?

DR. BOSWORTH: I do think of our datasets that particularly focus on things like prior

authorization and others, and I also think of the Community Care of North Carolina, which is the Medicaid management arm, which actually is a capitated system with these sources of data.

I will specify that I think you can get at what is happening, but what you can't get in any of these datasets is the why. So that would be a nice research project, to actually look at the point of care because the prior authorization is actually at that point in time.

Literally, there in the pharmacy, so to be able to then have the pharmacist ask why are you coming in to see me to get an extra prescription could be something that could be easily done in a research environment if there's interest.

But I think the why, I can't imagine any dataset at the moment that would have the why only because I don't know all the different factors, so having a qualitative methodology to connect those two would be really incredible, I think.

So those are some things to think about.

DR. AIKIN: With that, I think we are going

to close the panel portion of Session 6. We will have audience participation after we return from lunch. Please return at 1:30 p.m. and thank you very much.

(Whereupon, at 12:31 p.m., a lunch recess was taken.)

AFTERNOONSESSION

(1:31 p.m.)

DR. AIKIN: Welcome back, everybody. Welcome back from lunch. So just to remind you, we're going to continue with the audience participation section of Session 6, which is the topic of misuse and pre- and post-marketing data and labeling considerations.

Any audience members who would like to speak, please line up behind the microphone. There will be a staff member to help. We ask, as we have before, to limit your comments to this particular session's topic and just a brief review of the rules; you will have up to three minutes for your comments.

There is a red-yellow-green light system to assist you. It works just like a traffic light. If the light is green, you can talk. If it's yellow, you have one minute remaining. If it is red, please conclude and return to your seats. And

just as a reminder, the docket will be open until February 12, 2018. You're welcome to submit comments to the docket up until then.

Are there any members of the audience who would like to provide comments at this time?

DR. STAFFA: Try not to knock anyone over on your way to the microphone, please.

(No response.)

DR. AIKIN: Okay. Then we are going to continue on and move to Session 7. The topic of Session 7 is about Pre-MarketAbuse for Third Party Access, and I'd like to introduce Dr. Dominic Chiapperino -- thank you -- who is the acting director of the Controlled Substances staff.

Session 7 Presentation – Dominic Chiapperino

DR. CHIAPPERINO: Thank you. Yes. Good afternoon. I'm Dominic Chiapperino. I'm the acting director for the Controlled Substance staff in CDER. I'm pleased to open Session 7. I'll be talking about a few study methodologies we already use for some regulatory purposes, from which we might borrow some concepts or principles in the

design of new studies, pre-market studies, intended to determine or predict packaging, storage, or disposal options that could potentially reduce third-party access to opioid medications.

So my comments today are my own and do not represent any official FDA positions. And I won't read the rest of this disclaimer, what you've seen in previous sessions.

The objectives in my talk a bit more specifically will be to first describe pre-market human abuse potential or HAP studies, studies that are done to measure subjective effects such as the likeability of a drug substance or product.

I'll also discuss a particular subtype of the HAP study, one intended to evaluate the effectiveness of purported abuse-deterrent formulations. I'll then talk about some other methodologies such as human factors testing and other forms of social science research, which may not be specifically in the drug abuse or abuse potential context, but which may be helpful to have in mind as we move to the panel discussion.

Ultimately, we want to see what we might borrow from these methodologies to bring into studies of packaging, storage, and disposal options as a means of deterring third-party access, which implies abuse.

As I go through these next slides, I think we should have at least two different categories of these options in mind, those based on physical barriers or deterrence to third-party access and those based on cognitive and behavioral deterrence to third-party access such as the intent or interest to not have one's tampering or theft of the opioid medications easily discovered.

So a human abuse potential study is fundamentally a study of subjective responses to a test drug as an indicator of that drug's abuse potential. The studies measure how much the drug is liked and, in a crossover design, subjects are also exposed to placebo and to a positive control and report their subjective responses to those administered treatments as well.

In these studies, a positive control is a

known drug of abuse for which we would expect a subject to give responses indicating that they do indeed like the effects of the drug, whether it be an opiate like an effect, or a stimulant, depressant, or hallucinogen effect.

These studies are considered very valuable pre-market indicator that a drug has abuse potential. The FDA's guidance for industry updated in January 2017, assessment of abuse potential of drugs, outlines when a HAP study is appropriate or necessary to do based on any signals of abuse potential seen during pre-clinical and clinical drug development.

To give a sketch of the design elements of a HAP study, they enrolled recreational drug users and are done as inpatient setting. These are not very large studies. Usually 35 to 40 completers will be a sufficient study size. I've talked about the crossover design and treatment arms, and the primary endpoint is the question to subjects as to their level of drug liking.

Secondary endpoints may include asking

subjects whether they take the drug again, whether they felt high, whether they felt good effects or bad effects from the drug.

All these measures are taken at multiple time points after drug administration to measure the subjective responses and to be able to see how the subjective effects of correlate with the PK profile of the drug.

The subjective responses are provided on a visual analog scale typically ranging 0 to 100 on either bipolar or unipolar scales. The statistical analyses will determine first if the positive control differentiated significantly from placebo, which is expected, so this is a means of validating the study.

The next analyses will determine if the test drug significantly differentiates from placebo and if the test drug differentiates from the positive control. So typical scenario for a study that has been validated, where the test drug is significantly more liked than placebo and is not statistically significantly different from the

positive control, we're able to conclude that the test drug does have abuse potential and it's on par with the positive control. We treat it accordingly in terms of drug scheduling and labeling to describe its abuse potential.

We'll shift now to HAP studies in the context of abuse-deterrent formulations. This is a different type of HAP study that is done to measure the effectiveness of the formulations of an abuse-deterrent property or strategy.

There are many of the same design elements of the conventional HAP study, enrollment of recreational drug users, done as inpatient. The study will investigate a particular and relevant route of abuse such as intranasal, oral, or intravenous abuse, and it's still based on measurement of subjective effects such as drug liking.

The positive control in these studies is often an immediate-release formulation of the same active opioid drug substance. The main question at hand is whether the ADF treatment, when

administered with or without any manipulation intended to defeat the ADF strategy, resulted in a significantly lower reported drug liking when compared to the positive control.

These HAP studies, also called category 3 studies, are discussed in detail in FDA's 2015final guidance, Abuse-Deterrent Opioids Evaluation and Labeling.

It's important to note that category 3 HAP studies are typically preceded by category 1 in vitro studies. The in vitro studies investigate basic physical and chemical characteristics of the ADF and investigates various methods or tools an individual might use in trying to defeat the process intended to confer abuse deterrence.

The in vitro studies provide important information about the ADF and the feasibility of manipulating the formulation to make it suitable for a particular route of abuse. The HAP study can then investigate whether that manipulated form is able to elicit the positive subjective effect or not.

Lower subjective responses relative to the non-abuse-deterrent positive control implies some effectiveness as an ADF, whereas responses not significantly different from the positive control indicate that the ADF fails as an ADF.

As an example, let's consider the lead-up to an intranasal HAP study. You can see here many of the parameters that might be relevant to characterizing category 1 studies that precede the HAP study: resistance to crushing, particle size, achieved by using various tools, sensitivity of these processes to pre-freezing, or heating, or microwaving, all characterized such that a sample of suitable particle size for snorting purposes can be prepared and serve as the relevant test drug treatment.

In the HAP study, we will look at the ability of subjects to successfully snort the material and whether the snorted material elicited drug liking responses comparable to positive control.

Many ADFs operate on a strategy that the

moistened material on the nasal membrane will gel and will not so easily allow snorting of the ground, powdery material, which will impact absorption of the active opioid substance and thus reduce rewarding effects. There may also be unpleasant effects such as from aversive agents, and this too could impact subjects' overall drug liking scores.

I want to note some aspects of this methodology that might be relevant or informative for designing studies in the packaging context. The category 1, category 3 sequence considers the level of effort an individual may put forth, the tools that may be used to defeat a strategy, and has an endpoint in the HAP study that is accepted as a pre-market indicator of abuse potential.

There is a study population, recreational opioid users, accepted as representative enough for this purpose, although this is one type of individual across a broad spectrum of individuals who may engage in abuse with prescription opioids.

Shown here is an actual labeling claim

obtained in section 9.2. This is fairly typical language for drug products that have demonstrated through pre-market studies some evidence that they have properties that are expected to make it more difficult to abuse the product by a certain route.

No products have yet obtained a claim based on category 4 post-marketing studies that show there is a meaningfully reduced abuse of the product in a post-market setting.

Moving on to other methodologies, human factor testing is conducted as a means of evaluating the intended users' ability to use the product as intended. This may include measuring the effectiveness of the instructions section of patient labeling. Knowledge tasks can evaluate patient understanding of critical information.

In the context of packaging and storage strategies to deter third-party access by means of a physical barrier or security feature, HF testing could be very important to ensure that the security feature is not preventing the patient from their appropriate and intended use of the product, but

also can HF protocols be adapted or turned around from the perspective of third-party access and measurability or inability to access the medications.

Other social science and survey research FDA has engaged in, we've looked at public perception of our risk communications, comprehension of product labeling and warnings. We've investigated compliance with labeling and other messaging.

In doing this work, the project is often approached in two phases. It will lead off with extensive qualitative research to understand the issue as thoroughly as we can and then use that knowledge gained to formulate a good follow-up study, one that may be more quantitative. This is much like the ADF context of category 1 before category 3 and may also be advisable as we consider new studies to investigate packaging.

Shown here are some types of qualitative social science research and these can all feed into the development of a more quantitative method. For example, literature reviews, observational studies,

focus groups, social media monitoring, and from these, we can devise a survey to measure perceptions, preferences, or maybe likely decision making.

Shifting now to the context we're presently interested in, packaging, storage, and disposal options, we heard yesterday many comments suggesting a need to prioritize what types of misuse, accidental exposure, or abuse, maybe more successfully targeted by these strategies.

Within the category of abuse, there is undoubtedly a spectrum of individuals who may currently or at some point have or may engage in abuse of prescription opioid products. This raises the question, who should we endeavor to enroll in studies to investigate packaging strategy effectiveness to deter third-party access?

Bear in mind that to study the effectiveness of these options and packaging, one does not need to administer study drug at all. This is a distinct difference from the ADF HAP study methodology.

We can go on the presumption that the drug formulation, once in hand, is abusable and capable of providing the drug effects being sought. So we can consider subject enrollment and what we can learn from various individuals and view any potential ethical issues with the study population in this different light.

There's a wide range of individuals for whom we might discourage product tampering or theft or individuals we can simply ask about their experiences and preferences, investigate their motivation or their abilities to defeat a particular strategy, and perhaps devise some quantitative measures if we need studies to be comparative across a range of packaging options.

We heard yesterday about some comments about the need for data that indicate an expected value of effectiveness of a new packaging, storage, or disposal option before taking steps which may be disruptive to manufacturing and the pharmacy setting. For the methodologies I've discussed, there seem to be some elements to adapt to the

study of packaging and they seem doable as pre-market studies.

In mechanical or manipulation studies of packaging security features, we can devise ways of measuring a success rate to get at these medications. As far as studying cognitive and behavioral factors, we'll want to try to measure the likelihood of attempted tampering or willingness or unwillingness to have one's tampering attempts detected by the patient or caregiver. Perhaps we could predict through a quantitative survey instrument the decision-making that might occur in response to new packaging.

I've not talked about any specific endpoints or possible claims language that might be obtained from some new methodologies. I hope these might be explored during the panel discussion.

So in summary, HAP studies, human factors testing, and other social science research may each have elements that could be useful in designing new pre-market studies around packaging and storage and disposal options and the goal of deterring third-

party access.

Thank you for your attention, and now we'll move on to questions to the panel. Thank you.

(Applause.)

Panel Discussion

DR. AIKIN: Thank you, Dr. Chiapperino.

Welcome to Session 7. Let's start with our first question, which actually has a question and then a sub-question, but we'll start with the first one.

Are there existing methodologies that can be utilized to evaluate whether packaging, storage, and disposal options minimize third-party access to prescription opioids?

I'll just go ahead and ask the sub-question. Beyond that, if so, how can they be leveraged or adapted?

DR. BIX: This is Laura Bix from Michigan State University. The only study that comes to my mind that's even remotely close that I can think about was the study of ivory and illicit trade of ivory, where they actually embedded a GPS item into

the tusk and then tracked it as it moved through a system.

So I don't know what the ethics of such an approach would be, but it seems to me that you could put bait somewhere with GPS and potentially, I don't know, optical technology. How to hide that might be trickier than ivory, but that's the only study that I can think of that sort of even comes remotely close. But they were able to track where it was going and where it was being handed off through the system.

DR. AIKIN: Would we need to hide it?

DR. BIX: I suppose it depends on how smart the person that picks it up is. Maybe we can hide it in plain sight. We can make it look like a legitimate RFID tag or something like that.

DR. AIKIN: No. I'm just wondering, from the standpoint of hiding it, if our goal is to minimize third-party access, especially people who might or might not use depending on how the package is designed, would not hiding it be an advantage in this case.

DR. CHIAPPERINO: Ms. Cowan?

MS. COWAN: If you didn't hide it and had it out in plain sight, or they knew it, they'd remove it, and then it would negate that; correct? If they knew it was there, and word gets around amazingly, so they would remove it if they knew where it was.

DR. HERTZ: Just to separate this into a few buckets, I think there's already a fair amount of RFID tracking of shipments of product that is at risk for being diverted on a larger basis, trucks being stolen, shipments being intercepted.

When we're talking about something like the medicine cabinet, which is I think more where we're going on this, is there value in its screening? There's an RFID chip in the middle of me, so beware we will know where you go until you digest it through.

That's one question versus I think, a different question, which is, do we want to figure out where it's going? And I think we have a pretty good idea in many circumstances where it's going.

So what do we think might help lessen the use of product by household contacts that aren't the patient?

DR. CHIAPPERINO: Yes. I think that's right, and I also wonder to what extent the patient knows when some of their medication is missing. We've talked about the amber vial, and here we're trying to solve a problem, and we're not really sure to what extent the patient is aware when their drugs are coming up short toward the end of their prescription period and what happens at that point?

DR. THROCKMORTON: Dan, this is Doug. You and I had a conversation at noon that may help here. I mean, we talked about lock boxes and the data about their long-term efficacy, and I think came away with the impression that long-term efficacy hadn't been very well established. I don't know how that was studied, though, but it would at least address the storage aspect of this question. I don't know what those methods were.

DR. BUDNITZ: Dan Budnitz, CDC. I don't have the studies in front of me, but there are

older studies about even giving out lock boxes to communities to store medication that children might get into. And I think the bottom line from the studies are that they fall into disuse over time.

DR. THROCKMORTON: How did they study, though?

DR. BUDNITZ: Sorry. So the mechanism of this is, as far as I recall, were basically home visits. An interviewer would deliver the lock box, come back six months later, say, "Please show us the lock box," and see were there any medicines in it. Often the study subjects would not have it or were not able to demonstrate that there was any medicine. But it was his re-visits that we studied.

DR. BIX: So we've done video diaries before, so how about putting an optical device in the lock box that triggers when it opens, where the optical device could record what's in it and what time it's opened. And if you have WiFi capability, you can hook that into a wireless network that will transmit it in real-time back to the Cloud, so you

can access it as it's happening.

DR. CHAN: So now we're talking about a design, a specific design. How do we want to study that? What do we want it to telling us is happening?

DR. CHIAPPERINO: There were some hands up earlier. Maybe we should try to catch up on people who wanted to speak.

Dr. Emmendorfer, did you still have a comment?

DR. EMMENDORFER: No. I was just going to comment that, in VA, we do use the tracer methodology. We work with the Office of Inspector General for the United States Postal Service, and when we start getting a cluster of reported lost packages, we introduced tracer packages into the system to help identify and capture the folks. So that's a good point.

DR. CHIAPPERINO: Dr. Spitznas?

DR. SPITZNAS: I don't know how acceptable this would be, but I think for parents of teenage children, you could definitely look at some sort of

calendar-related packaging so they'd know when they used -- they personally have used the medication and perhaps look at pre- and post-hair testing of the family member or adolescent, just to have an idea of if this deters misuse.

DR. CHIAPPERINO: Thank you. Dr. Miech?

DR. MIECH: This is Richard Miech, University of Michigan. I want to go back to surveys again. I read the question to be how would you evaluate whether different packaging, or storage, or disposal is more effective than others in terms of third-party access to opioids.

Monitoring the Future, we survey 13,500 12th graders every year, and we're moving to tablets, so in terms of technology, it's a new technology we have. We can build in complex skip patterns for that kind of stuff. So the kids who say they've abused opioids, we can ask specific questions just for that population, which would be nice.

So we could ask them, have you run into this type of thing or this type of packaging, and we could see how often we're able to defeat it and how

difficult was it to defeat it.

We could even do open-ended questions. About 5 percent now of our 12th graders report that they misused opioids in the past year, so we could have open-ended questions if you wanted to. So that's one idea I want to throw out there.

DR. CHIAPPERINO: Thank you. Dr. Mendelson?

DR. MENDELSON: Most people are probably unaware, but I worked as a medical director for methadone clinics for some time, about 400,000 people on methadone. About 20 percent of them eventually get take-homes, and they're all required to have a lock box to take home their drug in.

It basically makes them a target on the way home, and it doesn't prevent overdoses. And they're also required to bring back their empty bottles if they're going to get more and that doesn't work to well, either, but I think it works better than the lock boxes.

My suggestion would be, you incentivize people. If you want to actually get them to do something, they should get some reward out of it.

And whatever system you ultimately come up with ought to have less punitive rules and not make people targets on the street.

We see the people coming out of the clinic and they have like a bright orange spangly box with a little combination lock on it. They're just sitting ducks. They don't make it home with those ones often.

DR. HERTZ: I just want to follow that up a little bit. I mean, maybe the lock boxes should come with a knapsack.

(Laughter.)

DR. MENDELSON: Yes.

DR. HERTZ: When you say they don't prevent overdoses of family members, of household contacts, is that right?

DR. MENDELSON: Has the methadone data appreciably changed in the last 10 years? And as clinics increase their use of lock boxes, I just don't think -- and people take them out of the boxes when they get home because they're also a target in the home if someone gets broken into.

DR. HERTZ: But is it that they are possibly not having an impact on third-party access for abuse, but they're not having any impact on anything?

DR. MENDELSON: I don't know if it's been studied, really. I think it's one of those punitive things that methadone clinics do that make it just more difficult for people to get their take-homes, which advantages the clinics. But that would be an area for study and that would be an area you could actually get SAMHSA to ask people to give you some data on.

DR. CHIAPPERINO: Thank you. Yes, Paula?

DR. RAUSCH: Hi, Paula Rausch from FDA, the Office of Communications. I just wanted to say one thing. This is sort of a precursor to specific research related to packaging, storage, and disposal, but I think it's really important to understand the different perceptions among parents and caregivers versus among the actual teenagers and adolescents who may be the third-party users of these things, both on the qualitative side asking

some of these questions to figure out what's going on and then moving into surveys, which has been mentioned already.

But really, having that understanding, that very considered understanding before going into surveys of the differences between parents, and caregivers, and teenagers or potential other third-party users.

DR. AIKIN: I think that's a good segue and also what Dr. Mendelson said. We've got some pitfalls that have been identified with particular methodologies, but let's go back to the methodology of measuring the effectiveness of this, and what existing methodologies can we use, and what are the pitfalls of particular methodologies to gather the data we need to evaluate the effectiveness.

DR. CHIAPPERINO: Yes, Ms. Whalley Buono?

MS. WHALLEY BUONO: Liz Whalley Buono. Thank you. The only thing that I'm thinking is, I have heard and I don't know what percentage is implicated here, but reported short-fills to pharmacy seems to be one backdoor way to perhaps

identify when pills are being diverted in the home because my understanding is that the large retailers are having a certain amount of volume of patients coming back in on these medications and basically accusing the pharmacy of not giving them all their medication because let's say second or third encounter with the vial, they're short. And they didn't count it when they left the pharmacy, so you can imagine the mind automatically goes to, I didn't receive the medication in the first place.

So I'm wondering, I don't know what percentage of these issues that occurs in, but it might be one way to engage with large retail and ask them for a baseline of how many of these reports they get and whether that goes down. It might be one indicator.

DR. CHIAPPERINO: Yes. Thank you. Let's see. Mr. Webb?

MR. WEBB: Kevin Webb, Mallinckrodt Pharmaceuticals. I guess, as we think through where the wheels can fall off, it's going to be who's the data going to. So is it going to a

parent? Is it going to the pharmacy? Is it going to the FDA? Is it going to the DEA?

So knowing and someone thinks that their movement or their pills are being tracked, the other part is, does it have an on-off switch? So if you have some type of a sensor on it, can someone turn it off and now your data is corrupted just because it's incomplete data?

DR. CHIAPPERINO: Mr. Smith?

MR. SMITH: This is Chris Smith from NACDS. What specific data would you want from the retailers? You just want to know how often they're being accused of shorting the fill or what? I just want to make sure I understand what you're asking.

MS. WHALLEY BUONO: So what I understand -- and again, admitted knowledge base here -- in the literature, you read that oftentimes, however much that is, their first response to having less pills in the vial than they think they should is to go back to pharmacy and complain.

MR. SMITH: Sure.

MS. WHALLEY BUONO: I would imagine that that's some sort of event that gets recorded and there's some sort of follow-up research or something that goes on at the pharmacy level.

So it just might be interesting. It might be irrelevant if it's a very small percentage of the population that's actually going back into pharmacy, but if it's an event that occurs at any significant rate, it might be interesting to look to see, in some sort of population where you've distributed lock boxes or whatever the intervention, whether those reports go down.

It's a grasp, but it might be one source of available data.

MR. SMITH: Yes. So the data itself, assuming it even exists now, that there's any sort of tracking of that, you would want it compared to a scenario where --

MS. WHALLEY BUONO: A pre- and a post-

MR. SMITH: Yes. You'd need to have post-.

MS. WHALLEY BUONO: We are trying to just wrack our brains on whether there's any kind of

data you could look at as to whether, if you send lock boxes home in three zip codes, does diversion go down? And perhaps that's one way of looking at it.

MR. SMITH: Yes. I don't know what to tell you. Again, it's too speculative and too far out at this point to really weigh in much on it.

MS. WHALLEY BUONO: I'm sure retail would be thrilled to share the data around the number of events that occur.

DR. CHIAPPERINO: Mr. Berghahn?

MR. BERGHAHN: Walt Berghahn from HCPC. My wife's actually a pharmacy tech working for Rite Aid and the frequency of people coming back on short-counted C2s is so severe that they now triple-count the C2s.

The tech loads it, pharmacist counts it, and when the patient comes to the counter for some particular patients, who have a habit of being shorted, then they count it right in front of the patient, and they sign off with the 30, and then they don't get shorted.

MS. WHALLEY BUONO: So that was my understanding, that it's not infrequent.

MR. BERGHAHN: No.

MS. WHALLEY BUONO: It would seem like there would be not a lot of risk to the retailer to look at this data, especially if they're putting correction action plans in place.

MR. BERGHAHN: They may have it and may not want to share it. It's a good question.

MR. SMITH: Yes. This is Chris Smith again. Yes. I don't know if they would share that information. I don't know enough about that to give you any sort of assessment right here and now. But again, it doesn't necessarily sound like it has much value without that, because if I'm understanding where you're trying to go with it, here's what the situation's like now. Then we introduce this solution, let's call it, or proposed solution. Here's what it looks like then.

So on its own, the data now doesn't seem like it really -- but maybe I'm misunderstanding, gives you one.

MS. WHALLEY BUONO: Here's what I'm thinking. If you can identify some stores that have a particularly high rate of this occurrence, and they've put in place some corrective action plans to make sure that, indeed, the pharmacist is not shorting the prescription, that's probably not going to deter these patients from coming back in and continuing to report in case they happen to get some night shift manager that's going to give him more medication.

So if you can look at these high-report event stores and then distribute these innovations, and then look to see whether the trend goes down. That's my only simple cause and effect.

DR. CHIAPPERINO: Dr. Ciccarone?

DR. CICCARONE: Dan Ciccarone, UCSF. Just as a quick follow-up, if the data were available -- and I know that's a big if -- this actually sounds like a good idea because if you're starting from -- just statistically, if you've got a lot of complaints, pre-, post- will show some effect if there is an effect.

So from that point of view, this is feasible from the is the data available, countable, reliable? That's the iffy part.

DR. AIKIN: Just going back to this whole packaging issue, is there utility in measuring time to defeat the package? And if so, how would we study that?

MS. WHALLEY BUONO: Can I ask, do you mean time to defeat the child resistance feature or time to defeat, let's say, a locking mechanism?

DR. CHAN: So if you think about Dr. Chiapperino's talk and he was talking about looking at category 1 studies, which might identify all the different ways, right, that the attributes overcome -- so think about this now in the packaging space.

You create some option, and then you're trying to proactively identify all the different ways that option will not do what it's supposed to do because someone's found a workaround or a way to get into it.

So there are obvious things that come to

mind because we've already heard the analogy someone can just take a sledgehammer and break into it. But if we're talking about people actually trying to manipulate features that are there without the use of another tool, they're trying to do it in a way -- think about someone who's contemplating first-time abuse. We keep coming back to that example when thinking about this spectrum.

Someone in that scenario who may not want to be discovered, so to speak, then sledgehammer is too obvious. So they're working around with this package, and where is their value in looking at a time to defeat, and how do we correlate whether time to defeat has a deterring effect on whether someone even attempts.

I know there's a lot of questions that are buried into that, but curious what thoughts are around that.

DR. CHIAPPERINO: Yes, Mr. Webb?

MR. WEBB: Kevin Webb, Mallinckrodt Pharmaceuticals. I think through the question.

There is logic to that because while much of our discussion has been around the family member walking away with some of the medications, most of the diversion occurs from a guest or someone slipping into the house and then trying to slip out undetected.

So without sounding too crass, how long does it take someone to go to the bathroom? Time it that way because if someone needs to use the bathroom, they're going to get in, get out of your medications, and then leave the house like a paper boy or a pizza kid.

So there's a way that you can put some kind of parameters around what should be a reasonable expectation of someone trying to be working and not be discovered.

DR. CHIAPPERINO: Yes?

MS. WHALLEY BUONO: Liz Whalley Buono. I'm guessing, since we don't have unlimited resources and I could be incorrect, but in my mind, it would be a more worthy cause to study how deterrent the innovation is versus how quickly it can be

defeated.

So if we had an understanding of whatever the teenage age bracket is that's the primary diverter within a family scenario, to do some panel work to understand, would you be more frightened to even take a pill out of here for fear you get caught.

As far as the FedEx guy using your bathroom, I don't know how. That's just so weird I can't even imagine studying that.

(Laughter.)

MS. WHALLEY BUONO: But I think you could do some informative panel work with these various age groups to say would this make you less likely to; would you be scared that your mom would catch you, kind of deal, and then you can maybe start to do some cost-benefit analysis of do you need to lock it or is it sufficient that the kids understand that they're going to get caught kind of thing?

DR. CHIAPPERINO: Dr. Ciccarone, did you have another comment?

DR. CICCARONE: Yes, Dan Ciccarone, UCSF.

So there's been a lot of, I would say, some agreement the last day and a half about the extreme end of the spectrum. I prefer to look at this as a pyramid, where the high-level, high-intention abuser, if you will, they're going to get through most packaging, and I think time to break through is irrelevant. But if we recognize that, further down on that pyramid, there are a lot of people who it is about time and opportunity.

So I would be very curious about the effect of slowing down or inhibiting that process to break some of the casual, low-level recreational. I'd be less cynical about that than I would be about the higher end of the pyramid.

DR. CHIAPPERINO: Dr. Budnitz?

DR. BUDNITZ: Dan Budnitz, CDC. I was going to respond to the analogy about the child-resistant packaging and the time to open. I think the fundamental assumption, though, of that time to open kind of testing criteria is that these young children are supervised, are not left unattended for any longer lengths of time.

I don't know if that's the case. I don't know enough about the area, if it's someone who goes and visits an open house, and is running into the bathroom to go through the medicine cabinet, if that really is the major culprit for people pilfering medicines, or if it is someone that is in the house and is in there 24 hours a day, so time is not really the issue.

So I think I might approach it as Liz said. Maybe it's a panel, but maybe an enriched panel of folks, folks that got the case control methodology, the cases of people who have already gone down this pathway to abuse, and have started, and admit to it, and ask them if various attributes of the packaging would have deterred them.

This is hypothesis generating, of course, but it's way to kind of enrich your samples as opposed to asking a generic teenager. It's unclear how useful that data might be because maybe they're not at risk at all. And most people are not at risk of abusing, so maybe go through enriched populations, bottom line.

DR. CHIAPPERINO: Are there any other comments on this question? Yes, Dr. Cox?

DR. COX: Yes. I just wanted to comment about some of the methodologies that were floating around, for example the panels and things. I loved the idea of getting teenagers and both teenagers who are naïve to this and teenagers who have already experienced this. But I wonder at times how forthcoming they may be in those scenarios.

So I just want to point out the idea of also using vignettes and survey information or survey methodology that was mentioned earlier, where you would describe a scenario and a vignette and have them respond to, perhaps on a visual analog scale, how likely they would be to do this behavior.

DR. CHIAPPERINO: Interesting. Thank you. Dr. Bateman?

DR. BATEMAN: Brian Bateman from Brigham and Women's. I'm wondering if we have a handle on the types of opioid prescriptions that third parties tend to access, whether they're opioids that are prescribed to chronic pain patients or to acute

pain patients and were the medications left over from an excessively large prescription.

I think the types of solutions you would contemplate to limit third-party access would be different depending on which of those two populations you're targeting.

DR. CHIAPPERINO: Yes?

DR. HERTZ: Dom?

DR. CHIAPPERINO: Yes?

DR. HERTZ: We actually do know a little bit about that. This is Sharon Hertz. We know that in terms of absolute numbers, the immediate-release opioids are by far more frequently identified in abuse situations, right, than the ERs. And that makes sense, because the difference in the prescribing numbers are many-fold different.

Aside from whether you go into things like ratios that we use for other purposes, it's just a sheer number thing. And whether or not those IRs are being prescribed repetitively is another question. And that's a little harder to, I think, sort out.

DR. CHIAPPERINO: Mr. Berghahn?

MR. BERGHAHN: Walt Berghahn, HCPC. So I think it would be very easy to start up front with the styles of packages and how much evidence the package itself will leave that it's been tampered, which if you're dealing with a 30- or 60-count vial, it's up to your memory how many were in there.

Unless somebody dumps out half the pills, you won't know. Even when you get into certain blisters, it's about your memory. How many did I really take out of this? Is there more than one or two missing? For this particular exercise, until you electronically lock it down so you can know when the dispense events occurred, you're not going to have evidence. Then you get to the extreme where there's these lockable carousels with thumbprint access and so on.

DR. CHIAPPERINO: Dr. Spitznas?

DR. SPITZNAS: So I don't know how much luck you will have, but maybe because you are part of HHS, one thing that you might contemplate is

talking to CMS about the post-hospitalization survey and also talking to some of the vendors for those types of products like Press Ganey, to just get an idea.

I know they still are holding on to some pain questions. They like to take those through their quality measure forum to get them approved, but I think this is going to be, like, a long-term endeavor if you're going to be doing this seriously and having this as, like, a labeling type of thing.

So maybe a partnership with them around a disposal type of intervention so they're collecting data on it about if it was brought up and if any kind of device is provided. And then you would be in a position potentially or researchers would be in a position to provide the device in a clinical trial kind of way or quasi-experimental way and then look at their data afterwards.

They also have quite a bit of data in terms of, does a person develop a disorder down the road. So that may be a way, especially with these acute episodes. And I don't know if the VA has anything

similar that they do, where they would be in a position to look at the aftermath with people who have gone through surgery and gotten a prescription, for example.

DR. CHIAPPERINO: Thank you. Ms. Morgan?

MS. MORGAN: Thank you, Sharon Morgan, ANA. So I have a question about the actual collection of pills in a home at any one time. So I don't know whether the data does exist, but does the number of pills at home in any one time make a difference?

For example, when the VAAs were coming out for hep C treatment, I happened to be working in the VA at the time. We only gave a certain amount a week, primarily so that they wouldn't lose a pill that was very, very expensive. So is there any existing data that exists that talks to, if there are less pills in the home at any one time, there's less chance of diversion.

The other thing, going along with surveys, the use of gaming and simulations, particularly among the young, to really try to get answers to some of these questions.

DR. CHIAPPERINO: Thank you. I think that might actually come up in Session 8 also.

DR. AIKIN: So since questions 1 and 2 got combined, let's move to question 3. For packaging, storage, and disposal strategies that rely on physical deterrence of third-party access, what qualitative and quantitative research strategies could be applied to investigate potential endpoints and study designs?

DR. CHIAPPERINO: Yes, Ms. Whalley Buono?

MS. WHALLEY BUONO: Liz Whalley Buono. So on the disposal point, it seems to me that take-back concept is somewhere where you could take ground very quickly with some pretty creative ideas.

We had been talking a little bit about whether there's a potential to provide mailers to mail back unused drugs. But I mean, if you designed that correctly, it's simple. You're just looking at how much you get back.

So I don't know enough about how it's currently done, whether the drugs received back are

tracked, whether it's just simply a poundage, like in the VA system, or if there are these receptacles in police stations, or at Rite Aid, or wherever else, who is collecting the drugs out of them and what happens to them. But if you could somehow centralize that effort, that wouldn't seem to be a particularly expensive proposition.

But it seems potentially pretty effective in getting BAC out of the home drugs that aren't being used, and then measuring that is as simple as pill count or weight.

DR. CHIAPPERINO: Yes. I think that would have value. I'm thinking about the lag time in people making use of things like that and the opportunities for diversion during that interim, so even though we might get some of the prescription back, I'm concerned that we would maybe draw incorrect conclusions from that as to how much might have actually been diverted before they took advantage of that program. It's just a thought.

Yes, Mr. Smith was first.

MR. SMITH: So this is Chris Smith, NACDS.

In terms of tracking, if you're talking about a take-back receptacle, all you're going to know is the weight.

Your problem is, to start with, the DEA regulations. They prohibit you from looking into the contents. You can't access them. That's it. You collect it. You go through a hazardous waste handler or reverse distribution system, sends it back for destruction. That's it.

You don't know whether there's Tylenol in there or hydrocodone. You have no way of knowing and the regs prevent you from doing that. So there's really not much you can do with that until you change the regs, so that' just not really a starter.

You can't do anything. And then the same thing would apply for the mail back. I think that's just sent directly to destruction.

DR. AIKIN: So as a clarifying question, we're talking about physical barriers as well as things that are tamper evident. Can we use the same methodologies to evaluate the effectiveness of

both of these or do we need different methodologies, I mean, keeping in mind that you can see if a tamper-evident package has been tampered with as opposed to a physical box that someone might take from you?

Can we evaluate their effectiveness similarly? Are there methodologies that can cross both of these?

DR. CHIAPPERINO: We will go to Mr. Webb.

MR. WEBB: My question was answered.

DR. CHIAPPERINO: Then Dr. Emmendorfer?

DR. EMMENDORFER: Just saying, for the endpoints, one thing to consider maybe going to some of what's already been talked about, some of the lock box-type of opportunities. Whatever is for the methodology, a potential endpoint needs to be looking at, I would assume, end user acceptance and are they still using it at various intervals over time. Then if not, why not?

I think that will give information back to those companies that are able to develop better mousetraps or better end user acceptance into a

product.

DR. CHIAPPERINO: Dr. Mendelson?

DR. MENDELSON: So yes. Dr. John Mendelson. So the inverse of abuse and diversion is proper use. It's adherence. And there's a whole bunch of science around adherence measurements. So why not measure the adherence and just assume that whatever's not taken is potentially excess, or divertible, or something and then find ways to decrease the amounts of supply to match what people actually use?

But I think, rather than look for the negative, which is going to be very hard to find, it'd be fun to track down some of these people who steal and divert medications. And I think Dan really enjoys that. He does that for a career and understands them.

But I think it'd be much better just to understand adherence and understand proper medication use, and then you'll understand improper use by definition, the difference between those, what's used and what's left over and not available.

Countering [indiscernible] deposit.

DR. CHIAPPERINO: Dr. Izem?

DR. IZEM: Rima Izem, FDA. I just have a clarifying question. I think the end points that you are discussing are at the unit where the unit of analysis is the person who's getting the drug. Since we're talking about third-party access, I was wondering whether you could think of study design or endpoints where the unit of analysis would be the household, or a geographic area where the intervention happens.

Can you think about that?

DR. CHIAPPERINO: Thank you. Dr. Walsh?

DR. WALSH: In thinking about behavioral type studies that could evaluate different technologies or compare across technologies for those who may be interested in misusing, I mean, you could do qualitative things and do questionnaires and subjective responses about desirability. You could look at timing.

But another potential approach that I don't think we've really used would be behavioral

economics, so looking at demand curves which basically puts into the same formula how much effort is required in order to get a particular reward.

If you were using people that were experienced drug users, you'd be able to quantify what that particular reward was, even though they wouldn't necessarily have to get the reward in the study, which would be contained in the locked box or container.

But you would be able to then generate curves that would compare across different technologies to see what was more or less desirable and what kind of work effort people were willing to put forth for different technologies.

DR. CHIAPPERINO: Thank you. And I don't know that we know to what extent the diverted prescription in the house ends up being used by the person who took it and or is it taken for its resale value. Then you talk about the monetary aspects of this scenario.

DR. WALSH: Right. I think the reality is

that every possible scenario that we can imagine exists, but we also know from large surveys that are pretty well powered that the majority of diverted medication is really coming from friends and family, especially for adolescents.

So it's not necessarily the FedEx man using your toilet, but rather teenagers raiding their parents' cabinet, knowing that they're going to a party or people sharing with good or bad intentions their own medication.

DR. CHIAPPERINO: Thank you. Dr. Cox?

DR. COX: Yes. Elizabeth Cox from the University of Wisconsin. I mentioned this yesterday. I'm just going to bring it up again because we're talking about outcomes that are relevant not to the patient.

As was just said, the range of scenarios out there boggles our minds. And everything that we can come up with happens and things way beyond what our minds can come up with. So I just want to encourage us that we also think about potential unintended consequences that can happen from these

things, the social dynamics and interpersonal relationships in families where abuse is happening are things that we often are not as familiar with if we're not in that scenario.

So when someone discovers that their pills are missing, all sorts of things can happen from there. And one of the things that happens commonly in pediatric offices is, they call up and make an appointment for that adolescent to be seen in the clinic because they suspect use.

But it may not be that adolescent at all. It may be someone else. So just thinking about the unintended interactions that would get created by someone thinking that this person is diverting their drug and maybe it's not them at all.

DR. CHIAPPERINO: Thank you. Dr. Green?

DR. GREEN: Thanks. Sharon, sorry to put you on the spot, but do you know how much of that -- we know the primary source is family and friends -- is willing and how much is actually kind of being taken without their permission or unknown?

I think, when we separate that part out,

because friends and family share, sharing is caring, however you want to look at it. So it's a portion of that that really can be affected by, I think, the strategies that we're talking about and what really is that population. And is it something we can actually move the needle on? Because I don't know that we have quantified what these actions will actually impact in terms of the outcome measure.

I'm just not sure, in all of the discussion, how much effort goes into this for what. What are we going to get for the return on that investment? I'm not sure. Does anyone have good information? I don't know.

DR. MENDELSON: Sold versus given away.

DR. GREEN: Sold, given. I mean, we're talking, I think, about unwilling or unknowing third-party access, not the willingness or just I don't really care, I'll share with friends or my kid has a migraine, 6-year-old, go ahead and try this because nothing else is working. I mean, there's that willingness part, too, so I guess I'm

struggling with do we know how big the issue is that we're actually trying to impact with these measures?

If anyone has a number, that'd be great.

DR. CHIAPPERINO: Dr. Twillman?

DR. TWILLMAN: As I recall, the numbers are about 55 percent or so was given by a friend or family member. The other remaining 50 percent is divided between being sold and being stolen.

DR. CHIAPPERINO: Thank you. Dr. Spitznas?

DR. SPITZNAS: I will check with SAMHSA before the meeting is over to see if they have the most recent NSDUH, and if that is something that is broken out, because I agree. I mean, if it's a very small percentage that are being stolen, then you might not want to be going down this rabbit hole.

DR. CHIAPPERINO: Thank you. Why don't we move to the next question, number 4?

DR. BATEMAN: Can I just make a quick comment?

DR. CHIAPPERINO: Yes.

DR. BATEMAN: I just pulled up the most recent data from SAMHSA, and they do break out in their survey of people who use prescription opioids non-medically, whether it was given by a family or friend or stolen from a family or friend, and the given vastly exceeds the rate of stolen.

DR. CHIAPPERINO: Thank you. And that was Dr. Bateman for the record.

DR. GREEN: Can you repeat those numbers again? Sorry.

DR. BATEMAN: So of people who used any prescriptions, opioids, non-medically -- this is Brian Bateman -- it looks like 55 percent or so were given by a family member for free and on the order of about 10 percent were stolen from a family member or friend.

DR. MIECH: Can I add to that, too?

DR. CHIAPPERINO: Yes. Dr. Miech?

DR. MIECH: So I've been busy looking up numbers as well from Monitoring the Future and they're very similar. For 12th graders, 50 percent were given the prescription opioid. It's a little

higher in terms of taking; 30 percent report that they took it. So it seems to vary by age somewhat.

DR. GREEN: So maybe the better target is adolescents, because I don't know, because adults have other resources. If you're not going to get it there, you're going to buy it on the street, you're going to look online, or there's all kinds of others. Dan can probably speak to all the different avenues of how these medications can be sought.

So maybe that dose help target. Maybe there is some benefit of targeting that specific population instead of trying to address everything.

DR. CHIAPPERINO: Thank you. So we can move on to question 4. For packaging, storage, and disposal strategies that are cognitive or behavioral and designed to limit third-party access, what qualitative research methods can be applied to gather information to inform development of quantitative measures such as questionnaires?

Dr. Ciccarone?

DR. CICCARONE: Dan Ciccarone, UCSF.

Dr. Spitznas of ONDCP brought this up earlier, the notion of ecological momentary assessment. So for those who don't know, this is a tool which uses a cohort design. And this could be a cohort of folks who are -- it could be any behavior, but it could be anywhere in the spectrum from a group of folks that are just ordinary medication users or it could be a group of population at risk, followed over time and then measured randomly momentarily about what a behavior is at a given moment.

So given these technologies, these options here, it could be about the burden of packaging. Is this package easy to use or does it get in the way? Are you cutting through it because it's too difficult?

It could be about the household. Do you have any concerns about where your medications have been? Just like they asked you at the airport, has your bag been with you the whole way in the airport? Do you know where your children are? No. Do you know where your medication is?

So it could be both on the positive side, as

John brought up, or it could be on the negative side. But this is somewhere in between, a cohort study and more qualitative because you can actually have people text you back an open answer.

DR. CHIAPPERINO: Thank you. Others? Dr. Cox?

DR. COX: Yes. Elizabeth Cox from the University of Wisconsin. I'll just quickly point out that NIH has a large initiative going with the promise measures, where they're using qualitative techniques to develop many of those measures and then the ultimate goal is to have validated quantitative measures. They have quite a bank of pain-related measures at this point, both for adults and kids as well as smoking-related measures.

I don't know what they have in the way of adult opioid-use measures, if anything at all, but there's always someone from the FDA at our panel meetings for that and it might be worth connecting with her.

DR. CHIAPPERINO: Thank you. Others? Yes,

Ms. Whalley Buono?

MS. WHALLEY BUONO: Liz Whalley Buono. So I don't know how feasible this would be, but I wonder if there are learnings from the 99DOTS program for TB. And those are in underserved regions, obviously, but there's a tremendous amount of information on directly observed therapy and how effective it is.

Now, in that case, they were looking at obviously disease control and taking the medication, but I think what you learned from directly observed therapy strategies could also be used for detecting issues like having insufficient information, taking too much information, that sort of thing.

So it's a big throw-it-against-the-wall kind of comment, but there's a whole lot of information on directly observed therapy strategies. And that's gone remote now, so now, DOTS are using things like telephone applications where there's cellular coverage, so it's not necessarily either the clinic or a loved one who gets trained to

directly observe, but now they're using technology in those modalities as well.

DR. CHIAPPERINO: Any others?

DR. AIKIN: So let's move to question 5. In the post-marketing setting, are there existing or modifiable data sources that could allow detection of tampering with product packaging as well as third-party access?

DR. CHIAPPERINO: Dr. Emmendorfer?

DR. EMMENDORFER: Tom Emmendorfer. Has there been any thought at having or utilizing the FDA MedWatch system? Or I don't know if there's MedDRA terminology that could even be coated to detect this. But have you looked at any spontaneous reporting systems like modifications of existing systems to try to capture this?

In the VA, we have our system that reports up to the MedWatch program and we use the same MedDRA coding systems.

DR. STAFFA: Right. This is Judy Staffa. I think we can occasionally use our adverse event reporting system for signal generation, so it can

be helpful in instances where, when we approve a product, it doesn't appear to us that it needs to be scheduled, that it's anything that's abused.

It's sometimes based so that we can get reports in of people abusing it. And that can bring to our attention that maybe we need to do a little more thorough analysis. Maybe there's something about this drug we weren't aware. But for drugs, when they're known to be abused, we typically don't use it because people just don't think to tell us about it because it's typically a labeled event.

So they tend to not report. So in the era of opioids, so many of them are older drugs. Typically, I mean, we do get some reports, but it's hard to know what's driving them. And they're so incomplete. With a package, I guess, if we did something new with packaging, there's a possibility we could get signaled reports, but I just don't know.

DR. EMMENDORFER: I was just looking at it, at existing or modifiable data sources, and trust

me, I understand that's outside the scope of MedWatch program, but thinking outside the box, is there a way to adjust that form with this opioid epidemic where is it valuable information to try to encourage healthcare providers to report these type of events into that system to try to generate a signal?

DR. STAFFA: So would it be the provider or would it be the patient that would report that?

DR. EMMENDORFER: So I think that, at some point, it's going to come back up to the healthcare provider in some way, shape, or form. So for us, this gets back into the early refill requests. Right? So most of us probably that work in a pharmacy have some sort of standard protocol where they're coming in, saying the prescription has been lost, stolen, damaged, or early refill.

Depending on the scenario, do you require a VA police report? If you require a police report, what is it that you're capturing? So at some point, if that supply is running out and there's some sort of tampering has gone on, at some point I

believe that patient's going to probably either present to a healthcare provider or they're going to go obtain it illegally in the streets.

So for those where they come back to the healthcare providers, there may be an opportunity there if you're looking for a modifiable data source.

DR. CHIAPPERINO: Ms. Cassidy?

MS. CASSIDY: I guess, in thinking about in the post-market setting, existing or modifiable data sources, there might be some utility in data sources that already exist that are monitoring misuse and abuse and as it relates to detection of tampering.

So we're already looking at internet discussion as it relates to tampering with products, opioid formulations that are intended to be abuse deterrent to see if people are trying to manipulate those individual tablets and extract the active ingredients.

So similar conversation could be taking place around products that have been packaged with

specific types of packaging and third-party individuals who are intending to use them illicitly, trying to interact, and their experience with being successful or not.

The other data source that comes to mind that might have some value as well in terms of being modifiable is from the substance abuse treatment center data that we're using from the NAVIPPRO dataset.

We collect source of drug for different product-specific prescription opioids and one of the items that was mentioned earlier -- I don't know if it was earlier today or yesterday -- was, if we have the ability to package things so that it's more difficult for people to break into them, the third party might -- it might have already been broken into when they receive it.

So understanding whether maybe we could modify or add to data collection through those sources to understand whether somebody who is entering treatment or being assessed for treatment received a particular drug that was already without

package or in package could be helpful to understand whether any package that was provided in a post-market setting would have some kind of barrier for individuals who might be intending to use them illicitly.

DR. HERTZ: So I wanted to just try and drill down on that -- this is Sharon Hertz -- a little bit because people receive their drugs from the pharmacist. So I'm not sure. And frankly, pharmacists break into the packaging all the time as they refill them into amber bottles. So it feels like what you're saying is a little bit more about something outside of the chain.

MS. CASSIDY: Yes. I guess I was thinking about individuals who are not prescribed necessarily these medications, but are misusing them or get their hands on them. So this don't necessarily be the patient population.

DR. CHIAPPERINO: When you talked about source, what level of detail do we have in that database about source?

MS. CASSIDY: We have similar level of

detail as in Monitoring the Future and NSDUH, but I guess I'm just thinking about whether we could modify those questions and adapt them to understanding whether somebody who doesn't get prescribed that particular product but received it somehow is intending to misuse it, if there was packaging or non-packaging involved as part of their source.

DR. STAFFA: I also wonder. This is Judy Staffa. As part of that, I don't spend a lot of time on these internet chatrooms where folks share recipes for defeating abuse-deterrent formulations, but I know it goes on. But I'm wondering if there's a way to expand that to chatrooms where teenagers might be sharing information, because I'm thinking they're probably not on Bluelight or some of those, but maybe, again, given that they're always on their phones, they're probably somewhere where they're sharing that information.

MS. CASSIDY: Right. I think you are right about that in terms of the adolescent population, maybe, like Instagram, YouTube, those types of

social media sites, where adolescents are sharing information could be another data source, data stream.

DR. CHIAPPERINO: Dr. Scharman?

DR. SCHARMAN: Yes. I think in looking at modifying data sources to look for possible areas of diversion, let's say, or a teenager that's entered the healthcare system, whether it was their prescribed med or someone else's med that they got into, I think sometimes if we look at national data sources to modify the Monitoring the Future study or change the National Poison Data System, to change a national database is very difficult.

There are multiple layers of approval and this and that. But if you look at more of a cohort design and you get pieces of that national database, so a state within the Monitoring the Future or a state within the NPDS that's willing to because they have the capability of modifying their database internally, do it differently, and then do larger cohort studies, looking at a state where you make an intervention with packaging and a state

that you don't, that might have some possibility.

You make it a state where the school system is willing to accept and modifying Monitoring the Future survey rather than saying, no, no, no. Unless it's proven nationally, we won't let it into our school system.

So maybe let's try not to go nationally and go state by state, where you make an intervention and then check that state. That might be a more meaningful possibility.

DR. CHIAPPERINO: That's a very good idea.

DR. CHAN: Can I ask one clarifying? Also, if we're thinking about tampering -- because remember we've also talked about inpatient, which gets a little bit trickier, and we talked about the fact that sometimes, with these single tamper-evident features like a vial or whatnot, that still slips through the system.

I think, to get at what Dr. Emmendorfer was just saying, too, you had asked a question about the surveillance and what we'd look at. Probably some of those things could show up theoretically as

quality reports. Right?

They may assume, if they're seeing something without a cap or something else going on, they're thinking this was a transport issue and it's something that's a manufacturing issue, and that's where we might glean some of that.

But when that's not the case and you are talking about someone who has gone in and replaced a substance or whatever it might be, is there a mechanism we can think of? We know these are like incident reports being filed at hospitals, but is there a mechanism that we think collectively we can look at, that broader data?

Do we look at a closed system, which has many facilities? Are we looking at the VA? Are we looking at the Kaisers? Are we looking at these types of systems to get a broad set? So I'm curious, throwing that back out there until we get the inpatient angle as well.

DR. CHIAPPERINO: Dr. Mendelson?

DR. MENDELSON: Yes, John Mendelson here. So a couple of interesting data sources for you

guys to consider, first the DEA Microgram. If you're not on the list, you should get on the list. And it actually used to be public, but now you have to get on a list. And I think I've fallen off it because I haven't gotten one in a while.

But it's all the DEA wild cases, the fake pills they've collected, the interesting smuggling techniques, like frames of bicycles. It's sort of a DEA hit list of what was odd this month, and it's got some great stuff in it, and it actually is useful.

The second, we actually published a paper with Erowid. Erowid is a drug information service that collects trip reports and has all this information on how to abuse hallucinogens, and marijuana, and stuff. And it's run by two people named Earth and Fire. That's their actual legal names, because they had that on the paper, Earth and Fire, and they wanted to know whether we would be okay with being on a paper with someone named Earth and Fire.

So I am. But they're actually very sweet

people and they're actually interested. I just looked. They don't have a specific section on packaging or adulterants, but I think they'd be interested in that. I think if someone from the FDA approached them, that they might actually go for that.

Doug's shaking his head there like he's waiting for the congressional question, why is the FDA working with Erowid? And Earth and Fire? Exactly, exactly. It's a little different than some of those southern names. At any rate, the Microgram and Erowid would be two interesting extant databases for you.

DR. CHIAPPERINO: Thank you. And Dr. Spitznas?

DR. SPITZNAS: I'm just going to back you up and say we had them into NIDA for a meeting on adolescents. And the other one that comes to mind on the light clear web is Bluelight. And there's a lot of information out there. They I think are amenable to partnering with researchers, as long as you're --

DR. MENDELSON: Only unreputable labs publish with Bluelight. Only good labs publish with Erowid.

DR. SPITZNAS: As long as you are on that thought, the other thing is that I've seen at least a recent CBD of fairly interesting work on analyzing the Twitter sphere. So I think that might be some place that you could look for some of those qualitative information, that there are some people out there that are doing some of this innovative work in that area, looking at diversion and, to some extent, where it could be located.

DR. CHIAPPERINO: Thank you. Mr. Webb?

MR. WEBB: Kevin Webb, Mallinckrodt. As we think about the inpatient setting, would it be possible -- and I know there'd have to be some patient blinding -- as patients leave the hospital with prescriptions, either through surgical or through the emergency department, is there any way that you can use such as address data to then check re-admissions at a future date?

It would obviously have to be from an

overdose, but I think that would infer that some type of tampering took place or some type of diversion. And so if there's a way that you can just kind of maybe close the loop using the health systems that we have to show what's coming out and then maybe what's going back in to the system and try to connect it from that perspective.

DR. CHIAPPERINO: Thank you. Ms. Cowan?

MS. COWAN: Penney Cowan, American Chronic Pain Association. What Kevin just said -- I think that it could be that their pain is out of control. I mean, I don't know that it's always administering. People take far more than they should just because their pain is out of control and then they'll take wine, and beer, and everything else with it, too, because they're trying to get rid of the pain.

MR. WEBB: Yes. You have to look at the reason why, but is there a way that you can drill down into it?

DR. CHIAPPERINO: Thank you. I think we are going to move on to the next question, question 6.

So within the spectrum of potential prescription drug abuse behaviors, where should efforts be appropriately focused to achieve the greatest benefit from packaging, storage, and disposal options? Yes, Mr. Webb?

MR. WEBB: Kevin Webb, Mallinckrodt Pharmaceuticals. We've been, as all of us in this room have been grappling with this issue for many years, our approach four years ago, five years ago was looking at it from the bookend approach, the beginning and the end. How are we as a manufacturer can be influential in trying to minimize the amount of supply, but then how can we help to advance disposal initiatives?

So we look at trying to -- in the next section, we'll be getting into disposal, so we'll share some thoughts there. But if we're focusing on the middle, where that diversion or that accidental misuse may be occurring, I would suggest that we look at -- we're trying to prevent the diversion, recognizing that accidental exposure is important. But trying to do something beyond the

85 percent of confidence interval of having child-resistant packaging, I don't know what more we can do to try to prevent accidental exposure. But if we can do more to prevent the intentional diversion of it through safe packaging, I think that gives us the benefit of starting to have an important impact on minimizing the intentional misuse of medications.

DR. CHIAPPERINO: Thank you. Yes, Ms. Cowan?

MS. COWAN: Penney Cowan, American Chronic Pain Association. I think it goes back to -- and I sound like a broken record -- education. I think that's a critical part of all of this. I mean, we can invent the best mouse trap in the world, but unless we really educate people about the dangers of using these or making access to these medications in any way they can -- I mean, if you invent it, they're going to probably figure out a way to get through it. But I think, if we can educate a larger population, general public, I really think that there will be an impact. And

there hasn't been a massive media campaign around inappropriate use of opioids.

I think some of the wrong people are getting hurt. People living with pain are losing access because of this. So while we're thinking about all this, I think we need to think about the education and reaching out to the public.

DR. CHIAPPERINO: Thank you.

Dr. Emmendorfer?

DR. EMMENDORFER: I believe it was said that, what, 55 percent of people and 30 percent of adolescents use when they get it from a friend or family member? So to me, I would think that makes a pretty strong argument for improving disposal options and promoting those disposal options in our healthcare system with the take-back receptacles or the other mechanisms that are available.

I agree having a better educational campaign around the importance of using that to get them out of the house.

DR. CHIAPPERINO: Thank you. And last question so we could get to the next question,

Dr. Miech?

DR. MIECH: Clarification first and then a question. So when you talk about the spectrum of potential prescription drug use behaviors, what does that mean?

DR. CHIAPPERINO: I think we mean individuals with varying levels of opioid-use disorder or the casual opioid user.

DR. MIECH: I see. That's what I thought. I just wanted to clarify. This is Richard Miech, University of Michigan. And I want to second the call for education.

We published an article in Pediatrics this year where we looked at kids who had legitimate prescription opioid prescriptions. And we wanted to see if that put them at risk for misusing two or three years later. These are 12th graders.

It did slightly, but what was really interesting is that the people who used prescription opioids were most likely to go on to misuse them later were the kids who were drug naïve, who had very little drug experience.

The kids who have a lot of drug experience in 12th grade, it didn't matter whether they had a legitimate opioid prescription or not. They were just likely to misuse. I mean, the fact that they had experienced a prescription opioid made no difference to them.

So it seems like it's the drug naïve -- this is the conclusion we reached anyway -- who are very impressionable and also I would think very open to public health campaigns and from statements from their doctors and medical professionals. I think it's those kids who are not very drug experienced who are at a substantial risk and also would be very open to potential messages.

DR. CHIAPPERINO: Thank you.

DR. AIKIN: So question 7, what types of pre- and post-market studies might be useful for supporting a claim that a packaging solution is expected to reduce use by persons other than the intended patient pre-market or reduces in the post-market setting, used by persons other than the intended patient?

You were talking about studies that might actually support a claim.

DR. CHIAPPERINO: We heard yesterday that there may not be a great interest in industry to obtain these claims, but then we also heard that, in fact, some companies are already pursuing these sorts of claims, but we're certainly not at a point yet to figure out appropriate language for that because we have not had a successful venture in this area.

Anyone have any thoughts what a claim might look like in this context? Dr. Mendelson?

DR. MENDELSON: Increased adherence. I think that would be right and therefore less diversion.

DR. HERTZ: I don't know that. I mean, that's an assumption that would require some work to connect those two concepts.

DR. MENDELSON: If they took them all, it's not -- if someone takes every pill that you give them --

DR. HERTZ: Well, we don't necessarily want

to encourage that with opioids. It's not antibiotics.

DR. MENDELSON: Give a smaller amount.

DR. HERTZ: I think what we're trying to get at is more the study design a little bit, but what's the way to communicate? What advice should we be giving you guys when you're coming in with packaging solutions? And if you really want to be able to talk about it as something that's been reviewed, that is expected to reduce the problem that's being targeted.

DR. CHIAPPERINO: This panel is third-party access, so we're talking about abuse and not so much misuse on this panel. Mr. Webb?

MR. WEBB: Kevin Webb, Mallinckrodt Pharmaceuticals. It's a complicated question because you're trying to associate a value to an investment. What we learned as a manufacturer is that physicians, when you're talking about such things as abuse-deterrent technology or formulations or just abuse in general, physicians are very reluctant to even acknowledge the fact

that their patients may abuse or misuse their medications.

So when we've had the conversations or when we've had the market research -- and again, I'm not generalizing across all physicians, physicians in the room here -- more often than not what we hear is that, well, that's not my patient, or they don't abuse, or I don't need to be worried about that, or we've heard physicians not really understanding what the value proposition of abuse-deterrent technology is, thinking it's a less addictive medication.

Physicians and patients for that matter don't associate a value to safety on the medications. They're not willing to pay more for it. So when you get to what type of claims do we want to put on types of packaging -- and the other part I was going to make on the research we've done through the Cancer Society and the Partnership for Drug-Free Kids, when it came to physician-patient interaction regarding the use of opioids, they did a fantastic job of helping to educate the patient

regarding what to watch for, what to avoid, how to take your medication, adverse events, et cetera. But when it came down to storage and preventing misuse, it just fell off the radar. There were so many other things that they were trying to discuss that you just never got to that.

So to suggest that we're going to change that behavior by putting something on a claim when they are not there yet to identify that there's a value of trying to prevent misuse of medications, it's a struggle we're trying to deal with as well.

So I guess it goes back to Penney's comment that the better job that we do of just educating the healthcare community and the patient community on the importance of disposal, on the importance of safe use, this is an important area that requires discussion before we even get to any claims. Those discussions haven't taken place yet.

DR. CHIAPPERINO: Dr. Mendelson?

DR. MENDELSON: Yes. So I feel your pain here, but what you want you're going to measure on a population outcome basis. How much diversion

happens, you're going to measure that on a population. And the individual behavior of the patient is going to be measured at that level. Those are two separate measurement points and ways of thinking.

So I think from the patient point of view, you're going to won't adherence and disposal? And I think, like that product you had there was very nice. If you come in with a product that really looks great on adherence and disposal, then there's no excess to divert if you can really assure yourself of those statements.

So you frame it in the positive for the patient. The patient's got to be using it. And you're right. The physician's got to understand that his or her patient is using a medication and not like being labeled a thief, or a crook. The docs, we're defensive about our patients. We don't like them to be thought of as bad because that probably means we're bad people, too.

So I think you've got to keep, from the patient side, everything on the positive, and on

the population side, it's a different set of equations.

DR. CHIAPPERINO: Now, on the patient side, though, there's still this sort of black box in terms of the patient adhering to their use of the medication and hopefully or maybe not needing to use all of it. But we'll never really know in our present system, as we heard, the way the DEA is just going to destroy all returned medicine.

So how do we fill in that information as to patient adherence resulted in such-and-such number of pills taken out of the diversion pathways?

DR. MENDELSON: I think if you received them back in a particular way, you can do a count.

DR. CHIAPPERINO: I think that is a big if in terms of the present system, the way we've been hearing about it today.

DR. MENDELSON: I think people could photograph it before they send it. Again, if you incentivize them in some way -- if you incentivize them, they'll do it. I think it's a question of whether it's worth it or not.

DR. CHIAPPERINO: Yes, thank you.

Yes, Ms. Whalley Buono?

MS. WHALLEY BUONO: Liz Whalley Buono. So if I'm not mistaken, we're not talking about treat, mitigate, cure claims. We're really talking about an FTC, business-to-business claim here. And the standard for that is set. The standard is not false or misleading.

So I'm not sure whether FDA, really -- if we're talking about the type of claims, that FDA needs to be regulated, because we're talking about a package. And the package, yes, is technically regulated through FDA and that it's got to be approved as part of the drug application.

But a B2B sale to a manufacturer of a package type is an FTC business claim. So that's a lower bar that's already been set, and usually the type of evidence that stands behind an FTC claim, which does not require a pre-submission but needs to be defendable, is really things like consumer engagement, panel work, that sort of thing, 9 out of 10 dentists prefer.

So those standards are set, and to set a third type of bar, I think, just maybe complicates things.

DR. CHIAPPERINO: I wouldn't argue that at all, but I think, in thinking about labeling more broadly, for example a house-applied section in the prescribing information, that's more communication to the healthcare provider, and if that provider can learn in the house-applied section that these packaging configurations are potentially less likely to result in diversion --

MS. WHALLEY BUONO: Then I think you use the typical type of FTC language, which is the package is designed to. In my mind, we're putting way too much import on that claim substantiation, that this package has been clinically proven to. I don't think you're ever going to get all the way to right on that type of -- especially not in the time frame we're looking at.

DR. CHIAPPERINO: Thank you. Dr. Mendelson?

DR. MENDELSON: Yes. That's really smart because if it's FTC cleared, then it can be

advertised and sold. It can be advertised, so you can give little cups out, and little pens, and the little things that make doctors prescribe things.

MS. WHALLEY BUONO: I didn't say that. What I said was that I think the bar is an FTC, not false or misleading.

DR. MENDELSON: But if it's not a drug sale --

DR. RAULERSON: Sorry. Let me interrupt for a second. The question was getting at the kinds of studies that might support an FDA-approved claim in a regulated drug product labeling. I think the conversation went way outside of FDA's jurisdiction for the last five minutes.

DR. MENDELSON: Which maybe where you want to go.

MS. WHALLEY BUONO: I just question whether there should be an FDA-approved claim. That's all.

DR. RAULERSON: We discussed yesterday that there's disagreement amongst stakeholders about whether there'd be value for something like that, but that's what we were getting at here. And that

kind of thing is, if it's within the prescribing information or the instructions for use for the patient, it's going to be held to a standard that we hold labeling to.

MS. WHALLEY BUONO: So let me challenge you on that.

DR. AIKIN: We want to make sure we have time for audience participation. We have a couple more people on the list to speak.

DR. CHIAPPERINO: We have two more people to get to. Thanks so much for your comments here. Dr. Spitznas?

DR. SPITZNAS: I just want to go back to what I said earlier around I think that this new knowledge that we have about the adolescent population and their likelihood of diverting being higher than populations where they're not likely to divert more, the adult population, I think that that could be a target population, and I would really like to see because a lot of these things aren't going to be necessarily drug specific. They'll be specific to opioid pills.

A large health system will take a look at this and look at literally signing these parents up, and get that snip from that adolescent's hair, and do the hair sample with something like this, because I think it could be worth it and it could be done maybe in partnership with CMS and their innovation center, to just answer the question, does one of these disposal solutions actually work or does the calendar method of the 7 days of pills actually work.

It's an investment, and I guess I would like to know from the manufacturers here what is that worth to you. How much of a business case can be made for that? Is that something that you would actually be willing to sponsor or is that going to have to be something that another company comes in and tries to pull off, in which case, they're going to need to look at getting insurance coverage. And CMS or the other provider plans, insurance plans, they're going to have their own standard.

It just sort of depends on if anybody's going to be willing to pay for it at the end of the

day. It's not just will FDA adjudicate that claim or allow the claim, but then to get it into the healthcare system, it's got to add value down the road.

DR. CHIAPPERINO: Thank you. Dr. Cox, last comment?

DR. COX: I'll just yield my time. It was covered. Thanks.

DR. CHIAPPERINO: Thanks so much.

Audience Participation

DR. AIKIN: Thank you all very much for a very robust discussion. We'd like now to offer the audience a chance to participate. Any audience members that would like to speak, please line up in front of the microphone. There will be a staff member to assist you. Just to remind you, please focus your comments on this session's topic. Limit your comments to three minutes or less. Utilize the red-yellow-green light system.

DR. SULLIVAN: I am John Sullivan. I am an entrepreneur. We're developing an electronic blister pack monitor. And I think that there's

been some great ideas. We started off that we didn't want a 5-year-old to get into the drug. Now we don't want anybody to get into the drug.

That's all doable, but it really gets down to at what cost level, and back to the manufacturing. Our goal is to make this monitor as cheap as possible because, if it's not a low-cost product, it'll never make it into the marketplace.

So we're using off-the-shelf blister packs, so it's not anything custom. Anybody can make this thing. Any manufacturer has a blister pack machine, they can mold the blister. What we do is the label that goes over that pack. So when you pop a pill through this conducted ink-printed material, it records the date and time.

Back to why is that important? Well, we have a predictive software that looks at the patient's consumption, so you're taking it every 8 hours, every 7 hours, every 6 hours, every 4 hours. We can model that and come up with what is an addiction cycle, what does it look like.

That's what's never happened. We don't know

what addiction looks like. According to the National Institute of Drugs, some people can get addicted to opiates in less than 2 weeks. So we're saying, the 7-day people, don't worry about them.

The point is that the person that's that 2-week person, they will show up in that 7 days because they're going to have a completely different consumption than the average person because of the fact that they do have that lower marker for addiction.

So the other important part of this is that, if you know you're being monitored, you're going to take these drugs differently. That's number one. But the second part of it is that we identify who those early addiction people are that are starting to take them closer, and closer, and closer, and closer. The software will look at that and say, hey, we've got a problem here.

So they notify the doctor, they notify the therapist. We do an early addiction treatment on this person before they get into the full blown. And the second part is that the person that's

addicted, they're going to take this monitor off, and we want you to. This monitor comes right off the blister pack. You push two buttons and it comes right off. We want you to take that off because you're identifying yourself as somebody that needs treatment.

So a lot of these people are going untreated with this addiction. I have a friend of mine who's been on opiates for 7 years. And I asked her the other day, I said, "How are you doing?" She said, "Well, I'm doing 4 opiates a day and a fentanyl patch, but I'm not addicted." I said, "How do you know?" She says, "Because when I try to go up for 24 hours, I just couldn't get out of bed." I said that's withdrawals. But in her mind, she's not addicted because she's never been told by the doctor that she is.

So these pain mill doctors that are overprescribing, 100 percent of their patients won't be able to take back this monitor, and it'll show up in the data. It'll alert people that that doctor needs to be brought in as well for

overprescribing for profit motivations.

In my case, I lost a son to a doctor in Frederick that for $300 a prescription, every kid could go and get one. It got into his high school and it killed 20 kids. That doctor would have been notified the first 30 days because none of his patients could have returned this monitor, and they all would have come up with a failing grade.

So in addition to diversion, it's also a valuable tool for law enforcement to shut down these pill mills. And if you don't have that data, there's no way to shut it down, because typically they shut them down when they get the body count. That's how they know that they've got a problem.

This is an early warning system to say that not only is the patient not following the rules, but the prescriber's not as well. So it's a dual-use system. And I would love to work with any of these manufacturers that are working on this problem. I'm here to help. Thank you.

DR. AIKIN: Thank you for your comment. Are there other audience members?

(No response.)

DR. AIKIN: At this time, we'll take a break and we will reconvene at 3:30. Thank you very much.

(Whereupon, at 3:15 p.m., a brief recess was taken.)

DR. STAFFA: Hello. If folks could take their seats, we'll get started with the last session; that's right, the last session. The sooner we get started, the sooner we'll get you out of here.

Session 8 Presentation – Sharon Hertz

DR. HERTZ: Hello, you hail and hardy few who remain. I am just going to go through a handful of slides that you've already seen before, so I will go through them very quickly just to kind of hopefully focus us a little bit.

Basically, we're just going to be talking about excess supply. Now, we've already talked a lot about excess supply, so I'm really hoping for some innovative comments on excess supply, to put the pressure on you folks a little bit.

We already know that a lot of this is about changing behavior as really at the heart of being able to deal with this excess. So how can we reduce barriers and promote use of methods to reduce excess supply?

Let me just start off by saying, if anyone wants to say, well, we just need people to prescribe less, yes, we know that. And there are many efforts going on within the FDA that are looking at different aspects of that. So really, what I'd like to do is really try to focus this on, for instance, the example on the slide.

If people think that some type of blister/unit of use, unit dose, which I have learned recently are not the same thing, approaches may help, how can we garner more support on the prescriber side so that these have value? Right?

So how do we tackle the point that was raised in the last session, that we have to get prescribers to value the intervention in order to adopt the intervention? So how do we do all of that? And similarly, on the patient side, how do

we balance or get acceptance of perhaps a bit more inconvenience? Is there a way to help people understand the value to offset whatever imposition might be associated with new change?

Do we think that we want to pursue surveys? There was already some discussion on that. We need information on preferences, barriers, unintended consequences, utilization trends, and effectiveness. So how do we get that data? We're looking to you folks for these answers.

So going back to the beginning, the excess supply issue is really fueling this. We were having internal conversations. I think about this a lot. We think about this a lot. It's interesting because we regulate industry. I mean, we're not a board of physician quality assurance.

I kind of imagine the problem sometimes to be this large creature, and we're poking at it from many different ways, and the excess supply thing is really what's feeding it. So we can continue to poke at it in different places and make it uncomfortable, but really until we starve it and

shrink it, it seems we're never going to make any progress.

So with that, we're going to have to consider where along the different systems here and the different problems we can assess the impact of options. Is it enough to know that the options are being used? Is it useful to move some of the distal outcomes?

Obviously, if we can lessen the frequency of opioid-associated deaths that are related to prescription opioid products that have been prescribed -- so it's a narrow subsection. It's not all opioids. It's not the truckloads that get diverted.

Is that the goal, and should we be trying to measure that? That gets us back to the same kind of problem we have with the ADFs, the abuse-deterrent products, in terms of how do we do that.

Panel Discussion

DR. HERTZ: So here we have the questions. So we have five questions. We have 45 minutes. Paul is going to keep track of who's next. We've

been discussing over these days how excess supply potentiates the other problems of accidental exposure, misuse, third-party access. Today, we've been discussing methods and data sources that could be leveraged to evaluate options in both pre- and post-market setting. Basically, it's going to be tough is one very high-level summary.

What we'd like to know is whether, in the post-market setting, there are additional data sources not previously discussed that could allow detection of the packaging, storage, and disposal options intended to target excess supply.

So any takers? Who would like to be first?

MR. WEBB: Kevin Webb, Mallinckrodt. I'd just like to share with you a study that we funded through CADCA, the Community Anti-Drug Coalitions of America. The study was intended to flesh out how do we change the behavior in individuals to willingly dispose of their medications, knowing that we're all grappling with this issue.

But the study didn't deliver the results that we wanted, but I'm going to share with you

where and why it happened that way, but I'm more than willing and happy to share the data that we have.

I think there's a part of it or something else that really hasn't come up yet in the two days we've discussed as far as the whole environmental component. We set out to measure -- we knew that people held on to their medications. What we tried to find out is what would motivate them to dispose of their medications.

So we sought out to measure, would you dispose of your medication because of the risk it posed to you or your family, would impose a risk to the community, or to the environment.

What we have right now is a one-size-fits-all message, lock up your medications or dispose of your medications, or don't share your medications. But if we can be a little bit more granular in our messaging towards certain market segments such as teenagers, or young adults, or elderly, would someone who's elderly be more motivated to dispose of their medications because of the risk to their

grandchildren as opposed to someone who's 30, who may be interested in disposing unused medication because of the risk it may have to the environment.

So that's what we're trying to determine, and in that way allowed us to direct our messaging to certain subsets of the population to hopefully have an incremental success based on who it is that we're actually speaking to.

The challenge we ran into, though, was the that it was a sample bias. We had a disproportionate of elderly white women who volunteered to take the survey. So what that meant to us is that we couldn't understand -- we had the chance at getting -- because they would have to then go to do something, like go to this website, complete this survey, or come back to this place, and did you actually dispose of your medications?

So we were asking them to do something after the fact. So we had to figure out first, we could think about future studies, realizing that you're asking them at the time, before they acted on did they dispose of their medication. We don't have a

response yet, but then now they had to think about coming back for the survey afterwards. So that now became a challenge in and of itself.

We believe, and I still believe, that if there's a way to get to some type of message that changed behaviors based upon the age group or socioeconomic class or who they are, I think we'd have better success in actually motivating them to dispose of their unused opioids.

DR. STAFFA: Dr. Bateman?

DR. BATEMAN: Brian Bateman from Brigham and Women's. So I guess as we're thinking about this idea of a Z-Pak of opioids for a particular pain indication, my question is how is FDA going to determine what goes into the Z-Pak? What type of opioid? What strength? And how many tablets?

I think for many or most pain indications, we don't really have a handle on what patients actually take. And I think having those data are really an important prerequisite to putting together packages that make sense. So that might be an area for FDA to invest in some research.

DR. HERTZ: So you know I'm just going to ask you how to do that.

(Laughter.)

DR. BATEMAN: I'll give you an example of a study we did. We did a survey study of 700 patients that had Cesarean deliveries that were taken care of at centers around the country. We phoned them up two weeks after their C-section and asked them to do count-backs of how many pills they took, and found that the average number of tablets prescribed was 40. Patients on average took about half of that.

Interestingly, there was a correlation between the amount that patients were dispensed and how many they took that was independent of their pain in the hospital or any particular characteristics of a procedure.

So I think doing these surveys is going to be challenged by the fact that there's an expectation setting in the amount of opioids that patients are prescribed and what they actually end up consuming. So despite the fact that patients

were prescribed more took more, there was no difference in refill rates or in patient pain scores or satisfaction.

But I think at least that kind of a design would be a starting place for thinking through what would go into these kinds of packages.

DR. STAFFA: So this is Judy Staffa. I'll push you one step further. I think those kinds of data can help us understand what those package sizes are that we would then put in some size package, and it may be very different for different indications or different specialties.

But then once we do that, how do we measure how much of that has impacted? How do we define what excess supply is or was and whether we've impacted it?

DR. BATEMAN: Yes. So I think you're going to need data sources where you capture the amount prescribed for a particular indication and see whether there's some reduction associated with the introduction of this technology. And that'll have to be coupled with some type of interaction with

patients to evaluate satisfaction and pain scores.

I think something you could measure, EHR or some other data source, would be the refill rate, so you'd certainly be interested in understanding how these limited prescriptions impact on that as well.

DR. HERTZ: So I want to describe a challenge that we've had, one of the ones we've learned from abuse-deterrent opioid formulations, and see if -- so when we've had the very first abuse-deterrent formulations that went on the market, they replaced prior versions of the same product. And at the time, there weren't generics.

So there was something of a before and after. After we got through the overlap period in distribution, we had a before and after. And we've been trying to understand what happened in that before or after. We discussed some of that at an advisory committee, but what we found is that, with other situations where there's already a number of products on the market, introduction of a new abuse-deterrent formulation faces several

challenges, market penetration being a big one. So even if that new product had a lot of market penetration, there's still no clean before and after.

So if we wanted to look at blister packs, Z-Pak, let's say we did the work and came out with some well-thought-of numbers of tablets to include or some series of things and storage, wasn't a problem for pharmacies -- if we wanted to really find out what the impact is, is it possible to do that if we don't do the whole line, like for instance, all oxycodone immediate release? And if we were going to try something on that scale, what are the potential unintended consequences that we'd have to look for as well?

MS. WHALLEY BUONO: Liz Whalley Buono. So I'm thinking of a study that just was accepted for publication out of the China CDC, where they used a combination of blister packaging and incented gaming, and they did it at a very large scale. So I don't know whether you could contemplate this as a pre-market type of analysis or whether you could

launch a product and do a post-market type of surveillance, but it was fairly simple.

Each blister had a peel-off tab. When the tab was expelled, there was a code. If they texted that code in, they received an incentive. I would envision that you could do that and then have an instruction to the patient that, when you're finished with your medication, how many pills are left, text it in.

So I guess what I'm suggesting is creating a new data source, but in doing so, you could also evaluate various parameters of the packaging, so has it improved adherence, because you're going to have the date and time of those texts. Has it improved drug disposal? Because now you know there's 15 extra pills floating around in this home.

It was a very inexpensive, creative study, and they were really pleased with the data that they got from it. And I think they rolled it out to about 250,000 individuals. And at the end of the day, the points they accumulated from texting

in -- I forget what it was, pretty nominal, but there was some sort of reward. But it focused attention on the whole calendar concept. It focused attention on tracking medication, all those sorts of things.

DR. HERTZ: Was that done with opioids?

MS. WHALLEY BUONO: No. It was done with TB medications.

DR. STAFFA: Dr. Bateman?

DR. BATEMAN: So thinking about your question -- Brian Bateman, Brigham and Women's -- I could imagine there would be some trial designs, like large pragmatic trials where you would get healthcare systems to buy into randomizing patients to these blister packs or to routine care, or a step wedge design, where there was uptake at different time points and different health systems, where you could get at some of the questions that would be relevant.

I think the danger of going all in is that you're going to get the number wrong in the blister pack and you're going to find that large numbers of

patients are undertreated or are prescribed too much such that you don't really address the problem you're going after.

I alluded to this a little bit yesterday, but there's a lot -- ideally, opioid prescribing is something that's highly individualized, where if you're prescribing for a patient that's leaving after a surgical procedure, you take into account what they've been consuming in the hospital and where they are on the trajectory of recovery.

What's proposed here, while eliminating the outliers on the upper end, don't allow you to go down to maybe prescribing 5 tablets or 10 tablets, which you might want to do for some patients.

DR. STAFFA: Dr. Twillman?

DR. TWILLMAN: So yesterday, in one of the presentations, there was a chart that showed some outcomes from the studies and we looked at how much people were prescribed. And one of those studies was a study by Hill, where they looked at 5 common outpatient searches, and they looked at how much was prescribed, called the patients afterwards,

found out what they actually used.

Then they said, now, if we prescribed for these patients at what was the actual 80th percentile need for the patients, out of 680 patients in the study, we would have saved almost 10,000 tablets that wouldn't need to be prescribed.

So they followed that up with another study, where they did an educational program with the surgeons and said, how about if you prescribe this amount that represents the 80th percentile? And they did that for about 250 patients. Only one of those patients needed more medications.

So I think to the comment earlier, if you would just look at how many of those people have to come back and get more medication, I think you've got a pretty decent idea about how much you've reduced prescribing, because you've got the pre-measure and now you've got the post- as well.

DR. STAFFA: Dr. Izem?

DR. IZEM: Yes, Rima Izem, FDA. I just wanted to go to the pragmatic trial, because it was mentioned also in a previous session. Can you say

a little bit more about what that study design would look like? Is it a cluster randomized design? What type of outcome would you be looking at?

DR. BATEMAN: I could imagine a cluster randomized design would maybe work well in this context if you've got a hospital where all of the surgeons agreed to prescribe the Z-Pak equivalents for their surgical patients, and then hospitals that continue their routine care practice and surveyed a sample of the patients with respect to their pain scores, the number of leftover tablets, that would be a pretty effective way of addressing this.

DR. STAFFA: Ms. Cowan?

MS. COWAN: When I looked at the question initially, I think that we have to remember that there's two different groups of people. There's acute and there's the chronic. And I think the discussion we've had right now is more around the acute than it is the chronic, because you don't want to limit doses and say, okay, well they should

have this. I mean, there's no take-back when it comes to somebody who's on long term.

So I just want to clarify that we're talking about acute pain right now with a limited dose and all that.

DR. STAFFA: Dr. Spitznas?

DR. SPITZNAS: So I just wanted to say I think that there's dramatic differences in prescribing across country and awareness in different professions about this or different specialties about this problem. And I'm not sure that you necessarily want, in some of these cases, what the usual prescription is to be driving what the prescription should be.

Getting the actual counts, to some extent, I think is a good way to do that. But at the same time, I think, especially if there's going to be, we hope, a drive to promote more alternatives and different kinds of pain management, I think that there can be some opportunities to really try to look at ways to minimize it further than the 80th percentile and to keep in mind that patients can

always come back.

What providers hate is they hate their patient being high and dry over the weekend and having to go into the ER. So I was originally going to say look to the CDC guidelines for the numbers for acute, but I think there needs to be some flexibility.

There have a range of packages, so that person doesn't need to come in over the weekend. And maybe it's going to be 3 and maybe it's going to be 5. It's just depending on the provider's convenience, with the instruction that you don't have to take this, or you don't even have to get this filled if you don't want to get this filled, because I do think that there are a lot of situations where we're just doing it to have it available in case, and that's not necessarily needed, and then it sticks around and causes problems.

DR. STAFFA: Dr. Budnitz?

DR. BUDNITZ: Yes, Dan Budnitz from CDC. But speaking just for myself, not for the agency,

to address the question if there is going to be a Z-Pak type approach, should that be mandatory across a product class or just voluntary, I would suggest, based on what we've done with some of the child ingestion work, it would be mandatory across an active ingredient/formulation.

What happened with the buprenorphine/naloxone packaging change, which was voluntary, is that we started to see some kind of backsliding or changes from unit-dose packaging back to bottles, because not all manufacturers made a switch. And we are concerned that if that trend continues, we'll eventually have a slide of ingestions. And I think it'll be hard. Unless you have very high penetrance or very low penetrance, you don't know what to do with the national data and use data you'd collect.

Specifically if you have low penetrance, then you haven't done much of anything and can't interpret the data. If you have very high penetrance, then that's good, but you're hoping for that. If you have a moderate level of penetrance

and you have some moderate change, it's hard to interpret.

There are secular trends going on. There are other factors. People are switching to other products. So I think you do want to go for a very high penetrance of your intervention or else you can't use national data. And you still might be able to do some institution-specific or health system-specific studies, but you have to wait for those results. There are other complications we could get into.

DR. STAFFA: Dr. Twillman? Actually, what you said and what Dr. Bateman said made me think of something. We were thinking about this idea of needing to identify. We use these studies where we look at what's dispensed, and then we ask the patient what they took as a way to identify what is the right amount that a patient needs.

But it strikes me that given that some of your data, Dr. Bateman, suggests that how much people take is correlated with how much they receive, which means there's an expectation perhaps

that may be independent of the amount of pain, it strikes me that even after we pick these numbers or set out these Z-Paks for different indications, it may be worthwhile to continue to do that research, to continue to assess whether there still remains excess opioid, because we can't just assume that we've hit it right.

So we may be readjusting expectations, and it may be that we are, by our action, driving down perhaps what patients need because also we will have other hopefully alternatives coming into play more often.

So it strikes me that this could be something -- in terms of an outcome measure, there's a need to still assess if there's excess because that's still going to be in a medicine cabinet, and in terms of getting at what we're trying to do here, it's not going to accomplish that if there's still leftover.

DR. TWILLMAN: To that point, in that Hill study, in the follow-on study, if you're prescribing at the 80th percentile, you should

expect 80 percent of the patients to have to come back, but there was one-half of 1 percent who came back. So clearly that 80th percentile number was still much higher than it needed to be.

DR. STAFFA: Dr. Green?

DR. GREEN: So this discussion actually sparks another thing to be aware of I think as we evaluate any intervention because as I've seen all the packaging types pop up, I'm thinking product identification because we struggle with that so much already in the post-marketing surveillance and how you could use that space to really get better product identification, should they be in those blister packs and really help you identify and differentiate little white pill to little white pill.

So one, I think that's a benefit, another added benefit of the potential blister packs. But if not all of them are moved to that type of packaging, we'll have to be aware of differential identification of products because that might have a better specific product identification than those

that aren't in that packaging. So we'll need to be aware of that in an epi design in the post-marketing surveillance; so both a benefit and a consideration.

DR. STAFFA: And that's not even really taking into account solutions that might be something that's added after dispensing.

DR. GREEN: Yes.

DR. STAFFA: That's a whole different ballgame.

DR. GREEN: Yes, that, too.

DR. STAFFA: So perhaps we'll move on to the next question.

I think we've beaten this to death, frankly, don't you?

(Laughter.)

DR. STAFFA: I think we've been through the barriers and all with patients, pharmacists, and prescribers. I think we've got there. Does anybody have anything to add on that, that we missed? Mr. Smith?

DR. SMITH: You are just talking about

measuring. This is Chris Smith from NACDS. For pharmacists or pharmacies, which maybe I did already state it, but the costs, those are easy to measure if you're talking about the cost of putting in a drug disposal kiosk, so the cost of installation, the cost to empty the inner liners and ship those off. You can figure out those costs, and that is a barrier for pharmacies.

Same thing, for example, in Kentucky, there's a proposal out there to potentially put on pharmacies to give out the disposal pouches, not the mail-back, but the pouches that destroy the contents. But from what I understand, there may not be any funding on that.

So again, you can easily figure out the volume and how much it's going to cost pharmacies if they're forced to do that. And again, cost is a barrier. So I would just say that's one thing you can look at in terms of pharmacies when it comes to disposal.

DR. STAFFA: On that note, Mr. Smith, can I ask a naive question? A few years ago, when we had

public discussions about rescheduling hydrocodone, that's one of the things that was brought up, that there would be a significant cost associated with that to change the storage and get all the Vicodin, which is a big seller, lots of volume, into safes.

It was a big concern, and I think it was a very reasonable thing to raise. We have since rescheduled. And I'm wondering, do pharmacies collect, or study, or publish that kind of information of what costs are involved with those kinds of activities when they have to revamp?

DR. SMITH: When that occurred?

DR. STAFFA: I mean, I'm using the rescheduling. It's just one that I know about. But would this be information that is collected or could be shared? Or is that just stuff that goes on behind closed doors?

DR. SMITH: As an organization, I'm pretty sure we don't have any information on that. Individual companies, I don't know, possibly. I'm not sure.

DR. STAFFA: I just know there are

pharmacoeconomists that study things and publish things, and I just don't know if that's in their space.

DR. SMITH: It wouldn't surprise me that they do, that that information is out there. But I can't really say. I don't know.

DR. STAFFA: Ms. Whalley Buono?

MS. WHALLEY BUONO: I'll go out of order, sorry, just to answer your question, which is, from the work we've done with large retailers, everything is measured, documented, time-in-motion studies, the difference between a unit count versus pharmacists counting pills, how much money do we save; handing out information will take X amount of time and that will cost X, so we have to question whether we want to do that.

So yes. The metrics are there. Whether they're willing to share that information is another story. Perhaps they shared at an aggregated level to answer specific questions. That would seem like a reasonable request.

DR. STAFFA: Presumably, there are data

around that, around other kinds of packaging interventions that pharmacists have dealt with in other areas.

MS. WHALLEY BUONO: I mean the whole pharmacy rubric is so tightly measured and planned from a profitability perspective because it really has to be.

DR. STAFFA: Right. Thank you.

Dr. Budnitz?

DR. BUDNITZ: Yes, Dan Budnitz, CDC. Just to answer this question about measuring barriers that impact maybe prescribers from using, for example, a Z-Pak, again, it's been mentioned about using web surveys, but that's something that we actually did do with providers, for example, on whether they would use milliliter dosing for pediatric prescriptions.

That was something that was able to be done quickly, cheaply. And it was informed or it would be found that there would actually be differences by physician specialty, and the perception that their patients wanted teaspoons, for example, in

this particular survey. So that was something that was quick, easy, and actually provided useful information that helped us target, identify barriers.

DR. STAFFA: Dr. Twillman?

DR. TWILLMAN: It strikes me that if you start to ask the question about how much this costs at the pharmacy level, then you're beginning to beg the question of can you measure what the downstream savings is as a result of that, and that's obviously a much bigger challenge.

DR. STAFFA: Agreed.

DR. HERTZ: So we have already touched briefly on unintended consequences in one setting in terms of utilization of some of these options to reduce excess. So for instance, if we attempted to make a very large switch to some type of unit-dose situation, we could get it wrong.

Are there any other unintended consequences that we would want to try and look for? I want to maybe ask specifically about access issues that would have to be looked for if that's thought, even

if we're still focusing on the acute. But here also, I think it's a little bit broader in terms of acute versus chronic because we still have the storage issue.

So can people think of unintended consequences here for these different populations and then how to evaluate them?

MS. COWAN: Penney Cowan, American Chronic Pain Association. I think for a number of people, it would be the cost associated with repackaging these. I'm sure there's more cost to do like a blister pack when there is the amber bottle. And there are people who will just not fill their prescriptions because they can't afford it and this is more on the acute.

So I think that would be a real problem, is the expense to the consumer itself, especially if they don't have co-pay or if their co-pay is too high. And newer drugs always cost more than the generics.

DR. STAFFA: Dr. Miech?

DR. MIECH: This is Richard Miech,

University of Michigan. With teens, I don't know if it's been mentioned already -- I don't think it has. And I don't even know if this is true, but I'm sure someone's going to bring it up, so it's something you'd want to take into consideration is that teens who were taking prescription opioids from their friends' or their parents' medicine chest, if they can't have those anymore, they might go on to something else. They might be forced onto the street.

So that would be something you'd want to try to take into account, ideally with a survey.

(Laughter.)

DR. STAFFA: Ms. Whalley Buono, did you have a comment to add?

MS. WHALLEY BUONO: I'm sorry. We just did that offline a little bit.

DR. STAFFA: Did you want to share that with the larger group, Ms. Whalley Buono?

(Laughter.)

MS. WHALLEY BUONO: I think I shared enough today.

So as far as cost, if we're going to be thinking about these models, it has to be cost neutral for the patients. And it has been in the instances where either the retail pharmacy or the pharmaceutical manufacturers have put product in this package, either one of those entities have absorbed the additional cost per script. And the theory behind that is the various streams of ROI that they get from it. But it does have to be cost neutral to the patient in order for there to be uptake.

Actually, on the unintended consequences, this is one of those big egregious problems that I don't think we can solve for, but I think we have to be mindful about. You just read in the literature so much about, as we're tightening access to the opioids, people are turning to illegal substances because, frankly, they're cheaper and easier to get.

I think about, as we're thinking of ways to tighten access to the opioids, is there an opportunity there to be thinking about, perhaps

we're the last touch with this individual before they unfortunately turn to other substances, and is there some sort of opportunity there to be thinking about, if we're tightening access, how do we try and make that event a go-to-treatment event versus go to the street corner event?

DR. STAFFA: So I'm wondering -- this came up I think in a conversation yesterday, and I'm not sure it got a clear answer, because I heard both sides of it.

Would something like this increase the street value of these products? And someone else -- I can't remember who brought up the point that maybe it's not bad because they'd be labeled and they'd actually know what was in it, which is better than what's on the street now.

Any thoughts on that?

MR. WEBB: Kevin Webb, Mallinckrodt. They already have a high street value. To Elizabeth's point, I mean, that's why we see such a huge diversion to low cost, synthetic opioids like heroin or fentanyl. But it would increase the

value of the fact that people would actually seek those out because of the purity of it. Pharmaceutical-grade opioids obviously are highly priced versus something that's unknown. And then, when you have it in a pill press, that's illicit, and they think they're getting the right thing.

I think that's one of the reasons why we see such a spike in the use of illicit, that you have these opioid-naïve or first-time users experimenting with these medications. They think they're taking a Percocet or a Vicodin, and they don't know what's in it. So they both seek data out, so you will then see an incremental supply and demand of the costs we you go from the street[indiscernible].

DR. STAFFA: Dr. Scharman, did you have a comment?

DR. SCHARMAN: I just think we have to be really careful when we consider costs filling up a negative. I'm in West Virginia. We lead the world in prescription drug abuse. It's costing our state billions, which means tax dollars and paying

billions.

So if it's a society globally, we can do something like this, which may have marginal increases in one area that may eventually drive down costs across the tax base. So I don't think we can get it down to what does an individual person pay for.

If you have insurance, you're not paying for it; it's the insurance companies. And they're also the ones that are paying for the hospitalizations for misuse. So I don't think it's as simple as to say it would cost more.

Again, if we're talking about acute pain, where we get a lot of the excess use in prescribing and people keeping it, those are pretty infrequent events in an individual person's life. So to pay a couple of extra dollars once every 10 years you have a surgery, I don't think people are really going to notice as opposed to a chronic med, where they are taking every month, and then those costs really skyrocket.

MR. WEBB: Can I clarify that comment

regarding costs? And I agree with the fact that the cost to the patient, legitimate patient, we want to keep that as neutral as possible. But if you have a medication that now becomes highly desirable from a street market value, from a black market, you may see a higher degree of diversion taking place because, now, instead of being $60 a tablet, it might be $80 or $100 a tablet. And you would create a higher reward for someone diverting that medication to sell it on the street.

MS. WHALLEY BUONO: Can I also just clarify, too?

DR. STAFFA: Ms. Whalley Buono?

MS. WHALLEY BUONO: Liz Whalley Buono. The drugs are not reimbursed at a higher rate because they're in these packages. So just to be clear, the patients don't pay -- the payers don't currently pay. Currently, it's either an investment by the pharmaceutical manufacturers because they see a value from an adherence perspective or a brand differentiation perspective, or it's the retail pharmacies for really the same

purposes. But simply because a drug is placed into an adherence package does not qualify it for an up-charge, if you will, in reimbursement.

DR. STAFFA: Mr. Smith?

DR. SMITH: I completely agree with that. That's the concern that we have. This is Chris Smith from NACDS. If you're talking about costs and who's going to bear those costs, we have concerns. And I'm not saying it will happen, but we definitely have concerns that those costs could fall on pharmacies because they're not going to be able to go to an insurer and say, pay us more because we've changed how we're packaging this product or something to do with disposing the product. It's not going to happen. And pharmacies operate on very thin margins, so there's not much to work with there.

So that's a major concern for us, and we don't have control over the pricing of these products.

DR. STAFFA: Thank you. Any other comments?

(No response.)

DR. STAFFA: Let's go to the next question. Anybody have anything to add on this one? I think we've beaten you up on this one, too.

(No response.)

DR. STAFFA: Question 5, last question of the day. This is the one I alluded to earlier this morning when I was impersonating Dr. Meyer. This is a real challenge because if we're trying to target excess supply, are we targeting excess supply as a proximal outcome of this packaging or as an outcome down the road? Is the proximal outcome different than that?

How do we actually target this? I look at excess supply as something that both influences the other behaviors we're concerned about, but it's also this overriding concern. So for example, is it enough to just figure out how to measure excess supply, call it a day, and not worry about everything else, or do we really need to understand how these things all interrelate to make sure we're going in the right direction?

Is it dangerous to think we all know this

without actually trying to figure this out?
Mr. Webb?

MR. WEBB: Kevin Webb from Mallinckrodt. Realizing that there's still a lot of data that we don't know, I think at least what we have is a path forward, but there seems to be consensus that putting it into some type of configuration, whether it be tamper-resistant or abuse prevention packaging, whether it be child resistant or trying to keep someone from intentionally trying to access the medication from unintentional use, from a manufacturer's perspective, we can roll these things out in sheets of 100 blisters, send them to the retail pharmacy. And as we get to trying to figure out what is the right configuration, maybe it may take a year as we try to figure out is it a 7-day supply, is it a 5-day supply as we do the studies the other panelists were referring to.

But in the meantime, the retail pharmacists can have the flexibility of peeling off 7 tablets or 5 tablets and dropping that in at the point of service, at the point of dispensing into some type

of a locking blister package, where then they can -- until we figure out is this going to be whatever the Z-Pak configuration will be, we can get there. But let's start putting them into something to prevent the unintentional use of it, but still put it into a packaging configuration. You just lock it down at the pharmacy and then hand it over. That way, you can keep the process moving.

DR. STAFFA: I think that's a great short-term suggestion. I guess my question is, if we're going to go down the road of labeling, which of these outcomes do we need sponsors to actually study in relation to these packaging interventions?

DR. HERTZ: So how do we know when we've had enough of an impact on excess or had a meaningful -- not even enough because we'll know when there's no excess, but that's not going to happen. But how do we know when we've had a meaningful impact? Is it just good enough to reduce the number? Should we just all strive for 80 percent and then assume that's better, or is

there any kind of way to target the downstream, the more important ones, in terms of bad outcomes?

MS. WHALLEY BUONO: Liz Whalley Buono. So my concern is that this is such a multi-factorial problem, and we're going to be throwing a lot of hopefully informed helpful innovations at it. I don't see how we're ever really going to be able to study and identify cause and effect for all the various interventions that are now part of a REMS, or a multi-layered innovation, or whatever you want to call it. You're not ever going to be able to parse out what of that did the packaging help, and what of that did the increased communications help, and what of that did the public health correspondence help.

So I think that we'll make ourselves crazy trying to figure out a study design to try and clean that data and identify what cause and effect was associated with each individual innovation. That's what we've seen with the adherence programs, just virtually impossible.

DR. STAFFA: So if we go down that path,

then what we're saying is that labeling, based on what pre-market data are available, will suffice. That's the labeling that should be worded and that post-marketing labeling is really just not an attainable thing in this space.

MS. WHALLEY BUONO: I mean, unless you have a manufacturer who is so interested in making the type of claim that it borderlines on a health claim and is willing to pony up the time and money, and otherwise investment to get the type of data that would be needed to back that sort of claim, I just don't see it happening.

DR. STAFFA: Then any kind of post-marketing surveillance or studies would focus on any unintended safety consequences or unintended harms that that might cause.

MS. WHALLEY BUONO: If you are able to back into a claim 10 years down the road that is a substantiated health claim associated with a package that maybe turns it into a device, great, but I don't think we're in a position to be able to wait to do that.

DR. STAFFA: Dr. Green?

DR. GREEN: I'm going to go back to what I said yesterday, too, where I don't think there's a blanket answer because with the pediatric exposures, there's definitely a way to evaluate the exposures and the emergency department visits, and then even do some additional follow-up to that to evaluate the role of the packaging and storage that was associated with those types of exposures. I think we've said probably a couple of times now those are probably the cleanest exposures that we've been talking about yesterday and today.

Then we talk about the other metrics that you actually do want to impact, and how does that relate back to the packaging and storage when you're talking about the therapeutic mishaps or whatever we want to call them.

But I think that there's this tug of war. If you're restricting excess, you're restricting the amount the pain patients are getting, they're sure not going to give up and dispose of what they do have left. So those are going to be competing

metrics that I would actually expect maybe potentially less disposal as the excess is decreasing.

But a way to figure out how to mitigate that would be to work with -- I'm sure Penney has some good ideas, how to reach out to the pain community and evaluate what would reassure them that it's okay to dispose of the extras or at least store them appropriately to reassure them and reduce the anxiety that's potentially coming along with the reduced access.

But certainly, Penney and smarter people than me probably have access to that community and that population to do survey research, to reach out to the stakeholders, to mitigate that and prepare for that resistance to disposal. So it's hard because you're trying to impact things that I think are going to play tug of war with each other.

MS. WHALLEY BUONO: Liz Whalley Buono. Dr. Green raised a point. That's an excellent analogy, and another one was Dr. Bosworth's in that when you look at the reduction in childhood

ingestions, at the same time, as you started to see an increase in calendar blister packaging and CR-qualified packaging, Dr. Budnitz's excellent work at the CDC under PROTECT was ongoing.

So there have been multiple forces at play trying to reduce childhood ingestion. When Dr. Bosworth did the clinical trial in the VA on adherence packaging for patients to take cholesterol medication, it just so happened after the trial started, the VA began to focus its reduction in cholesterol guidelines.

So there was a tremendous push within the VA to lower the average cholesterol levels within its population treated. So it was very difficult at the end of the study to try and clean out those variables and determine what was packaging related and what was the overarching VA cholesterol program related.

So that's just two very good examples of how I think the same thing would come into play here.

DR. STAFFA: We have that same issue with abuse-deterrent formulations as well with all of

the interventions going on around the country.

DR. GREEN: You can use comparators, and temporal relationships, and convergent and divergent validity to do that. And there's more sophisticated epi models that can help parse out, probably not 100 percent, but at least get to the specificity and sensitivity of those measures.

DR. STAFFA: Any other comments?

DR. CHIAPPERINO: I have one question. Since we have so much pharmacy and manufacturing expertise here, we talked about the Z-Pak concept. And I'm wondering if it's at all feasible that a sort of makeshift Z-Pak is something that can be achieved in the pharmacy setting if prescribing patterns were to change.

I mean, you just think of maybe simple equipment that could be within a pharmacy that might duplicate for a small prescription number of tablets, basically the functional equivalent of blister packaging.

MS. WHALLEY BUONO: I can take a shot at that. So under the state-by-state pharmacy

regulations, pharmacists have a lot of discretion as to how the dispense and in what packaging they dispense. And particularly for long-term care facilities and things like that, there are rudimentary bingo cards. They're actually permitted to comingle medications in daily blisters. There's all sorts of really creative things that can be done.

The problem is, from an economic standpoint, it's a nightmare. It is just, absolutely -- even the specialty pharmacies have a hard time keeping the doors open if they're doing that kind of activity because it's labor intensive, it's mostly manual. There are some automated machines that do that, but even the automated machines are so difficult. They have to be cleaned every time a sulfur drug goes through, the whole nine yards.

It's sort of untenable at any sort of scalable level beyond an inpatient facility.

DR. STAFFA: Mr. Smith, did you want to comment on that?

DR. SMITH: I agree.

(Laughter.)

DR. STAFFA: Man of few words. Any other questions down the row? Ms. Spitznas? Dr. Spitznas? Sorry.

DR. SPITZNAS: That's okay. I just wanted to say I think that the question of use/misuse of their own medications is really important, and that it doesn't necessarily need to be. Did they develop a full-blown problem, but are they on their way to it, and does the packaging reduce that likelihood?

I am not sure why that can't be answered in a post-marketing environment in some way with just making changes or randomizing hospitals to get this or not get this type of packaging, and then just looking at whether the likelihood is higher, that if they get more or get a standard, if you think of 30 as a standard, that this will matter.

DR. STAFFA: So those kinds of designs would be prior to any kind of mandate or requirement to do that.

DR. SPITZNAS: Are you asking --

DR. STAFFA: I'm asking, is that what you're thinking, is that kind of along the lines, that we would do those kinds of studies?

DR. SPITZNAS: Sure. I mean, you're not going to mandate it.

DR. STAFFA: Because once you mandate it, then you've lost your chance.

DR. SPITZNAS: Right. And you're not going to mandate it unless you have evidence that it does something. I would think. And there may be just some natural experiments that are going to have it in terms of some of these states that are putting pill limits into legislation and some of these states that are putting the blister packaging in so that you might not have to do some big random study to get an idea.

But I just think that that's a really important area, and we shouldn't just disregard that particular one.

DR. STAFFA: Others? Ms. Whalley Buono?

MS. WHALLEY BUONO: So this is probably going to get filed under somewhere between "good

luck with that" and "you're crazy," but it just seems to me like we've heard some really good ideas today that immediately get dismissed because there are other sets of regulations in place that would prohibit us from doing it. And I'm thinking just off the top of my head about the DEA regulations, which is something I was not aware of.

So I just really feel like in order for us as a country to really address this epidemic, we are really going to have to have some unprecedented interagency collaboration on some of this stuff. And maybe it takes the form of a CMS innovation project at scale for the DEA to say, okay, opioids are exempt for this project, where we can actually receive them back, and look at them, and see how many pills are left in the package.

But if there isn't that type of collaboration, if we're working within the same old paradigms, we're not going to be able to do a lot of this innovative stuff that we're thinking of doing.

DR. STAFFA: I think that's actually a very

nice comment to end the discussion on. Oh, sorry. Got to do something better. Mr. Smith, take me home.

MR. SMITH: I'm going to add that it's not just the DEA if you're talking about disposal. You've got to also bring in the EPA because you're dealing with household hazardous waste. There's also a problem with conflicts at the state level, in the state environmental regulations.

I've also heard issues involving the transportation regulations, DoT. So it's beyond two agencies. We're talking three, four, at least agencies when you're talking about disposal. I'm just talking about disposal.

So I agree, but I would add there's more to it than just the DEA. But yes, they should be in the room today. The fact that they're not here hinders your ability to deal with disposal, in my opinion.

DR. SPITZNAS: Just to that, I think there have been some examples where there have been agencies that have pursued waivers in certain

regulatory circumstances with them. I think a largest challenge would be rewriting the regulation at this time, but that's something that I'm willing to bring back and inquire over about.

If FDA had a study plan, would they be able to collect for a disposal study and actually measure in just a research exemption from that? It's a little dicey right now because of the leadership issues, but I think that might be something that they would be willing to think through. I'll ask.

Audience Participation

DR. STAFFA: Thank you very much for your comments. And now, we'll turn to the audience participation part, which green, yellow, red. I think we've got this now. So you can line up at the microphone, and you have three minutes, so if the first person could step up and introduce yourself.

DR. HOBOY: Hi again, Selin Hoboy with Stericycle. And I just wanted to comment on a few things. I think Mr. Smith hit on it, that DEA,

DoT, EPA, and OSHA are all the regulatory issues we need to deal with as disposal and throw in there, like you said, the state by state. Now it's coming down to the county-by-county ordinances that we're seeing across the board as well.

So when the DEA passed the Safe Disposal Act, when Congress passed it and then DEA promulgated the regulations in 2014, it was really an unfunded mandate. That's why we're seeing more EPRs or extended producer responsibility bills being introduced at a state-by-state level and even now down to the city and county levels.

So it's really creating an even more complicated patchwork of regulatory quagmires that we as the disposal folks and the reverse distributors have to live with, and then the pharmacies have to live with, the long-term care facilities have to live with, and it goes up the chain.

So there are a lot of challenges, and I welcome the opportunity to sit down with anyone, and talk through them, and look at ways. And I

think even though this climate, from a regulatory perspective, is a tough one, this might be the time to actually open the door to making some changes or requesting some changes to the DEA, and sitting down with them, and saying, here's what's been working and here's what's not.

With regards to Dr. Spitznas' comment about has there been any kind of evaluation on the disposal side, the GAO was asked to do a study, and conducted a study, and found that 3 percent of the pharmacies or entities that could potentially have some type of a program are participating today.

So the chain retail pharmacies, the private pharmacies, anybody who is a registrant today that could become an authorized collector, out of all of those, there's only 3 percent. And the state that's participating the most widely is at 34 percent, and that's North Dakota. And that's because the Board of Pharmacy collects a specific type of fee that they then are using to pay for that disposal opportunity.

So without funding, there's not going to be

much in terms of participation because there's a lot of effects that came out of that study that explained why pharmacies are not participating. Cost is one. Liability is another. Stigma is another.

So I think that study would be a good one for you guys to review as part of this panel as well. Thank you.

DR. STAFFA: Thank you for your comments. Anyone else from the audience care to make a comment on this topic?

(No response.)

DR. STAFFA: Okay. Then I guess we'll end Session 8, and I'm going to turn it back over to Irene and Doug for any closing remarks.

Closing Remarks

DR. CHAN: Thank you very much. So I have heard a lot of things these last two days. Some that rose to the forefront included what I think was a general agreement that there is promise for packaging, storage, and disposal options to make a difference in this epidemic.

I heard there's definitely a need to focus on excess supply, especially since excess supply feeds into other problems that we've been discussing. I've heard these options are most meaningful when we consider them within a broader framework of education efforts that are needed, some of which might be achieved through the packaging itself, but some of which the packaging may not replace.

I've heard that we can't let perfect be the enemy of the good, whether we're talking about data collection, data requirements, or putting out guidance to allow industry, data vendors, and other organizations to really rally around the research and development that's needed when it comes to packaging, storage, and disposal of opioids.

I've heard we need to give careful consideration to any unanticipated consequences of implementing these options. And that's just the tip of the iceberg of what I've heard.

So you've really given FDA a lot of food for thought, a lot of really valuable information that,

trust me, we're going to bring back, we're going to dissect, we're going to ponder.

At FDA, we absolutely believe that packaging, storage, and disposal options have the potential to help in this crisis, and we know that we all have a part to play here. We need to leave no stone unturned in the face of an epidemic like the one we have.

So I want to thank the panel members and our audience for a very productive workshop. I know you took time out of very busy schedules to bring your considerable expertise here.

As you continue to think about these discussions the next few days, inevitably, I think there will be other thoughts that come to mind, ideas, and I'd really encourage you to please share those with us. Please absolutely submit them to the docket.

There are a lot of people I need to thank. I want to give a special thanks -- and I think I see her in the back of the room, so I'll embarrass her, to Michelle Eby, who is so busy, I'm sure,

still thinking about other logistics issues. But really, if the logistics had been left to me, we'd all be crammed in Starbucks upstairs trying to do this right now. So really, thank you to Michelle.

There's a bevy of other individuals that are deserving of thanks, many of whom have been running around the room, are dispersed, just tirelessly working behind the scenes to ensure that these last two days have been running smoothly.

I also really need to thank all my FDA co-panelists here, a lot of people who have considerable expertise, much more than my own, for which we couldn't have this meeting without their input. And whenever there's a large event like this, its success is really attributed to the hard work of many individuals.

So with that, I'd like to turn the mic over to Dr. Throckmorton, who will also provide some closing remarks.

DR. THROCKMORTON: Thanks, Irene. I will not belabor the point because I'm sure many of you have flights to catch and things. But I'd like to

return to a couple things I had said this morning because I think we've continued to talk about the same themes these two days in important ways.

First, I want to focus on you all, though. I said that packaging was a logical extension for the actions the FDA took this morning. We started with the molecule, and them formulations, and things. Packaging made sense to me.

Having said that, this is really the first time we've had a meeting of this size and this intensely focused on packaging. That created challenges for us, I will tell you. I suspect it may have been the first meeting for you all on packaging, especially around the opioid space.

I appreciate your flexibility, your creativity, your willingness to think about this relatively new topic for all of us from a different perspective, and I think we've all benefitted from the scientific expertise, the manufacturing expertise that you brought to this discussion.

Second, as I talked about this morning, for FDA, our goal was to identify things that we could

do to make a public difference. For us, this work is going on in the context of urgency, and I applaud the various sometimes dramatic suggestions you've come up with for us to consider.

We've listened closely. Yes, Dr. Bateman, we will consider requiring surveys at all times going forward.

(Laughter.)

DR. THROCKMORTON: Seriously, as Dr. Gottlieb said, we recognize that some of the ideas we're exploring are unprecedented, that the tragic truth is that this crisis is so immense that we need to consider a range of impactful options that we might not have considered before.

In that regard, you've given us terrific advice about how to focus our efforts. I also heard a focus on reducing excess supply, something that's consistent with what my commissioner said yesterday.

I also heard comments from you about the challenges of folks in there and the need for dramatic and potentially impactful things with the

need to be cautious to the extent that we possibly can to make sure that we achieve the positive outcomes while minimizing the unintended consequences.

Several of you reminded us about the need to assess the impact of whatever actions we choose and talked about the challenges of assessing the impact and new actions, given all we're doing at present to address the opioids crisis.

For me, the comments that several of you made about how to do this are critical when I go back to talk to Dr. Gottlieb. We routinely face the choice between mandating change and encouraging change as a regulatory agency and have heard a lively discussion about which of those two choices you all favor.

There is also a challenge between taking actions that are broad based and actions that are more targeted. And then finally, there is a tension between the laudable interest in getting data before making choices and the urgency to do something in this space.

Those are choices that we're going to confront as an agency as we go forward, working alone, and working with all of you, and working with all of the other many stakeholders, both government and otherwise, in this particular area.

Ultimately, FDA will make the choices that we have given the available information we have. We are determined to work, combined with our other efforts, to yield positive and meaningful results.

Thank you for everything that you did in the last couple of days to help support that effort, and I genuinely thank you. This has been an absolutely terrific discussion these last couple days.

Finally, let me thank Commander Chan and all that her group has done also. It is absolutely impossible to conceive this without all the hard work that they did. And give yourself a round of applause.

(Applause.)

DR. THROCKMORTON: Safe travels.

(Whereupon, at 4:39 p.m., the meeting was

adjourned.)