FOOD AND DRUG ADMINISTRATION

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STANDARDIZING AND EVALUATING RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

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PUBLIC MEETING

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THURSDAY

JULY 25, 2013

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The Public Meeting convened in the FDA White Oak Great Room, Building 31, Room 1503, 10903 New Hampshire Avenue, Silver Spring, Maryland 20993, at 8:30 a.m., Theresa Toigo, Panel Chair, presiding.

FDA PANEL

THERESA TOIGO, R.Ph., M.B.A., Associate Director for Drug Safety Operations, Panel Chair

CDR CHARDAE ARAOJO, Pharm.D., M.S., Deputy Director, Office of Medical Policy Initiatives

MICHIE HUNT, Ph.D., M.B.A., Program Analyst, Office of Executive Programs

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ADAM KROETSCH, M.S., Operations Research Analyst, Office of Program and Strategic Analysis

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CLAUDIA MANZO, Pharm.D., Director, Division of Risk Management
MEGAN MONCUR, M.S., Regulatory Health Policy Analyst, Division of Risk Management
KATE OSWELL, M.A., Health Communications Analyst, Division of Risk Management
CAPT KEVIN PROHASKA, D.O., M.P.H., Director/Medical Officer, Division of Safety Compliance
GARY SLATKO, M.D., Director, Office of Medication Error Prevention and Risk Management
ANAHITA TAVAKOLI, M.A., Health Communications Analyst, Division of Risk Management

SPEAKERS
GENERAL STANDARDIZATION SPEAKER SECTION 1
SARAH A. SPURGEON, Pharmaceutical Research and Manufacturers of America (PhRMA)
ANDREW EMMETT, Biotechnology Industry Organization (BIO)
PAUL SHEEHAN, Celgene Corporation
JEFF FETTERMAN, ParagonRx
JOANN STUBBINGS, B.S.Pharm., M.H.C.A., University of Illinois at Chicago

PAUL BROWN, National Research Center for Women and Families
PHYLLIS GREENBERGER, MSW, Society for Women's Health Research
GENERAL STANDARDIZATION SPEAKER SECTION 2
GARY APPIO, Pharm.D., M.B.A., Novartis Pharmaceuticals Corporation
JIM DEVITA, CVS Caremark
STEPHEN A. GOLDMAN, M.D., F.A.P.M., Stephen A. Goldman Consulting Services, L.L.C.
PAUL SELIGMAN, Amgen
BRIAN J. MALKIN, Partner, Frommer Lawrence & Haug, L.L.P.

BILL MARTIN, Express Scripts

PRESCRIBER & PATIENT DIRECTED TOOLS SPEAKER SECTION

ANN KARTY, M.D., F.A.A.F.P., American Academy of Family Physicians

MURRAY KOPELOW, M.D., Accreditation Council for Continuing Medical Education

ANDREW KOLODNY, M.D., Physicians for Responsible Opioid Prescribing

NATALIE O'DONNELL, B.S.N., R.N., United BioSource Corporation

REMS TOOLS IN DISPENSING SETTINGS SPEAKER SECTION

KEVIN NICHOLSON, R.Ph., J.D., National Association of Chain Drug Stores

STACIE MAASS, B.S.Pharm., J.D., American Pharmacists Association

CAROLYN HA, Pharm.D., National Community Pharmacists Association

DAVID CHEN, R.Ph., M.B.A., American Society of Health-System Pharmacists

MARY JO CARDEN, R.Ph., J.D., Academy of Managed Care Pharmacy

LINDSEY R. KELLEY, Pharm.D., M.S., University of Michigan Health System

KATIE STABI, Pharm.D., B.C.P.S., Cleveland Clinic

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(8:33 a.m.)

MS. TOIGO: Okay, so I have got 8:33. So we are starting a little bit late. But good morning and welcome to our public meeting on REMS standardization and evaluation. Good morning to both the people in the room and those of our participants who are joining us through the live webcast.

I am Terry Toigo and I am the Associate Director for Drug Safety Operations in the Center for Drug Evaluation and Research and I am going to serve as your moderator today and as the Chair of the FDA panel.

So before we start the meeting, I get to do the housekeeping. First, if you can turn off your cell phones or silence them so that we are not interrupted.

We ask that everybody sign in for the meeting on both days. We are trying to really understand who is interested in this topic and who joined us for the meeting. The

doors were open at 7:30 today and they should open at the same time tomorrow.

We are scheduled to go to 4:30 today and we probably will go to 4:30 tomorrow. It depends on the open public speakers as to how long the meeting is going to go. And we have had a few cancellations, so we have juggled the agenda but I think time-wise, that is what your expectations should be.

The restrooms, if you have never been here before, are in the halls outside.

We are planning for a 15-minute break in the morning and then another one in the afternoon. The lunch break is scheduled from 11:50 to 12:45. We are going to try and stick to that. If you haven't been here before, you know that you can get sandwiches, salads, and beverages in the lobby. And they do a pretty good job of moving people through in a timely manner.

We do have two open public hearing

sessions and they are both tomorrow because we wanted the standardization presentations to be finished and that won't happen until tomorrow morning. And so we wanted the open public comment after that.

So if throughout the meeting there are comments that you want to make that haven't been heard, please sign up at the desk and you can speak during the open public section.

And then importantly, the docket for written comments on this is going to remain open indefinitely. But if you want the comments considered either for the projects, the priority projects that we have to identify or for the report that we have to write, we need your comments to the docket by September 16th. And then the transcripts will be available in I will say plus or minus 60 days and you can check the meeting website and that is where you will find the transcript, when it is available.

So the rest of my presentation, of my moderator presentation is divided into two parts. Well my presentation is divided into two parts. The moderator part I will tell you what to expect for the day, the purpose of the format, and the meeting agenda. And then I will switch and put on my panel chair hat and I will give you an FDA update on REMS.

So the purpose of the meeting is to create a forum for interested stakeholders to provide input on REMS. Specifically, as the Federal Register Notice stated, we are looking for your feedback on standardizing and assessing REMS. And we are also looking for your suggestions for some potential projects that will help standardize REMS and integrate them into the healthcare system.

And then importantly, this meeting also serves to meet some PDUFA commitments that we made. Despite the fact that the resources haven't come yet, we have been able to accomplish this particular commitment under

our PDUFA agreement.

So the format for the meeting will include FDA presenters, stakeholder panels, the FDA panel, and then an open public session.

The purpose of the FDA presenters is to introduce the topics for the panel sessions and then highlight the information that was included in the background document that you will find on the meeting website. If you haven't read the background document, I encourage you to do so. We created this document to familiarize stakeholders with our experience with REMS since they were first introduced in 2007. So that is available on the meeting web page.

And then each of our stakeholder panels will provide input on the questions that were listed in the Federal Register Notice. So that is the intent of these panels.

We organized the panels based on

the outlines that were submitted by the presenters prior to the meeting and we acknowledge that some of the stakeholders intended in their comments to cover multiple topics but we tried to put them on the panels that we thought were most appropriate for what they told us they were going to cover.

And then our FDA panel and many other FDA staff in the room will be listening to the presentations and our FDA panel members will have an opportunity to ask the speakers questions at the end of their panel, as time permits.

So we only have about ten minutes for FDA questions on most of these panels but we are going to do our best to get some questions in.

And then as I mentioned, we have the two open public sessions tomorrow and we welcome you to sign up and speak during those sessions.

So as you can see from the agenda,

we have seven FDA presentations. And then you will hear from about 40 stakeholders spread throughout six panels over the course of the two days. Each of the registered speakers has been given a ten-minute slot on the agenda, with an opportunity, as I said, for FDA to ask questions after the panel members have spoken.

And I will be using a timer. The light will be green for the speakers when you start. It will turn yellow when you have two minutes left and then red when your time is up.

The microphone will not turn off at the end of ten minutes but if you go over, I will kind of encourage you to wrap up and then, at some point, if you continue to go over, you will be finished but we will not cut you off with the microphone.

So then before I put my panel chair hat on, I would like the FDA panel members to introduce themselves. They and many of our other FDA staff have been very,

very involved in planning and preparing for this meeting over the past few months. And thinking about standardization and the challenges really takes a lot of people to look at what we have done, look at where we are now, and think about possibilities for the future. So I would like them to introduce themselves just so you know who the FDA panel members are.

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

MR. KROETSCH: Hi. I'm Adam Kroetsch and I am here in the Office of Program and Strategic Analysis.

MS. OSWELL: Good morning. Kate Oswell. I am a health communications analyst in the Division of Risk Management.

MS. TAVAKOLI: Good morning. Ana Tavakoli. I am also Health Communications Analyst in the Division of Risk Management.

MS. MONCUR: Good morning. I'm Megan Moncur and I am a Regulatory Health Policy Analyst also in the Division of Risk Management.

DR. HUNT: Hello. I'm Michie Hunt. I'm in the Office of Executive Programs.

DR. KASHOKI: Good morning. My name is Mwango Kashoki and I am the Associate Director for Safety in the Office of New Drugs in CDER.

DR. MANZO: Good morning. My name is Claudia Manzo. I am the Director of Division of Risk Management.

DR. ARAOJO: Good morning. I am Chardae Araojo. I am the Deputy Director of the Office of Medical Policy Initiatives.

MS. LIPPMANN: Good morning. I'm Elaine Lippmann in the Office of Regulatory Policy.

DR. PROHASKA: Good morning. My name is Kevin Prohaska. I am the Director of

the Division of Safety Compliance, which includes REMS compliance oversight.

MS. TOIGO: Okay, thank you.

So now I am putting on my panel chair hat and I will give you the FDA update on REMS.

I serve as the chair of several REMS-related steering committees and working groups. So my intent is to just spend about 20 minutes on giving you an update on REMS.

Some brief background, a little bit about stakeholder feedback to date, some of the challenges that we face in our working groups, and then a little bit about how we are dealing with those challenges.

So every drug has risks. And it is important to point out that REMS are not intended to eliminate all risks from drugs. Instead, they are really targeted to circumstances in which FDA believes that additional safety measures beyond those that are mentioned in the product's label are

needed to ensure that a drug's benefit outweighs its risks.

REMS authority was granted to FDA in 2007 by the Food and Drug Administration Amendments Act and this authority enables FDA to approve and patients to have access to certain drugs whose risks would otherwise exceed their benefits and may not be approvable.

All REMS impose some burden and multiple REMS increase the burden on the healthcare system. So I think we would all agree that some changes are needed to improve REMS efficiency and reduce burdens on the healthcare system but we really haven't defined what those changes are yet.

And then finally on the background, PDUFA fees provide for some support for changes that will better integrate REMS into the existing and evolving healthcare system.

So where are we in 2013? If you

go to the FDA website and you type REMS in the FDA search engine, here is where it takes you, to a REMS website.

If you count, you will find that there are, depending on how you count, but there are about 200 REMS that have been approved since 2008. Many were MedGuide only REMS, which have been released. As of this month, there are 72 REMS; 66 are for individual drugs; and six are share system REMS that actually include 88 applications, both NDAs and ANDAs.

And over the period of -- since we have been working with REMS, we have regularly sought and received stakeholder feedback in a variety of forms. Public meetings like this, advisory committees, and listening sessions. And PDUFA V further highlighted the importance of gathering stakeholder input to better integrate REMS into our healthcare system.

My FDA colleagues will focus on some of the things we have heard from

stakeholders that are specific to their presentations related to standardization, evaluations, and REMS tools.

But my next three slides are going to present stakeholder feedback just a little bit differently. I have got some quotes that we have heard over the years.

So we have talked to healthcare providers and we talked to patients. Healthcare providers acknowledge that time-consuming REMS tools can be helpful but they are less helpful when the interrupt the workflow of the healthcare provider. We all need to do a better job about REMS, if there are healthcare providers who see REMS only as filling out paperwork. Some patients have told us that they liked the reinforcement and repetition of safety messages beyond just the first time they receive a drug.

And then we know from discussions that some prescribers avoid REMS drugs. But as one of the prescriber's said, we are always

afraid of things but when you try it, it is like eating your vegetables. You know when you try it, it is just a whole lot easier. And we have had discussions with stakeholders who initially were reluctant and when they actually got some experience with the program, found out that it wasn't just as bad as they thought.

So we have listened to the pharmaceutical industries. Industry stakeholders highlighted the need for flexibility within any standardization that we come up with. We also heard about the need to consider how REMS tools may impact patient access issues and industry reminded us that one size does not fit all.

And we also held the listening session with our FDA reviewers and the Division of Risk Management. And this slide lists some of the comments that we heard from reviewers. They are examples of things that sponsors can do to help facilitate the review

of REMS submissions. Our reviewers talked about the challenges we face in reviewing submissions when we really don't know company business processes, such as the relationship between the company and vendors. And this impacts developing and finalizing REMS materials and timeframes. And so us not having a complete understanding of that process sometimes we might be able to do things a little bit differently.

And then finally reviewers consider it a gift when companies do pretesting of materials and then actually react based on the pretesting that they hear. So that is sort of some selected, acknowledged selected feedback but it was interesting to talk to people or read about things that different people have said.

So you will hear a little bit more about stakeholder feedback from our other panel members. And we really are looking forward to this session to get additional

stakeholder feedback.

So as you can imagine, we have run into challenges based on our experience implementing REMS over the past five years. Pharmaceutical risk management science is relatively new and it is evolving and so is our statutory framework. We still have a lot to learn about REMS programs that can easily be implemented and integrated into the existing healthcare system as well as doing a better job of measuring effectiveness and burden.

At the same time, the lessons learned have highlighted challenges and opportunities associated with REMS policy, standardization, integration and evaluation. These are listed on the next three slides and you will hear more about these from my FDA colleagues during their presentations.

So what are some of the policy challenges. Well we have questions like when may an alternative to REMS be appropriate to

address a serious risk. What do you suggest as alternative to REMS in terms of things that can be done to minimize risks? What characteristics or processes or features within the healthcare system can help manage risks? What are the indicators that product labeling is insufficient to communicate the drug's risk and conditions of safe use? And what are indicators that REMS is no longer necessary to ensure that the benefits of the drug outweigh the risks?

So what about design and standardization? What are some of the challenges we face there? And none of these slides are comprehensive or exhaustive. They are really just some of the things that the working groups are grappling with.

So how do we best customize standardization? How do we balance customization and standardization? How much variation is necessary and unavoidable? How do you best target interventions to prevent or

mitigate failures? And what is the appropriate tradeoff between enhanced safety and the additional burden to the healthcare system?

So those are some of the questions that the Standardization Work Group is talking about.

What about assessment? Well these, listed on this slide, are some of the challenges that we face related to the assessment of REMS. So what are valid proxy measures of patient and provider behavior to determine if REMS goals have actually been met? How do you associate particular REMS interventions with particular outcomes? How do you use limited data to determine whether or not the REMS is actually effective?

Well, the challenges we faced implementing REMS over the past five years together with our anticipation of PDUFA reauthorization presented us with an opportunity to better organize ourselves

around some of the specific goals that are listed on this slide: policy for requiring a REMS, designing REMS that can be better integrated into the healthcare system, and improving REMS assessment.

So how did we do that? Well, we established what we called the REMS Integration Steering Committee or the RISC to oversee the activity of the work groups and then to ensure stakeholder participation. The Policy Work Group is clarifying and issuing guidance on the criteria for requiring a REMS. The Design and Standardization Work Group is focused on the standardization of REMS tools. And the Evaluation Work Group is looking to better understand alternative methodologies for evaluation -- for REMS assessment, including developing a REMS assessment framework.

So the next three slides will elaborate on the activities of the three working groups. Again, as I mentioned the

REMS Policy Work Group is developing a draft guidance to provide information about how FDA applies statutory criteria factors, as well as other factors, to determine whether REMS is necessary to ensure that the benefits of the drug outweigh the risks.

The guidance will incorporate considerations FDA take into account in the current risk-benefit assessment of drugs to maximize the agency's consistency and decisionmaking about the need for a REMS and it will also provide information about when it may be appropriate to employ measures other than REMS to address particular risk.

I am not going to spend time on the next two slides because my FDA colleagues will discuss these in their later presentations. Adam Kroetsch will talk about the Standardization Work Group on this slide and then Gary Slatko will talk about the Evaluation Work Group. But I just wanted you to have it in the overview.

So this slide, Slide 24, highlights our efforts over the past few months to engage with stakeholders on challenges and opportunities with REMS. We think that input from multiple stakeholders is critical in helping us meet our goals.

Today's meeting is an important stakeholder engagement activity for our REMS Integration Work Groups. We look forward to hearing from the panels on the specifics of the questions that we posed in the federal register notice.

And then today's meeting is not your last chance to comment. As I mentioned, the docket for written comments will remain open indefinitely but we need your comments by September 16th to be considered for the report of our findings on standardization and evaluation and for the identification of priority projects.

The background document and/or today's discussion may stimulate some thinking

or may encourage. It may prompt you to want to speak in the open public session because none of the panels have covered issues that you wanted to make sure that we heard publicly. So again, I encourage you to sign up to speak in the open public session because we welcome your input.

So then to summarize, stakeholder feedback is really important to us. And my previous job was I worked a lot with stakeholders. And so I am committed as the leader of the -- chair of the REMS Integration Steering Committee to ensuring that stakeholder input is involved through all stages of this project. We need to know where are things working. And I think the listening sessions that we have had over the past few months, we learned from stakeholders there are things that are working. So we really are interested in learning what does work.

At the same time, we need to know what we need to fix. And we can develop

something and it can be approved and we can think it is perfect. And once it gets out there and stakeholders are having to implement it, questions come up. And we have learned that as we have put REMS in place. But if we don't hear the feedback, we can't learn from it and we can't make the changes. So stakeholder feedback is critical.

We need to know where we can standardize. I think you heard from -- you saw from the quotes on all the stakeholder slides that one size really doesn't fit all. And so this standardization, we have to really think about where are the opportunities for standardization and where do we not standardize. We need your help on that.

And then what projects can help us better understand where those opportunities for standardization are. We really do need to hear your input on that as well.

And then that looks like I am finished for my overview. So I hope that sort

of sets the stage for today's meeting and how the groups have been trying to tackle this problem. And this meeting is at a critical point for us to kind of take a step back, what have we learned, and where do we need to spend more time on more focused meetings. And that is kind of the overall purpose of this meeting because we will do some expert panel meetings but we want to do those thoughtfully because that is going to take another investment of time and effort. So we hopefully will get some feel for that today, where we need to put some more resources.

So Adam Kroetsch who works closely with Gary Slatko, who leads our Design and Standardization Group is going to talk to us about standardizing REMS.

MR. KROETSCH: Okay, thank you, Terry.

So I am Adam Kroetsch and I am going to be spending some time today talking about some of the work we have been doing to

standardize REMS. And as Terry mentioned, the REMS integration initiative is composed of a few different work groups and one of them is the REMS Design and Standardization Work Group. So what I will be talking about relates to the work of the REMS Integration Steering Committee or the REMS Integration initiative as a whole, as well as our individual REMS design and standardization Work Group. And we will be talking a little bit about what we have been doing to standardize REMS.

And specifically, I am going to start by introducing what we mean when we talk about standardization, what exactly it is that we are standardizing and why we are standardizing. And then after I provide that introduction, I will be spending some time talking about the steps that we are actually taking towards standardizing REMS.

So I would like to start off by talking a little bit about our commitments

under PDUFA V because these are some of the major drivers of the work that we have been doing of this meeting today.

Under the PDUFA V commitments, we have a couple of things that we have committed to do related to standardizing REMS and integrating into the existing and evolving healthcare system and that includes holding a public meeting on REMS standardization with the goal of reducing REMS burden and issuing a report of our findings, where we identify some priority projects in several areas to help us move towards standardization.

And I should also mention that although these are the things that we have committed to related to standardization, we know that there is much more to standardizing REMS than just these two commitments. And so we are doing a lot of work that I will be talking about today to actually move us towards standardization of REMS.

Now when we talk about

standardization, it is really important to think about what exactly do we mean by standardization? What are standardizing? And we often find it is useful to kind of divide what we are doing into two pieces.

First, we talk about REMS design and standardizing REMS design. And by that, we mean the method by which REMS tools are selected. And this starts for drugs where we know we are going to have a REMS. We think about what the risk is and what is required to mitigate it. And once we know that, we are thinking about standardized methods that we may be able to develop to really help identify which tools are necessary. So we need to think about how we characterize how the drug is actually likely to be used in the real world and where it is going to get used.

And then we need to think about the gaps in the healthcare system that might lead to a greater risk because ultimately we often find that REMS are targeting some of

these gaps. And then we need to think about the safe use conditions. I mean what stakeholders need to know and do in order to address those gaps and then select appropriate REMS tools to help us address those gaps.

So these are all standard steps in kind of building the logic of a REMS to help us decide what tools are needed.

The other thing that we think about a lot when we talk about standardization is REMS tools. And these are the systems and processes and materials that we use to actually carry out what we refer to in a previous slide as these safe use conditions and what stakeholders need to know and do. And this includes -- standardizing REMS tools includes standardizing what REMS are used so the things like maybe having a standardized REMS toolkit, how exactly those tools are implemented and integrated into the healthcare system and then how we assess those tools. And this is one of the key links between

standardization of REMS and assessment of REMS and is part of the reason that we are talking about both of these issues today. And REMS tools happen to be a major focus of today's meeting. And a lot of the questions that we asked in the federal register notice in advance of the meeting are centered around ways that we might be able to standardize REMS tools.

So now I am going to talk a little bit -- shift gears and talk a little bit about why it is that we are standardizing and again what standardization means. And a good thing to think about when you are trying to figure out why we are standardizing is why REMS have varied in the first place. And one of the major reasons is simply that risks vary. So REMS are designed to address specific serious risks. So the steps that are needed to actually mitigate those risks is going to vary. And another important thing is that the context of care varies. And when I talked

about understanding the setting in which a drug is likely to be used, that can have a really huge impact on what kinds of REMS are put into place because different REMS drugs may be used by different providers in different healthcare settings and for different patient populations.

Another thing about things that is varied is the developers of those REMS. So there isn't a single body that is developing the entire REMS program or implementing it. Instead, there are actually REMS that are proposed by a diverse set of sponsors and negotiated with FDA review teams.

And finally, we are still learning about best practices in REMS. Those are still evolving. The science of pharmaceutical risk mitigation is relatively new and our REMS authority is relatively new. And so we have continued to develop best practices. And I think what all of these variations point out is that there are variations perhaps that are

necessary and inherent in how REMS are put together and that we might even want to preserve. But then there is also some forms of variation that might be unnecessary and those are some of the areas where there might be opportunities for standardization.

One other thing we have done, and Terry mentioned this before, is we have reached out a lot to stakeholders to get their sense of how they are affected by variation in REMS and what their thoughts are in standardization and how it affects them.

And variation, they have told us, makes it really difficult to adapt to new REMS. So there is a saying I have heard stakeholders tell us, which is if you have seen one REMS, you have seen one REMS. So even stakeholders with a lot of REMS experience can take a lot of time to integrate new REMS into their workflow and to actually understand those REMS and what they need to do to implement them.

Another thing we have heard is that REMS successes aren't actually always copied. So sometimes a stakeholder would tell us about their favorite REMS or a best practice that they noticed in a REMS but we didn't necessarily see those successes and those best practices repeated across REMS. A lot of them were more one off successes.

And another thing we have heard from stakeholders is that their perceptions of REMS and whether they were working and how they should work varied a lot depending on the setting that they were in. And this gets to this fundamental issue of standardization versus customization. A one size fits all approach isn't necessarily going to work because REMS really need to be tailored to the different stakeholders and settings in which they are implemented.

So when we think about addressing those concerns, we really are trying to set out two goals for standardization. And one is

to minimize that unnecessary variation, make REMS more predictable, more consistent, easier to understand but also have them customized to specific settings. And we think those two things are mutually compatible but they will require some careful thought and they will require their input to learn exactly how to do that.

And another thing we need to do is actually improve the quality. We heard about these best practices. We heard that they were not necessarily replicated across different REMS and we need to make sure that as we standardize we are establishing those best practices that could make REMS more effective, less burdensome and all the while maintaining patient access.

And I think if you put all of those things together you get a good picture of what exactly standardization looks like. It includes, in the world of REMS design, you could imagine a standardized REMS design would

mean that REMS with similar risks in similar settings are using similar tools and that the approach that we use to choose which tools the REMS are using are really rigorous and evidence-based.

And then in the area of the REMS tools themselves, you could imagine standardized REMS using similar tools that are perhaps drawn from a standardized REMS toolkit. And then those tools in the toolkit would be informed by the latest science, by stakeholder feedback, and by established best practices and the lessons that we have learned from previous REMS.

And so that kind of is a quick overview of what exactly what we mean by standardization. So now I will talk a little bit about what our Work Group has been doing to actually move towards standardizing REMS. And we really have mapped this out into three phases here, although the process is actually somewhat more iterative than that and not

quite as sequential.

But the first thing that we really needed to do in order to standardize REMS is to characterize the existing REMS and actually have an understanding of where it is that REMS vary and why. And that includes kind of having a catalogue of what REMS exist and what kind of tools they are using and what approaches they are taking and then think about ways to put some clear definitions around that and help us actually share information about REMS.

And then we get to the next step, identifying best practices. And this is really where we are right now. And this means getting feedback from external and internal even stakeholders and experts. And that was one of the major focuses of the PDUFA commitments and one of the major focuses of our meeting today.

And then we also want to be able to identify some really important priority

projects that will help us move toward standardizing REMS.

And then finally once we have characterized the REMS and we have identified those best practices, we can really start standardizing the REMS and that means actually completing those projects potentially, sharing findings about best practices, finding a way to actually get those out there and get those lessons learned incorporated into new REMS and perhaps develop or update some guidance around what REMS, what a standardized REMS should look like.

So I am going to -- since characterizing existing REMS is the first step and something that we have been working a lot on, I am going to go into a little more detail on what exactly we have been doing in that area. And really a lot of the need to characterize REMS is driven by the fact that REMS lack common definitions and clear requirements in many cases. So we know that

the format of the REMS documents and materials varies. And if you look at the background materials, you will see some links and attachments to REMS materials and it will give you a bit of a sense of exactly how much they vary and how they vary.

REMS also lack consistent terminology. And as a simple example, we will often see similar tools in REMS having different names. And we will even sometimes see different tools using the exact same name.

We have found that when we talk about REMS, these regulatory terms like elements to assure safe use for ETASU or communication plans, they don't necessarily actually provide really useful information about how REMS programs work and sometimes you can get caught up in regulatory questions that distract you from what the REMS is actually doing. So in fact when we talk about standardizing REMS and the standardized tools, we are going to some degree steer clear of

that terminology.

And another thing that kind of drove up to try and catalogue and characterize what we have in REMS is that it is not always easy right now with the REMS documents that are out there to find information on what is expected of healthcare providers and patients. You may, for example, want to know how many REMS have laboratory tests, let's say. And you can look in the documents and the information is there and it may even be in a logical place. But if you look across the entire span of REMS, it can be really tricky to find exactly what it is you are looking for in a systematic way. And when you have those sorts of unclear definitions, it can make standardization really difficult.

And this list is an example of what happens when those definitions are unclear and inconsistent. And this is just a small list of some of the different forms that prescribers and patients are asked to fill out

when they actually start using a drug in a REMS. And a large number of REMS have forms like these. I am not meaning to pick on the drugs on this list. This is just a small subset but there are a lot of forms like this and they all, you will probably notice right away, have very different names. And they all serve somewhat different functions but you will also sometimes see cases where two forms are serving very similar functions, for example, that rosiglitazone patient enrollment form includes patient agreements, prescriber agreements and patient enrollments. But then in the Thalomid REMS there is a patient physician agreement form which contains some of the very same things. So again there is some logic to the name and there is some logic to the REMS individually but in aggregate it can become very confusing and it can become difficult for stakeholders who are approaching us or even us trying to think about how to standardize REMS to really wrap our heads

around all the different variations.

And so what we have been doing has been to try to come up with a way to better describe how REMS vary. Because really before we can standardize REMS, we need to have that common language to describe what is in the REMS and how they vary. And we have catalogued and characterized a lot of the documents and materials, including the text of the REMS document itself, some of the information about the REMS materials, for instance training materials and tools, and then information about specific REMS requirements like the need to become certified. And a lot of the results of our characterization and cataloguing have been included in the background materials. And again, since we want to have a common language to be able to talk about this, I would really encourage you to take a look at those background materials, if you haven't done so already because it really tries to capture the

landscape of a REMS in a way that can help us kind of have a conversation about them.

One of the other things that we are going to be doing to try and improve how we characterize and capture information about REMS is we are interested in incorporating REMS information into SPL or Structured Product Labeling. And I should mention right from the start that the term Structured Product Labeling is a little bit of a misnomer because the actual SPL information captures a lot more than just labeling. But SPL, in a general sense, is a broadly used standard to capture structured information about drugs and their labels. And it is developed with the health of stakeholders. It is an HL7 standard so there is opportunity for public input into what goes into it and it is included in the materials that REMS sponsors send to FDA.

And one of the nice things about using SPL to help catalogue information about REMS is that it can include marked up

documents themselves similar to the drug label or the REMS document and then some structured machine-readable information to support electronic health records.

So if you were to kind of think about what exactly does SPL mean, you could almost think of it as a way of building a database of what is in REMS with standardized format and content and information.

One of the other benefits of SPL is that there is already an infrastructure in place to share that kind of information across the healthcare systems. So when an SPL document or information is submitted to FDA for a drug, once that drug is approved, it is actually entered into a repository that is kept by the national library of medicine and made available through their DailyMed website. And that allows patients and the healthcare providers and the public in general to be able to access any information that is included in SPL. And it is also able -- that information,

that repository provides information to the healthcare information suppliers who then give it to health information technology vendors. And that is a way of taking REMS information and incorporating it into electronic health records, ePrescribing, pharmacy systems. Once the information is included in SPL, it is possible for it to propagate through the healthcare system all the way to some of these point of care tools that prescribers and other healthcare providers are using.

And as I mentioned before, when you have a standardized way of talking about REMS, it really helps you develop standardized REMS. And one of the things that SPL can do is to help develop consistent REMS documents. Through SPL you can define the exact format that you would want in a REMS document and make sure that that format is actually followed. So it actually can facilitate efficient review of these documents and that allows us to have a standardized document in

a single point of reference for people who are interested in learning more about the REMS that are out there. And it also supports some of our future standardization efforts because it makes it a lot simpler to track how different REMS tools are being used and where we might actually need greater standardization.

And SPL actually goes beyond that because it really makes it easier for stakeholders to implement REMS. So it is actually helping us take a step towards standardizing the REMs themselves by clarifying what exactly it is that the REMS requires of patients and healthcare providers. We could use SPL to consistently describe what the REMS requirements are. And is putting relevant REMS information into one place. So when you have the information structured in a standardized format in a single place online, it makes it a lot easier for stakeholders to understand what REMS are and to even build

REMS portals with information about a wide range of REMS. And then it allows that information, as I mentioned before, incorporated into a lot of these electronic health records and health information systems.

So now I am going to talk a little bit -- we have talked about how we are going to capture and describe and define the information in REMS. We talk a little bit about how we can take that information and us it to help us identify best practices.

And as I mentioned before, a lot of the things that we are doing in this area are related to the PDUFA commitments that we made to have a public meeting and then to report on our findings and develop some priority projects.

So in the coming months and today of course, we are going to be seeking stakeholder and expert feedback on ways to build more effective and better integrated REMS tools. And we are also going to be

looking for more information on methods to assess and characterize the risks and select appropriate REMS tools or interventions. And this gets back to that REMS design piece I was talking about before. We want to be able to look at tools like for instance perhaps failure modes and effects analysis or other standardized methodologies that could allow us to design REMS in a more analytically rigorous way and in a more standardized way. And to explore this further, we are going to be holding an expert workshop in the fall.

On the area of specific REMS tools, which as I mentioned is one of the major focuses of this meeting, we put out that Federal Register Notice where we actually asked about tools and a few areas related to what stakeholders are actually dealing with. So we talked about -- we had questions about prescriber-directed tools, for example, what are the best ways to educate and train prescribers and other healthcare providers.

We asked about certification. How can we streamline certification and enrollment into REMS. And then on the area of patient-directed tools, we asked what are the most effective and efficient ways to educate patients, especially given the wide variety of information needs and learning styles that patients have. And how can we improve patient counseling in REMS. It is a really common feature in a lot of REMS.

And then finally, we also asked about tools and dispensing settings. How can we manage certification dispensers given that, again, wide variety of dispensing settings that we see in REMS. And how can we make sure that REMS, which have distribution controls, that those are compatible with some of the established systems for procurement and distribution and dispensing of drugs. That is something that we have heard a lot of concerns about from stakeholders.

And then next three presentations

after mine will focus largely on these sorts of questions and provide you with some background information to help think about how to approach answering those questions.

Another major goal for today, and this gets back to some of the PDUFA commitments that we made, we are looking for help in identifying priority projects. And these are projects that could help us identify or test new ways to standardize and integrate REMS.

And the PDUFA V commitment identified four project areas. And I am going to just state them exactly as they are stated in PDUFA V. They have asked us to look into projects in educating prescribers, providing benefit-risk information to patients, pharmacy systems, and then practice settings.

And then under PDUFA V, we have committed to developing a work plan for completing each project and that work plan will be included in the report that follows up

this meeting.

And then finally, once we have identified those best practices we have looked at those priority projects, we have gotten that feedback, we have characterized the REMS. At that point, we are going to be able to standardize the REMS. And that includes completing those priority projects and sharing our findings. And then perhaps developing and updating guidance, as I mentioned before.

And as we do this, it is really important for us to follow certain principles. And a lot of these come from the feedback that we have gotten to this point. And one of those principles is to listen to stakeholders. We need to work collaboratively with patients and practitioners and industry and outside experts to really identify the best practices.

We know that there are often concerns about the lack of input that stakeholders, healthcare providers and patients have into the development REMS and we

see standardization as a real opportunity to get their input included into REMS.

We also would like to build evaluation into standards, make sure that we are developing REMS that are measurable. As we standardize the tools that we are using and the approaches that we are using, we need to make sure that these pieces are aligned so that we actually start building an evidence-base of what works and what doesn't.

We also need to work iteratively. So we know that the healthcare system changes. We know that new risks will need to get addressed and we need to make sure that these standards are evolving over time, as we learn more about these best practices and as things change.

And then that also relates to this final point, which is we really need to be flexible. As we standardize, we don't want to -- we know that one size fits all is not going to work. We also know that we can't make our

standards too rigid. We really need to be able to encourage new and innovative approaches.

And when you actually do all of those things, what you can do is you get a positive feedback loop in which you are really continuously continuing all of the REMS. And the ability to do this comes down to the kind of standards that we set. When we incorporate what we know about know about best practices, what we have heard from stakeholders, when we use common metrics, when we build lessons learned into the REMS standards, we can then use those standards to improve all of the REMS. And then by building the evaluation into the REMS standards, circle back and continuously improve.

And with that, I am going to turn it over to my colleagues who are going to go into some more detail about the different tools that are used in REMS and help set the stage for answering some of the questions that

we asked in the Federal Register Notice. Thank you.

MS. OSWELL: Thank you, Adam.

Good morning. My name is Kate Oswell and I am a health communications analyst in the Division of Risk Management. And I am going to be speaking about prescriber directed tools in REMS this morning.

My objectives today are to provide an overview of prescriber-directed tools used in REMS, share some of the feedback from stakeholders about these tools, and finally to share some promising practices.

REMS programs use a number of tools to educate healthcare providers and ensure that healthcare providers carry out REMS requirements, including screening, monitoring, and counseling patients.

Please note that the title of my talk is called Prescriber-Directed Tools in REMS, however, the educational tools I discuss really apply to a broader category of

healthcare providers. These tools apply to professionals that may not have actually prescribed the drug, such as other physicians caring for the patient, nurses, physicians assistants, as well as pharmacists or any other dispensers of the drug.

A number of different tools have been used to educate healthcare providers. Although produce labeling is considered a tool, it is usually not a part of the REMS materials and is not reviewed as part of the REMS as the only educational component. Therefore, my presentation today will touch on the last four tools seen here that may be part of a REMS program. And these consist of REMS program communications, REMS training materials, additional REMS materials, and enrollment forms to support certification.

REMS program communications are a tool that have been used to deliver messages to healthcare providers about serious safety issues, including drug risks and REMS program

requirements. They also include resources of where to find further information.

The target audience of these communications may be healthcare providers, pharmacy representative, infusion center directors, and professional societies. A variety of REMS program communications have included Dear Healthcare Provider letters and emails, letters to professional societies, fact sheets, REMS dedicated websites and journal information pieces.

And note that journal information pieces were used in previous REMS programs but we have seen what the move towards electronic journals with minimal advertising, these have not been used in more recent REMS programs.

Training materials are another tool used in REMS programs. They provide comprehensive training on the risks addressed in REMS and how to mitigate these risk. And they explain how the REMS program operates and describe the prescriber roles and

responsibilities.

Healthcare providers are usually expected to review the training materials prior to prescribing and dispensing the drug. Some examples include program overviews, prescriber guides, and training modules such as slide decks.

REMS programs have used a variety of delivery methods to disseminate training components. This may be in person or over the phone, print or electronic form, such as online or DVD versions and may be with or without an audio component.

REMS programs offer different training options, as providers have different learning styles, as well as various limitations with access to these materials. For example, rural areas may not have access to in-person training or online training at the office.

REMS have also included additional materials to address specific issues related

to the safe use of the drug, as well as enabling tools to support ongoing patient care. For example, a checklist may be used to solicit information about a patient's risk factors for an adverse event, or their likelihood of benefitting from the drug to inform prescribing decisions.

A counseling tool may be used to guide a conversation with the patient about the benefits and risks of different therapies to determine if a REMS drug is appropriate or inform the patient about the safe use of the drug and any actions to take. And dosing and administration guides have been used to support ongoing care.

Enrollment forms are used to enroll the prescriber into the REMS program. These forms collect prescriber demographic information and include acknowledgments and agreements that the provider has met the requirements for certification and will adhere to the REMS requirements. Enrollment forms

allow sponsors to track certification of healthcare providers and communicate with them about the REMS program. They allow the sponsor to monitor or audit compliance with REMS program requirements and agreements on these forms reinforce key messages from the training through the certification process.

Some of the feedback that we have heard from stakeholders are to offer different options for training. And we have heard that including an option for in-person training initially and then online for certification may be helpful. Others have desired both online and print options for different preferences and learning styles.

We have also heard from stakeholders to standardize enrollment forms, including limiting the length of the forms. And then of course we have heard that streamlining the processes will reduce burden. And some stakeholders have stated that having a one-stop website for all REMS programs in

one place to find further information is helpful, as well as having an option for patient enrollment through the REMS website at the physician office which could reduce burden on both the patient and the prescriber.

Here are what was see as some promising practices with REMS programs. Offering CE credit for REMS training. Currently we are exploring this option as part of REMS programs; including checklists in REMS programs are helpful to healthcare providers, as well as quick summaries that describe the REMS programs and the role of the healthcare provider; and lastly, having a single web portal for similar programs can reduce the burden in regards to prescriber certification.

We look forward to hearing from you today. Thank you.

MS. TAVAKOLI: Good morning. My name is Ana Tavakoli and I am a health communications analyst in the Division of Risk Management within the Office of Surveillance

and Epidemiology. I am going to be speaking about patient-directed tools in REMS today.

The objectives of my talk are to provide an overview of patient-directed tools in REMS, to share feedback from stakeholders about patient-directed tools, and to show the importance of consumer testing materials prior to dissemination.

REMS programs use a number of tools to educate and counsel patients, provide patients with information about the risks of the drug, and to help ensure that patients use the drug safely.

At the present time, patient-directed REMS tools include the following: Medication Guides; patient print materials, which include patient guides, booklets, overviews in brochures; counseling tools, which may be part of prescriber or healthcare provider training materials; Patient-Prescriber Agreement Forms, also referred to as PPAFs or PAFs, short for patient agreement

forms; patient enrollment forms; and REMS-dedicated websites.

I will now discuss each tool further. Medication Guides are the most frequently used patient educational medication materials in REMS. Their purpose is to provide information when the FDA determines in writing that it is necessary to patient's safe and effective use of a drug product. They are usually about one to eight pages long, with a format consisting of text and bulleted statements for ease of readability. MedGuides are provided to patients by the pharmacist or healthcare provider or can also be accessed by the patient on the FDA and REMS-dedicated website. It should also be noted that in REMS elements to assure safe use or ETASUs, prescribers or healthcare providers may be asked to review the Medication Guide with patients and use them in patient counseling.

REMS print materials include patients guides, booklets, overviews, and

brochures. Their purpose is to focus on REMS risk and REMS program information. Prescribers may use these tools to counsel patients on risk and facilitate discussions. Their length has varied anywhere from two to eighteen pages, depending on the risk and requirements of the REMS program. Their format consists of text, bulleted statements, tables, and graphics. They are provided to patients by the healthcare provider and can also be downloaded from a REMS-dedicated website.

Counseling tools and printed material is used by healthcare providers to counsel patients about the safe use of a drug. They include the risk of a drug, patient responsibility, and encourage patient-prescriber discussions. They are usually about one to two pages long, with a format consisting of text, bulleted statements, and tables. These tools are provided to patients by healthcare providers.

Patient-Prescriber Agreement Forms or PPAFs also referred to as PAFs, short for Patient Agreement Forms, are used to document that an informed discussion of the drug's benefits and risks took place and that the patient understands the risk and REMS program requirements. Patient-Prescriber Agreement Forms support patient counseling by providing information for prescribers to review with patients. They are usually about one to two pages long with a format consisting of text and bulleted statements for ease of readability. PPAFs are given to the patient by the healthcare provider or prescriber and signed by both patient and prescriber to reinforce understanding of the risk message.

Patient enrollment forms contain agreements and acknowledgments of safe use conditions. They are used to enroll patients into REMS programs in order to receive the drug. Patient enrollment forms also allow sponsors to track patients and ensure that

only those who have completed the form and are enrolled in the REMS program can obtain the drug. Patient enrollment forms are the same length and follow the same format as the Patient-Prescriber Agreement Form and are given to the patient by the healthcare provider.

As you heard earlier from my colleagues, in the past few months the FDA has received feedback from patients. And these are some examples of what patients say about REMS programs. Patients state that repeated counseling by a healthcare provider can be beneficial in helping them retain information. They would like to see more straightforward patient documents, such as a checklist. Patients also want to be offered a variety of tools, including both print materials and digital media, such as apps for phones and tablets and websites with essential portal directed only to patients.

In addition and naturally, they

perform materials that are patient-friendly, and written at an appropriate reading level.

The Agency has seen modifications submitted by sponsors based on consumer testing of REMS materials that have shown improvements in them. Some REMS materials that have been previously tested by sponsors include the Patient Provider Agreement Form and a REMS dedicated website.

Results of consumer testing materials indicate that patients prefer forms that are formatted for easier readability and understandability. For example, including more shading and boxes to define sections of the form. Materials in which both risks and benefits of drugs are clearly defined and materials in which the content is written using plain language principles.

Since improvements can often be made when materials are pre-tested with patients prior to dissemination, we encourage sponsors to test their materials prior to

submitting them for review.

This concludes my presentation. We are looking forward to our stakeholders for help in ways to improve REMS materials and information dissemination. Thank you.

MS. MONCUR: Good morning. I am Megan Moncur from the Division of Risk Management and I am going to be talking about dispensers and dispensing settings in REMS.

So I am going to spend the majority of my presentation providing an overview of dispensers and dispensing settings in REMS. And I am going to talk a little bit about the variability across these different settings. And because of that variability, my presentation is going to have a little bit different focus than those that came before for prescribers and patients. And I am going to be focusing on the role of these different dispensers and dispensing settings in REMS and the requirements for dispensers.

Then, as with my previous

colleagues, I am going to share some example feedback that we have received and also share some promising practices.

So drugs are dispensed in a wide range of settings. They are dispensed in pharmacies, hospitals, and outpatient clinics. And as you can see even just from the limited examples I have included here on this list, there are different types pharmacies. There are different types of outpatient clinical settings. And each has their own set of needs and faces unique challenges.

However despite this diversity, there is one feature that they all have in common as dispensers. And that is, they are often the final checkpoint before a drug is administered to a patient.

So how is this critical role that dispensers and dispensing settings play in the patient care process. How is that incorporated in REMS?

So I am first just going to

provide some general requirements and then in subsequent slides, I will provide some specific requirements. So REMS may require all or any of the following: practitioners or dispensing settings that dispense a drug are specially certified. And by specially certified, that means that the dispenser is going to have meet certain requirements, such as being trained or enrolling in the REMS. Additionally, REMS may require that the drug is dispensed only in certain healthcare settings, such as in a hospital. Or the REMS may require that the drug is only dispensed after the dispenser has verified documentation or evidence of safe use conditions. So that may be lab test results or that may be verifying that the prescriber is certified or that the patient is enrolled.

Okay, so moving into the specific requirements. Just for the purposes of this presentation, we have organized these requirements by what a dispenser needs to do

to be certified to be able to dispense a drug. Sometimes we refer to these as startup requirements. Then next what dispensers might have to do on a day to day basis. So what might dispensers be required to do at the time of dispensing. And then finally, what are some things that dispensers may need to periodically do to maintain compliance with the REMS.

Okay, so to be certified to dispense, dispensers may be required to designate an authorized party who would enroll the facility. They may be required to train or ensure that their staff are trained. They may be required to enroll. And they may be required to establish systems or modify existing systems and processes to comply with REMS requirements.

So for example, they may have to modify existing system for tracking and training of their staff or they may have to create a new system. And they might have to

modify their process for procuring some medications because some REMS do include distribution controls.

So once a dispenser is certified, there are some things that they may need to do at the time of dispensing before the drug is dispensed. And one of those is verify documentation of safe use conditions. And so as we have mentioned before, that could include verifying lab results or verifying that the prescriber is certified. Now what that also involves is they may be asked to record or document that they have verified that the safe use conditions are present and that may be a manual process. And the other component of this is that they may have to resolve verification failures. So what we mean by that is that if they are going to dispense a drug and they find out that a prescriber isn't certified or the lab tests aren't available, then that is going to take some time for them to potentially sort that

out. And additionally, they may be asked to provide a Medication Guide or provide patient counseling.

And finally, there are some things that dispensers may be required to do periodically in order to maintain their certification. So they may be required to re-enroll. They may be required to train new staff as they come onboard. They may be required to participate in audits and also they need to be aware of any new or modified REMS requirements that may need to be implemented.

So I have just covered some of the common requirements that dispensers encounter in REMS. However, there are some things that we, in our experience with REMS, have determined that impact our decisions in what we require and how those requirements are implemented. So different features or dimensions that vary across these different settings.

So for example, the role that the dispensing setting plays in the care process. And some dispensing settings dispense directly to a patient and other will dispense to a healthcare provider who will administer to a patient.

Existing safe use controls. So what we mean here is what is already present in that context of care to assure safe use of the drug. So if you compare the outpatient setting to an inpatient setting, you can imagine that in the inpatient setting there might be controls to both monitor a patient for adverse events or treat a patient if an adverse event should occur.

And in terms of existing electronic health systems, this is things like pharmacy management systems or electronic health records. And in some REMS, these systems can be leveraged to automatically either document or verify safe use conditions.

Corporate or organizational

structure. So is the dispensing setting independent or is it part of a larger system? And so for example, is it a chain pharmacy or is it an independent pharmacy? Is it an independent hospital or is it part of a larger hospital health system?

And understanding that has implications for choices about what we refer to as level of certification. So who needs to be certified? Is it the pharmacist or is it the pharmacy? Is it the hospital or is it the hospital system?

And related to organizational structure is whether the dispensing setting is part of an integrated or closed healthcare system because that has implications for how the healthcare system might communicate with the REMS system.

And the procurement process. So as Adam has already stated, we at FDA need to make sure that REMS are compatible with existing procurement and distribution systems.

So it becomes especially important to understand this if a REMS includes distribution controls.

And in terms of transitions of care, so thinking of a transition between an inpatient setting and an outpatient setting, REMS can impact transitions of care and they can do that -- they can either facilitate that or it might interrupt that. So you need to be very aware of that.

So although there is this diversity across these different settings and across dispensers, we have heard some common themes in our feedback. And further, these themes highlight this principle of balancing standardization of REMS, implementation in a unique dispensing setting.

So first of all, we have heard that REMS need to clearly and concisely convey what dispensers are required to do. And the information that is conveyed needs to be relevant to that dispenser.

Additionally, REMS processes should be automated and integrated into the workflow. We have heard a lot from stakeholders that manual processes lead to a lot of interruptions in their workflow. REMS requirements should be customized to the different dispensing settings. And further, dispensers want flexibility in how REMS requirements are implemented.

So we have seen some promising practices or some promising approaches to how -- that have actually addressed some of the feedback that we have received from stakeholders.

So for example, some examples where REMS have been integrated into the existing systems and workflow, some REMS have used inpatient order sets to either document or verify safe use conditions. Additionally, we have a REMS that uses the outpatient pharmacy management system and the claims process to automatically verify that

documentation of safe use conditions has occurred.

And finally, we have REMS that provide instructions on how to adapt a particular REMS form to be compatible with an existing healthcare system. So again, that speaks to flexibility and implementation.

And then some examples of setting specific customization. So we have several REMS that have different requirements for outpatient and inpatient pharmacies, which again sort of speaks to that existing safe use controls that may be available.

And also we have customized processes for clothes or integrated systems, so that their systems -- so that they can participate in a REMS, even if their system does not communicate with it.

And finally we have taken standard forms, like an enrollment form and customized it for independent pharmacies, chain pharmacies or closed system pharmacies.

So these are what we consider some promising practices that both speak to standardizing REMS and also customizing them for different dispensing settings but we look forward to hearing from you to hear some other ideas. And with that, I will turn it over to Terry.

MS. TOIGO: Okay, so we set this panel up again to walk people through the background document and also to highlight some of the challenges that we are going to face with standardization.

So if you have had experience with REMS, you may have had experience with a particular REMS but hopefully these presentations have highlighted the variability in patient tools, in prescriber tools, and the diverse dispensing settings that we need to consider as we think about standardization.

So my FDA colleagues have been disciplined in keeping to their time constraints and that leaves us in the unusual

position of being finished early with this session and giving you a half hour break. So as opposed to 15 minutes, you get a half hour. Hopefully, the coffee is available. Extra time for networking, since we only have -- we may have a shortened lunch. And the reason we are not going to speed up is because the next panel is our public panel and we don't want -- our public panel had expectations as to what time they had needed to be here and we don't want to start a panel without them here.

So you will start back at 10:30 and we will get organized before but we will start right at 10:30.

So thank you and I hope this has walked you through the background document and stimulated some thinking and will encourage you to give us additional feedback.

(Whereupon, the foregoing proceeding went off the record at 9:48 a.m. and went back on the record at 10:30 a.m.)

MS. TOIGO: This is our first

panel and they are going to be addressing general standardization issues. And we have seven speakers. Each of them are going to spend -- or they have been allotted ten minutes. And then we have time for FDA questions at the end of the presentations.

So I think our speakers know the drill. You have got ten minutes. At eight minutes, the yellow light will come on. So that is two minutes left. And red will come on when your ten minutes are done. And at that point, it is time to think about wrapping up and turning it over to the next speaker.

So I think Sarah Spurgeon from PhRMA is our first presenter. And I don't think you have any slides, Sarah, right?

MS. SPURGEON: Right.

MS. TOIGO: Okay.

MS. SPURGEON: Hi, good morning. I am Sarah Spurgeon, Assistant General Counsel of PhRMA.

PhRMA is a voluntary, non-profit

association that represents the country's leading pharmaceutical, research, and biotechnology companies. We are dedicated to developing medicines that allow patients to live longer, healthier, and more productive lives.

In 2012 alone, PhRMA members invested approximately $50 billion in discovering and developing new medicines. We represent the vast majority of private investment in biopharmaceuticals in the United States.

For PhRMA and its member companies, protecting patient safety and enhancing the implementation of REMS are of utmost importance. PhRMA appreciates the hard work of FDA and its recent efforts to fulfill its commitments under PDUFA V. PhRMA, however, remains concerned that REMS programs can create an undue burden on the healthcare system, limiting appropriate use of and access to much needed medical treatment. We

appreciate this opportunity to convene with stakeholders to discuss ways to improve the implementation of REMS. In doing so, we hope to promote patient safety and public health.

During this morning's panel, PhRMA will comment on FDA's efforts to develop analytically rigorous approaches to standardizing REMS programs. Tomorrow afternoon, we will comment on the Agency's efforts to develop a consistent evidence-based approach for evaluating the effectiveness of REMS programs.

PhRMA and our member companies share FDA's views that standardization can make REMS more predictable, easier to measure, and may improve stakeholder compliance. However, PhRMA believes that some variation and flexibility in REMS is necessary and appropriate to address specifics risks posed by particular drugs and a wide range of patient populations in healthcare settings. And it is recognized that standardization

alone cannot mitigate the need for strong sponsor stewardship over a product's REMS.

For REMS elements that are amenable to standardization, PhRMA would like to share the following specific comments:

1) PhRMA believes that similar risks can and should be regulated in a comparable manner. For example, FDA should use the same REM elements across products that share similar risks. Such elements should be the least burdensome possible to achieve risk minimization. PhRMA recommends that FDA work to design general REMS templates and tools for elements that address similar risk, as well as a mechanism to share such standardized materials with stakeholders.

In developing these templates and tools, PhRMA supports collaboration with stakeholders who have experience in developing and disseminating standardized information. Possible stakeholders included standard development organizations, third-party drug

information providers, professional societies, accreditation organizations and continuing medical education programs. Once finalized, FDA should articulate in guidance the circumstances under which such standardized REMS, tools and templates are required.

2) Importantly, before any standardized tools are deployed, FDA should conduct user testing and make the results available publicly for comment. Furthermore, the standardization process should remain sufficiently flexible to allow for the innovation of new tools and methods, which can help to further improve REMS programs.

3) PhRMA members support the exploration of greater technology utilization to better integrate REMS into the existing healthcare setting. Any technology promoted must not disrupt the normal practice and workflow of the healthcare professional. For example, PhRMA encourages FDA to consider innovative technology platforms, such as

mobile applications. PhRMA also suggests that FDA explore the integration of REMS into existing healthcare information systems, such as EMRs and also to partner with companies that provide timely medical information to practitioners.

To gain insights on feasibility, PhRMA supports FDA's efforts to identify high quality projects that could offer stakeholders the opportunity to develop, test, and implement new approaches to standardizing REMS utilizing healthcare IT.

4) While PhRMA believes that standardization as a whole can reduce the burdens of REMS, FDA should still allow sponsors, without the need for prior approval, to make minor administrative and editorial adjustments. For example, moving from a paper form to a web-based system can improve the enrollment process. Another example is a sponsor adding a phone number to a phone to improve data collection. Such minor changes

create a more efficient REMS without altering the underlying risk-benefit balance.

As PhRMA is not presenting during the prescriber standardization session, we would like to share a few general comments on that topic now. With the caveat that different clinical specialties or disease areas may warrant flexible approaches to prescriber interaction, PhRMA believes that there can be certain common elements to REMS communications to assist with prescriber comprehension. Such common elements could include:

1) An FDA design REMS brand or logotype that sponsors would include on all REMS communications to prescribers. This easily identifiable brand or logo would alert prescribers that the communication relates to a REMS program.

2) A standardization for frequently used REMS communications, such as Dear Healthcare Provider letters should be

used. This template could incorporate elements such as standardized font and page design.

3) There should be a common one-stop shop internet location where prescribers could access REMS information online. For example, the current FDA portal listing approved REMS could be amended to include links to each product's REMS website, if available.

4) Streamlined prescriber enrollment forms that eliminate duplicative information contained in the prescriber training material would be appropriate. While streamlining the form, flexibility should be retained for the prescriber to complete and submit such form by fax, email, mobile app, et cetera.

In conclusion, PhRMA appreciates the efforts of FDA in organizing today's meeting. We hope to continue to serve as a constructive partner, together with other

stakeholders, as the Agency continues to implement its REMS authorities.

Thank you.

MS. TOIGO: Thank you, Sarah.

Next we will hear from Andrew Emmett from BIO.

MR. EMMETT: Good morning and on behalf of the Biotechnology Industry Organization, thank you for the opportunity to provide comments on the issues and challenges associated with the standardization and assessment of Risk Evaluation and Mitigation Strategies for drug and biological products.

BIO supports FDA's ongoing PDUFA V initiatives to identify potential projects that may help to standardize REMS and integrate them into the healthcare delivery system.

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers, and related organizations across the U.S. and in

30 other nations.

BIO has long advocated for a holistic approach to drug safety. And the PDUFA V framework demonstrates industry's commitment to a lifecycle approach to product evaluation by strengthening FDA's post-market surveillance and benefit-risk management capacity.

Drug safety is not absolute but rather a matter of balancing a drug or biologics predicted benefits against known risks. A product is considered safe if it has an appropriate benefit-risk balance for the intended population and use. And REMS programs can play an important role in minimizing risk to maximize the drug's potential benefit-risk profile.

Effective risk management approaches including REMS can help facilitate appropriate patient access to efficacious therapies with known safety issue that may not otherwise receive FDA approval.

As the Agency continues its efforts to make REMS less burdensome to all stakeholders and more predictable and simpler to understand, implement, and measure, BIO asked the agency to keep in mind the following principles.

First, FDA sponsors should communicate about REMS and risk management strategies as early as possible in the review cycle. Second, comprehensive REMS implementation efforts should be reserved for REMS with elements to assure safe use programs. Third, standardization should include establishing a standard set of best practice principles, regarding the design, development, testing, implementation, evaluation, and modification and termination of REMS tools. And finally, REMS program effectiveness assessments should evaluate the totality of the REMS programs.

I am going to speak to each of these in a bit more depth. First, to better

standardize a REMS program, it is critical that FDA and sponsors initiate risk management planning and dialogue early and often during product development and the FDA review phase. FDA and sponsor require an understanding of when and how to communicate regarding the potential REMS. For this reason, the PDUFA V NME Review Program provides structured opportunities for FDA-sponsored communication at key points in the review, including the pre-NDA/BLA meeting, the mid-cycle communication and the late cycle meeting.

The program also promotes early cross-disciplinary engagement by staff of FDA's Office of New Drugs and Office of Surveillance and Epidemiology to assess if a REMS is needed to mitigate a potential safety issue.

By proactively discussing risk management strategies and potential REMS earlier, FDA sponsors can reserve adequate time in the review process to develop an

optimized and standardized REMS program that could minimize the burden on the healthcare delivery system. BIO is looking forward to the release of the independent contractor evaluation of the NME Review program in 2015. So it would have been better assessed if risk management discussions are in fact taking place earlier than previous experience.

We also look forward to evaluating how early communication of draft REMS proposals can align with application requirements for assuring that commitments for a complete application are made at the pre-submission and have been addressed.

Second, to ensure that an approved REMS can be efficiently and effectively implemented, BIO believes that REMS efforts should be reserved primarily for REMS programs that include elements to assure a safe use or ETSU. Many approved REMS consist only of communication-based risk management strategies, rather than more restrictive ETASU

tools. For example, as of July 2013 only 36 of 72 approved REMS included ETASU while the remaining 50 percent of REMS focused solely on patient and provider communication elements through MedGuides and communication plans only.

BIO believes that patients and physicians need timely accurate and relevant information about the benefits and the risks of the drug, so that they can make well informed choices about therapies. But we think that more meaningful progress and effectively communicating benefit-risk can be achieved through complementary mechanisms outside of REMS programs. For example, BIO supports FDA's ongoing initiative to develop patient medication information or PMI, a single unified patient benefit-risk communication tool that would minimize redundancies and public confusion around the distribution of MedGuides, patient package inserts and consumer medication information.

Additionally, FDA's November 2011 guidance clarifying that MedGuides can be administered outside of the context of a REMS program was an important step in improving the efficiency of the REMS framework. We encourage FDA and stakeholders to also evaluate whether effective and efficient benefit-risk communication is better achieved by limiting communication plans to ETASU REMS to explain restricted distribution plans to patients and provides and by implementing routine benefit-risk communication to all non-ETASU drugs outside of the context of REMS programs.

These various approaches have the dual benefit of enhancing benefit-risk communication towards patients and provides while reserving comprehensive REMS implementation efforts for ETASU programs, so that all stakeholders in the healthcare system can focus limited attention and resources on the most critical risk minimization

activities.

With this in mind, we suggest that priority projects for standardizing risk management tools under the REMS and integration initiative should focus primarily on ETASU REMS elements.

Third, BIO supports FDA's efforts to standardize REMS where appropriate with the goal of reducing burden on implementing REMS on practitioners, patients, and other various healthcare settings.

While REMS standardization can help eliminate unnecessary variation between REMS programs, it should be noted that standardization for the sake of standardization alone is not always consistent with best practices for managing the diverse risks associated with different types of drugs and biologic products.

BIO recommends a standard set of best practice principles regarding the design, development, testing, and implementation,

evaluation, modification, and termination of REMS tools, which will promote program stability, while at the same time preserving the necessary flexibility to address and mitigate product-specific risks and associated REMS goals. These principles should include a shared understanding between FDA and sponsors of the standard principles and methods used by FDA to assess and characterize risk and related appropriated REMS tools or interventions.

BIO looks forward to working with FDA to develop these best practices and to ensure they are based on practical evidence of the latest advancements of the science of pharmaceutical risk management.

And finally, BIO supports development of an evidence-based approach to the measuring the effectiveness of REMS. BIO believes that any successful program assessment requires FDA and sponsor understanding and prior agreement on outcomes

goals. Without such shared understanding and agreement, assessment tools may not properly measure and capture whether any given program is appropriately mitigating the identified risk necessarily to ensure that a drug product's benefits outweigh those particular risks. BIO also believes that it is important for any assessment to evaluate the totality of the REMS program. For example, while the availability of information about a drug can empower a patient to make sound decisions about his or her health, it should be understood that patient knowledge of a specific risk does not always translate into actual behavioral change that can in fact minimize the risk involved. This fundamental limitation should be acknowledged when assessing REMS tools and medical outcomes, especially in light of reliance on assessment surveys that measure understanding, as opposed to behavior.

A holistic approach to assessment

should, therefore, also include measures of implementation fidelity such as engagement with and adherence to program-specific processes and procedures put in place to control exposure to risks and ensure proper use.

It is also important to recognize that program assessment tools can then themselves place a burden on the healthcare delivery system, including patient prescriber and dispenser time and resources. As FDA reliance on REMS grows, the effectiveness of REMS programs and the burden on the overall healthcare delivery system must be carefully measured. The effect of system burden measurements requires the collection and review of standard data that also look across programs, products and tools.

As sponsors are but one part of the healthcare delivery system and have limited access to such data, FDA and other REMS stakeholders should collaborate in

collecting and evaluating system-related burden data to judge whether a particular REMS program or tools overburdens the healthcare system and modify the REMS requirements accordingly.

In conclusion, BIO appreciates this opportunity to comment on REM standardization and we look forward to continuing to work with FDA and other engaged stakeholders to further streamline REMS programs and minimize the burden on the healthcare delivery system. And we plan on submitting written comments to the docket.

Thank you very much.

MS. TOIGO: Thank you, Andrew.

Next we will hear from Paul Sheehan of Celgene Corporation.

MR. SHEEHAN: Good morning. May name is Paul Sheehan and I am the head of the U.S. REMS Department of the Biopharmaceutical Company Celgene Corporation. I would like to thank the FDA for providing the opportunity to

share some of our perspectives regarding REMS standardization and assessment.

At Celgene, Safety is a hallmark of our commitment and our responsibility to improve the lives of patients worldwide. Beginning in 1998 in the absence of an existing model to reference, Celgene created, developed, and introduced the Thalomid Steps Risk Management Plan, followed by a RiskMAP for Revlimid called RevAssist in 2005. In 2008, both programs became the deemed REMS that include elements to assure safe use and implementation systems. Earlier this year, we developed and introduced the third REMS program, the Pomalyst.

REMS programs are introduced for a particular drug to ensure its benefits outweigh its risks. The goals addressed by the program components are unique to each REMS. Therefore, to increase efficacy and reduce patient and physician burden, standardization should be a desired policy

goal only in situations where the risk of the drug, the target populations, and the REMS designs are similar.

Celgene supports the recommendations that PhRMA and BIO presented at the December 2012 FDA public hearing about teratogenic drugs and risk management, which supported that REMS programs can be standardized and at the same time retain flexibility in approaches given drug benefits, risks, characteristics, disease, et cetera.

While we recognize that certain components of a comprehensive REMS program may benefit from standardization, we support the FDA's approach in designing specific solutions to each specific REMS situation.

REMS programs are typically designed after extensive industry collaborations. The success of a REMS program is not measured in the first few months after their initial release but is continuously assessed throughout the lifespan of the

program. Ensuring the REMS program is focused on achieving the stated objectives, analyzing results for continuous improvement, and evaluating proposed future enhancements is of vital importance. To ensure an effective execution of these concerns, they are most appropriately managed by a single accountable party.

In February of this year, Celgene introduced standardized and harmonized REMS programs for Revlimid, Pomalyst and Thalomid. Patient and prescriber enrollment forms were standardized, simplified, and technology was introduced to help increase completion accuracy and reduce the necessary burden. Redesigning the patient enrollment forms to ensure they are easily understood by providing content at the eighth grade level has reduced processing times by about 25 percent per form.

Celgene introduced the FDA's recommendations for standard terminology. We changed the titles of our patient risk

categories and REMS program names across our educational materials, forms, and computer systems. We expect that the transition period for these changes may take up to 12 months.

As the FDA considers further changes to the REMS environment, due consideration must be given to the implementation challenges of educating, distributing, and implementing changes to established REMS practices.

As part of our harmonization initiative, Celgene introduced an option or comprehensive online solution for prescribers to manage their REMS activities for our products. Celgeneriskmanagement.com provides a single site to obtain educational material, enrollment to any of our REMS programs, complete necessary REMS transactions and view an activity dashboard that highlights next steps.

This integrated environment offers tremendous advantages to the prescribers who

choose or are able to use it, as it delivers timely reminders and alerts and reduces the overall REMS administration processing time.

Although technology may offer advantages to some of the challenges facing REMS programs, it is vital to remember that the lowest common denominator for any REMS implementation system must continue to be a fax machine.

To facilitate future innovation within the implementation of existing REMS programs, we ask that FDA provide guidance on how companies with approved REMS can initiative pilot projects without requiring these ideas to be formally included in the REMS before they have proven to be successful.

Celgene is interested in pursuing discussions with representatives of the pharmacy industry to see how the REMS information is required to be sent to Celgene during a dispense, can be entered into and delivered from their pharmacy management

system. Such an approach will integrate REMS transactions into existing workplace systems.

Similarly, analysis should be conducted into how data elements from prescribing systems could be utilized for REMS purposes, how alerts could be provided to practitioners when they are prescribing a REMS drug and how ePrescriptions could be delivered to a certified REMS pharmacy for fulfillment.

The experience going from implementing REMS programs over several years provide Celgene with unique insights that we look forward to sharing further. Standardization of key definitions would be helpful but we recognize that there are limits to the extent of possible standardization if programs are to maintain effectiveness.

Thank you for your time today.

MS. TOIGO: Thank you, Paul.

Next we will hear from Jeff Fetterman at ParagonRx.

MR. FETTERMAN: Good morning. I

am Jeff Fetterman. I am President of ParagonRx and Adjunct Professor of Healthcare Systems Engineering at Lehigh University. And I appreciate the invitation to speak on the topic of REMS standardization methods.

I will start by sharing an observation that many have had in that it is somewhat paradoxical that during the time of greatest control of clinical trials that we use the greatest extent of standardization. But at the time that when the medication is introduced into the wild state of the real world, we use intuitive and ad hoc approaches to design risk management programs. And while this may not be logical, perhaps it is not surprising because most people consider themselves actually to be risk managers.

We are all risk managers and some of us have formal training but others have learned through life experiences how to manage risks. And we manage those risks constantly related to a variety of topics, health,

safety, financial, security. And this informal risk management is a way we cope with daily experiences and as such, it is something that we do subconsciously.

So think about the various activities that all of us do as part of our daily lives that we introduce some sort of standardization to minimize uncertainty, our morning routine, the way we drive to work in the morning, the way we go about our work habits during the day, and even what we do at the end of the day. And so this intuitive approach is good for everyday life but not for drug safety risk management.

So stakeholders who work in other risk-intensive industries do more. They have ingrained standardized methods and tools into their practices after years of using them. And I would suggest that that is where we need to be as an industry.

So standardized risk-intensive industries used standardized risk evaluation

methods. Let's think about some of these. The aviation, military, nuclear, aerospace, healthcare, are all risk-intensive industries that have adapted an advanced risk management method to evaluate and anticipate and prevent failures. All of us are familiar with aviation as an example, so let's look at that. Redundancy: there are multiple pilots, multiple engines on every aircraft. Training: not only is training provided in the form of educational content but also in simulations that enable learning. Passengers receive drills.

So if we think about all of these other industries, we can learn much from aviation and from others. As pharmaceutical professionals, we were not trained to think this way and we need to adopt some more effective methods.

Standardized risk evaluation methods that have been used in other industries are well-documented. The use of

probabilistic risk assessment and FMEA by the nuclear industry and regulated by the NRC is well-documented. HACCP by the food side of FDA and FMEA by other divisions like CDRH within FDA as well. I would like to look at FMEA as one of the most widely adopted practices.

So Failure Mode and Effects Analysis is a systematic approach to proactively analyzing and improving a product or process in order to achieve a better outcome. Some of the key attributes: it is preemptive; it looks ahead and anticipates to avoid risks; it is systematic and, therefore, it is comprehensive in its view; it prioritizes by means of degree of hazard; and it is flexible and feasible and as such, it has been demonstrated to be effective across a broad range of industries.

So I would like to look at some healthcare applications of this. The VA National Center for Patient Safety looked at

various risk evaluation methods. They looked at HACCP and they liked the idea of the decision tree. They looked at root cause analysis. It is retroactive but the scoring matrix was really appropriate. And they melded those with the fundamentals of FMEA and preserved the basic principles. And in 2002, published a tutorial about HFMEA methodology and the Joint Commission Journal on quality improvement.

Likewise, the Institute for Safe Medical Practice has been advocating FMEA since 1994. In this case, ISMP analyzed the IV patient-controlled analgesia process. They used the methodology to map the process, evaluate what could go wrong in that process, identify why those things went wrong, and then pinpoint specific interventions that measure follow-up. So it is this type of detailed process analysis that I believe we now have the opportunity to embrace as a new standard in pharmaceutical risk management.

FDA has also been advocating use of standardized evaluation methods for some time. There are multiple guidances that have cited FMEA in the past and I suggest there is an opportunity to use methods such as failure modes and effects analysis as a standardized part, a standardized methodology for pharmaceutical risk management.

I would like to walk through a pharmaceutical adaptation of HFMEA and some of the modifications that were made are attributable to some important disciplines. One is human factor failures and the recognition that we can never eliminate human failure. So the best thing to do is to put in place redundancies of tools and of stakeholders to make sure that you minimize the frequency of the failure and mitigate the risk when it occurs.

Second is adult learning and recognizing that individuals do not learn strictly by the communication of content but

they also need to have enabling tools that allow them to apply to their everyday lives.

And so with these modifications, here is a brief overview of what the process looks like. The analysis breaks down medication use into process and sub-process steps. It then looks at what why and how. What could go wrong? We call that the failure mode. And in this case, the healthcare professional did not counsel a patient. They didn't act.

The why, why did it occur? What was the underlying reason? In this case, the healthcare professional forgot. There could be other reasons as well. They could have ignored.

And then finally, how to go about fixing this particular problem. And in this particular case, there is both reminders for the healthcare professional as well as some enabling tools and then back up information for other healthcare providers, in this case

a nurse and a patient.

So here is the elegance of this approach. It defines what everyone needs to do to back one another up, when to do it, and it is linked back to the failure that can be avoided.

So there is many demonstrated applications of FMEA in pharmaceuticals that has been used to design a de novo REMS. It has been used to redesign existing REMS. There has been other applications as well. But I really want to focus in on its use to validate risk management planning. You will not that this says validate a RiskMAP because that is what this case study I'm about to share is from and it shows the duration of time, frankly, that methods like this have been applied.

So in this particular case study, an organization brain stormed a set of 30 possible risk management tools based on intuition. And while that is not particularly

unusual again, given my opening comments, many people are doing this via an ad hoc or intuitive approach, they wanted to validate their selections. And so they used FMEA to validate and identified all the high-priority hazards that could occur. And then they compared those to the tools and they found that of the 30 tools they identified, only 16 addressed high hazard failures; 14 were unusable because they didn't address any of those high hazard failures; and 12 new tools were required to mitigate risks of high hazards that were not mitigated by the original 30. Then all of those were combined into 18 enabling and educational tools, again, thinking about adult principles, and then implemented across a redundant group of audiences.

So here is the lessons learned out of this. Intuitive brainstorming, while it is common and while it is relatively straightforward is inaccurate and it creates

waste in gaps. FMEA validation generated a more focused program with fewer tools that were more targeted and redundancy has the promise of alleviating burden on any given stakeholder.

Some key takeaway points. Number one, risk minimization of medications, and devices for that matter, requires more than intuitive design. I hope that is clear through the discussion today.

Secondly, FMEA has a proven history of systematically guiding design of risk minimization and other risk-intensive industries, and likewise in healthcare.

And finally, our assertion that systematic use of FMEA or other standardized methods in the design of risk minimization tools for medications and devices enables standardization and transparency.

Thanks very much.

MS. TOIGO: Thank you, Jeff.

Next we will hear from JoAnn

Stubbings from the University of Illinois at Chicago.

MS. STUBBINGS: Thank you. My name is JoAnn Stubbings and I am Assistant Director of Specialty Pharmacy Services at the University of Illinois Health Sciences System. We call it UI Health. UI Health is a closed healthcare system and it is comprised of a 495-bed hospital and 11 federally qualified community health centers. There are seven health services colleges and an outpatient care center that has a 600-physician group practice.

We have pharmacies. We have seven outpatient pharmacies that service UI Health and we fill over 1,000 prescriptions per day. And most of our business is in the specialty pharmacy area, due to the nature of the practice in the outpatient clinic. We could be referred to as a controlled dispensing setting.

The population we serve is about

two million people, primarily an under-served community. Thirty-five percent of our population is Hispanic and another 35 percent is African American.

Just as a little bit of background, we believe that the conditions are becoming more favorable for integration of REMS into the healthcare system. So what I would like to talk about today is the proposal that we have developed for integrating REMS into the healthcare system. And the two main, most important points are that the lines between inpatient transitions in care and outpatient are beginning to disappear. And also healthcare systems have access to records that are required for implementation and evaluation for REMS. REMS can impact the system, such as inpatient and transitions in care, both in a positive and negative way.

There are four goals that are involved in integrating a REMS system into a healthcare system and I would like to go

through each of these goals individually. First is to improve REMS standardization and integration; secondly, to increase access to high-risk medications for patients; third, improve the potential for assessment and evaluation; and fourth, to reduce the burden on healthcare providers.

So the first goal is to improve REMS standardization and integration. And we heard discussion this morning about having web-based portals. And I believe that is a great start. And the web-based portal in a healthcare system can be used on its own or it can be integrated into the electronic health record or the pharmacy system.

Recognizing that hospitals use different EHRs or different pharmacy systems, then this integration could be designed or done at the individual systems or done through a series of links into the EHR. And we heard the discussion from Adam Kroetsch this morning about SPL structured product labeling and this

is something that would have great potential for integration into either the pharmacy or the electronic medical record.

I would like to show some quick examples of attempts that we have made for this integration. And one would be with ESAs, the second is with clozapine, and the third is with lenalidomide. And the starting point that we use for any of the integration or any of the REMS proposals is to develop a set of policies and procedures. And this is a policy and procedure for ESAs. And I will point out that we will be submitting these policies in their entirety to the committee in our written comments because this is not readable in this slide.

But this is a policy and procedure for ESAs and it basically states -- it defines the REMS when the indication is for cancer-induced anemia. So we have incorporated the indication into the electronic order entry and this is kind of a marked up prescription that

was entered for one of the ESAs. And basically, the prescriber has to provide the indication into the order for the medication. And here, this prescription is for anemia, which is non-chemotherapy related. So as a result, the remainder of the REMS is not required. But at the point of dispensing the pharmacist sees that indication on the prescription and the pharmacist verifies that by going back to the electronic medical record and doing a check.

So the advantage of having this integration into the healthcare system is that we have the access to the EMR and we can go back and do those checks.

The next one is the policy and procedure for clozapine. Clozapine policy and procedure focuses on inpatient and discharge care. And it basically incorporates the REMS and then goes above and beyond by incorporating other policies and procedures within the health system. For example, one

procedure that we have is that if the discharged patient is going to continue their treatment at UI Health, they are referred to a medication management clinic within the psychiatry clinic. So in addition to the REMS requirements that we are meeting, we have other procedures that we follow.

So the discharge policy for clozapine has emphasis on establishing access to the medication prior to discharge.

The next one is the lenalidomide procedure and we have access to all of the manufacturer information and checklists. And what you see on the upper left-hand corner of the slide is the checklist for pharmacist. And we developed a workflow document that helps in training and helps in implementation of the REMS at the point of dispensing in the oncology clinic. And this workflow is a series of links. So each of these boxes represent links to additional workflow information.

So for example, if you click on "New Rx-Male," you go to a series of decision points and a decision tree. And there are links on each of these -- at each of these points that take the prescriber or the pharmacist to some individual documents from the company REMS. So this is our way of attempting to provide integration. So you see how that goes further.

And then this is the same sort of thing for the new Rx-Female and there are links to the MedGuide and the other patient information.

So just to back up, to summarize, there is potential for integrating -- the integration of REMS into the standard of care in the healthcare system and we have attempted to do that for several medications and to improve patient care and to facilitate transitions in care.

The second goal of the integration of the REMS system is to increase access to

high-risk medications. And we would like to propose that the link between REMS and limited distribution be broken. We believe that sometimes there is a perception that if a drug has an ETASU REMS in particular, that the distribution must be limited and controlled. And we believe that there could be access to medications through health systems, through various controlled measures. And what we are starting to see, for example, is specialty wholesalers, where distribution can be only to health systems that can meet the requirements and provide access to medications and improve patient care.

We believe also that allowing access for health systems would improve transitions in care, would avoid delays at the point of discharge, and also shorten the time to start of therapy for patients.

The third goal is to improve the potential for assessment and evaluation. And the second point here is to utilize the

richness of electronic health record to assess and evaluate outcomes. And health systems have access to data that could potentially improve the assessment and evaluation and, therefore, make REMS more robust.

And then to the fourth goal is to reduce the perceived burden on healthcare providers. And health system pharmacists, especially those who practice in the clinical setting are many times an untapped resource for REMS implementation and management. And we believe that a new thing that is being talked about a lot is pay for performance and many models are being tested. And we believe that pay for performance, a mechanism for implementation and assessment, could be linked to improved outcomes and cost savings for REMS.

And many models are being tested. And these can be as simple as just allowing access for the health system or having discounts or incentive payments. And various

payers are experimenting with models such as Medicare, Medicaid, insurers, health plans, and pharmaceutical companies.

So in conclusion, the healthcare system is evolving into an integrated model. So I believe that REMS could be part of this integrated model. And I talked about four goals for an integrated REMS system, which would be a standardized REM integrated into EHRs and pharmacy systems; secondly to break the link between REMS and limited distribution; thirdly, to integrate into health systems, allowing for more robust evaluation and assessment; and fourth to include pay for performance in order to reduce the perceived burden on providers.

And finally, REMS should be a standard of care in all health systems. Thank you very much.

MS. TOIGO: Thank you, JoAnn.

Our next speaker is Paul Brown from the National Research Center for Women

and Families.

MR. BROWN: Good morning. Thank you for the opportunity to speak. I am Paul Brown with the National Research Center for Women and Families. I am also with the Patient Consumer and Public Health Coalition. My brief comments are from a consumer-patient point of view.

The REMS program made it possible for the FDA to approve drugs with known or potential risks that may outweigh the benefits. The plan was to develop strategies to reduce those risks. That is essential because if a known risk or potential risk cannot be minimized, these drugs should not have been approved.

The HHS Inspector General has done an excellent job in reviewing the REMS program. The HHS report FDA lacks comprehensive data to determine whether Risk Evaluation and Mitigation Strategies improve drug safety. That report found that nearly

half, nearly half of the sponsors did not include all the information requested for their REM assessments. That is a failing grade by any standard. Only seven of 49 met all of the FDA's goals. To industry representatives here today, your companies can, your companies must do a better job of providing this information.

The FDA should not be so focused on the burdens of REMS, given that the entire goal of REMS was to put riskier products on the market. For that reason, the focus should be on protecting patients from medications that are known to have risk or where the potential for harm is great.

There are some flaws in the current REMS program which affects the ability to assess the programs. Sponsors are not providing information needed to assess the success of their REMS strategies. FDA assessment plans are not enforceable. And nobody knows if the strategies are working.

The National Research Center for Women and Families has great concerns about the REMS program and many members of the patient, consumer, and public health coalition share those concerns.

We believe that drugs with higher risk are being approved under the assumption that REMS strategies will protect patients but there is little evidence that REMS are effective in providing that protection. And if it is, to what percentage of the patients.

Thank you for the opportunity to speak.

MS. TOIGO: Thank you, Paul.

Our last speaker on this panel is Phyllis Greenberger from the Society for Women's Health Research.

MS. GREENBERGER: Well, good morning and thank you for the opportunity. My name is Phyllis Greenberger, President and CEO of the Society for Women's Health Research and we are a nonprofit advocacy organization in

Washington.

I commend the FDA on convening this public meeting to evaluate Risk Evaluation and Mitigation Strategies and appreciate having the opportunity to speak this morning regarding REMS standardization. I hope that you will take our comments into consideration in your final meeting recommendations.

The Society has long advocated that FDA's approval decision should be based on evidence that is data-driven and science-based. Further, we believe in particular that these decisions should evaluate and consider the impact on women and sub-populations.

Society believes the reporting and analysis of demographic data, in particular that of sex, should be a part of any standardization at FDA in addition to the standardization of REMS. However, in the interest of safety, today I ask for some caution in the application of standardization.

We believe that in some cases such standardization can and will particularly and adversely impact women.

Many of you know, I hope, that the society is the thought leader in sex difference research and has been the driving force behind research into women's health since 1990. It has only been in the last decade that scientists have truly begun to uncover significant biological and physiological differences between men and women from the composition of bone matter and the experience of pain to the metabolism of certain drugs and the rate of neurotransmitters synthesis in the brain.

This is important to realize because in the context of establishing REMS years ago, it was the fact that there were clear sex differences between men and women, especially adverse reaction to prescription drugs and severe side effects that particularly spurred the need for REMS. We

know that of the ten prescription drugs withdrawn from the United States market between January 1997 and December 2000, eight caused statistically greater health risks for women than men. Thankfully over the last decade since that report, there has been a greater emphasis on risk management.

While we know that sex differences exist in drug metabolism and drug's effects on people, not enough has been done to date to provide this information to patients. We applaud the FDA's decision earlier this spring to change the dosing for prescription sleep medications and to particularly emphasize the impact on women and the need for women to take a lower dose. This is a step in the right direction but all patients should have access information regarding benefits and risks broken down by sex differences that is easily accessible on the FDA website.

It is our belief that to the extent existing REMS are collecting data

ensuring, we hope, that risk disproportionately suffered by women are mitigated, standardization should be approached with careful evaluation, consideration, and transparency.

Whatever standardization across different REMS the FDA might consider, such standardization should only modify existing REMS to the extent it will not compromise the safe use that the current REMS currently provides. To do otherwise would compromise patient safety in the name of standardization and this would not be an acceptable outcome for patients, providers or the FDA.

For example, certain existing REMS, including REMS that predate the Food and Drugs Administration Amendment Act of 2007, FDAAA, manage unique risks that may not lend themselves to standardization and, in some cases, have a particular disproportionate impact on women. A one size fits all approach can cause more harm and disrupt the drug

supply system and is not the direction medical practice is taking.

The Society believes that these REMS must ensure that harm is not done and extreme care is taken, as there are public health and safety concerns relating to those REMS which may not lend themselves to being standardized. Our focus on some of the older drugs and its concern over the risk mitigation systems is directly proportional to the particular impact many of these drugs have on women and the lack of study and analysis of sex in the approval of these drugs which is clearly not the same issue for new drugs that the FDA has yet to approve.

During the debate over the passage of the Food and Drug Administration Safety and Innovation Act of 2012, FDASIA, last summer, the Society wrote to Congress with respect to its concerns over REMS, specifically those imposed on high-risk drugs where expanded access to REMS restricted innovative drugs is

being granted to generic manufacturers to conduct bioequivalence or clinical testing. These drugs have frequently had a disproportionate effect impact on women and the Society believes that the safety standards for the generic drug should be as rigorous as those in place for the innovator drugs.

We recognize the importance of generic drugs to the medical community and to patients. We also recognize, however, that all drugs and biological products can potentially pose serious safety risks and that costs should never trump safety. FDAAA gives the FDA authority to require REMS from manufacturers to ensure that the benefits of a drug or biological product outweigh the risks.

In 2009, the Society convened a stakeholder meeting on REMS, resulting in the publication of a detailed report in March 2010 titled optimal futures for risk evaluation and mitigation strategies, where issues related to

generic drug manufacturers addressed, as several cases have caused concern within the advocacy community.

One specific instance involved the acne treatment isotretinoin where a less-rigorous risk management system for teratogenic drugs had caused unplanned pregnancies among patients. The society's report recommended that policies be in place that will assure all drug manufacturers are held to the same standards when implementing tightly controlled restricted distribution programs.

The society also recommended that the FDA develop quantitative methods to evaluate a generics risk management program and to develop a contemporaneous monitoring and enforcement policy.

In closing, I want to reiterate that the society believes risk mitigation remains an evolving effort and were of great importance in the weighing of benefit versus

risks to patients. Further, we believe that the focus of standardization should be on new chemical entities only. A one size fits all standardization approach could have unintended consequences of minimizing well-established safety protections, as well as potentially compromising access to treatments that but for the REMS programs would not otherwise be available to patients.

Patients and their advocacy organizations have fought hard for the access to and benefits of these drugs. And we thank you for the opportunity to provide these comments. Thank you very much.

MS. TOIGO: Thank you, Phyllis. And thank you to our panel for some informative comments.

Next we now have time for FDA questions to our panel members, either to clarify some of the points that they made or if their comments spurred some new questions in your mind that you might want to probe a

little bit more for our panel members.

So I will look to my left and see who might want to start questions. Okay, Claudia, and then Gary, and then Mwango.

DR. MANZO: My question is for JoAnn Stubbings. You made a comment about breaking the link between REMS and limited distribution. I wonder if you would elaborate a little bit more on that point.

MS. STUBBINGS: There is a perception that REMS is a requirement for limited distribution or that limited distribution happens or is necessary because of REMS. And that is something that in the health system that it would be better for transitions in care and overall patient care to be able to have access to the medication in addition to being able to administer the REMS.

DR. SLATKO: So my question is to Paul. Could you tell us a little bit more about the electronic system the celgeneriskmanagement.com? I think you said

that the system cues the person who is using it to complete that they walk them through the remaining steps of the process to get to completion. So it kind of gives a feedback mechanism about what they still need to do in order to achieve that. Can you describe how that works a little more?

MR. SHEEHAN: Sure. So one of the features of celgeneriskmanagement.com is a prescriber dashboard. And for the patients that prescriber has enrolled into any of the three REMS programs that we have, the dashboard will advise the prescriber either that the prescription has been dispensed, the patient needs to take a particular action, or that there was a problem with the prescription and the prescriber needs to contact Celgene. So it acts as a kind of workflow management system.

DR. SLATKO: And do you have any information on how that has been -- I don't know how long this has been in place but any

comparative information since you implemented that to prescribers and patients their ability to implement the program to be facilitated?

MR. SHEEHAN: Sure. So for those prescribers who choose and are able to use it, it is an optional element. But for those that are using it, we have had some tremendously positive feedback that it is helping them implement the REMS into their processes far more efficiently and effectively than before.

DR. SLATKO: Thank you.

DR. KASHOKI: Hi. My question is, and I have, I think, three, for Andrew Emmett with regard to the information that you had on your principles for REMS integration slide. You had two bullets that are of interest to me. The first one was about that said comprehensive REMS implementation efforts should be reserved with REMS with ETASU. And then your last bullet there that said REMS program effectiveness assessments should evaluate the totality of the REMS program.

So with regard to your first -- that first one. I was wondering if you could say a little bit more. I believe I heard you say that we should try and limit or consider limiting our communication efforts that are done under REMS to specifically those programs that have elements to assure safe use or ETASU and have those communication efforts be targeted around what are the requirements for providers and patients as to what they should do.

And I believe you prefaced that by saying that in other areas of communication, for example, about what the risks are, we have other tools or other mechanisms that can be used. You highlighted the PMI and MedGuide as potential tools.

So here is my question. What information are you using or what is your belief about the effectiveness of these non-REMS communication efforts that you said we could do outside of the REMS program that

would adequately convey information about a drug's risks and how to appropriately use them. So what is the basis of that kind of belief or assertion?

MR. EMMETT: Sure. Thank you for the question. And as I noted, half of the proof REMS have elements to assure safety use and the other half are a combination of MedGuides or communications plans or communication plan or normally MedGuide only.

And I really have to commend FDA for the progress that you have made in driving the patient medication information initiative forward. And I think it is quite exciting about how we can improve benefit-risk communication not just for REMS products but routine benefit-risk communication for all products.

And I understand the Agency is going through the process of validating the PMI tool to really ensure that it is a more effective way of communicating benefit and

risks in a balanced manner.

And as that tool and others come onboard, I think it may be an opportunity for us to think about how we utilize benefit-risk through REMS. And as we look at communication plan-only REMS, does that make sense? Or should we really be looking at the communications plan as an opportunity to describe the ETASU elements to REMS, to describe the limited distribution or other risk mitigation steps to patients and providers and then utilize PMI and other routine risk management tools to complement that REMS.

And I believe that the communication plans would be much more effective in that manner describing the ETASU elements. And I think that that would really free up much of the time and resources of stakeholders to really focus on the risk mitigation elements related to the ETASU REMS themselves.

DR. KASHOKI: My second question has to do with your suggestion that we have the assessments evaluate the totality of the program. And unfortunately I don't have the statute in front of me but it does talk about the REMS - that sponsors are required to assess the effectiveness of their programs. And it seems that in part of our assessments as we recommend for sponsors to do are often targeted toward the goal.

So if there is a goal to inform patients, inform providers, we will focus the assessments to ensure that the REMS is meeting the goals. So I wasn't sure what you meant by evaluating the totality of the effectiveness of the program. It seemed to be saying look at what the program is doing overall in terms of our global outcomes where there is decreased adverse events in terms of percentages or whatever or whether you were indeed echoing some of what we were already doing and saying yes we can look at various

aspects of the REMS, how it is working in those specific aspects but consider the information together.

So could you clarify that?

MR. EMMETT: Yes, I think to a certain extent we were making both points, that it is important to look at the REMS in its totality and is it successfully mitigating the risks that it purports to risk. But we also need to evaluate whether each individual tool is being effective and if it is not, how it can be improved or further amended or released.

To the other point, it is important that as FDA and sponsors design REMS and discuss REMS during the review stage, that they have a clear understanding around what outcomes the REMS are intended to rest and that the assessments fully address those outcomes. And I think that there has been some tension about whether the assessment is intended to understand things such as patient

comprehension of risk management communications and tools or actual behavior change is the risk actually being mitigated.

And I think that there needs to be a greater understanding between FDA and sponsors about which goal we are working towards. And that needs to be part of the up-front discussion of the REMS and the REMS outcome. And to my earlier point, making sure that there is adequate time during the review process to have that robust discussion is absolutely critical.

MS. TOIGO: Thank you, Andrew. Megan and then Adam.

MS. MONCUR: Thank you, Terry. My question is also for JoAnn Stubbings and it is also related to the discussion about breaking the link between ETASU REMS and limited distribution.

You mentioned an entity and I wrote it down as specialty wholesaler. Can you clarify what that is and sort of what that

entity makes possible?

MS. STUBBINGS: A specialty wholesaler could be a division of a major wholesaler and they are kind of a form of restricted distributions. So they, instead of providing medication to anybody who orders it, they restrict distribution.

So we are able to orders some medications only from specialty wholesalers. So rather than getting the medication from the general larger wholesaler, for example like McKesson. There is McKesson and then there is McKesson Specialty. So some specialty medications are only available from McKesson Specialty or a specialty wholesaler. And then those can be designated only for certain customers such as health systems.

And I would propose that as a way for allowing access not to the entire market or if there is a need to have some sort of control, then that control can be established by having the product distributed only through

the specialty wholesaler.

MS. TOIGO: Adam?

MR. KROETSCH: My question was directed towards the comment that Phyllis Greenberger made but actually probably something that all of you have been talking about. And that is to say that we should be focusing our standardization efforts on new drugs, NMEs I think was what I heard, and that we should not do too much to disrupt some of the REMS tools that are being used in some of the existing programs.

So my question is how do we balance this idea that we need to standardize, make REMS more consistent and incorporate best practices with the desire to make sure that the individual REMS don't undergo changes that could be confusing. And I am curious how we might reconcile those two things.

MS. GREENBERGER: Are you asking me how to do that?

MR. KROETSCH: So this question is

directed towards everybody. But I mean if you have thoughts, I know since you brought it up, I am curious how would we reconcile those two things?

MS. GREENBERGER: I'm not sure how you would reconcile it. Our concern is that there are a number of drugs out there that are specifically related to women who have risks that are specifically for women and that those particular drugs we would not like to see changed for the reasons that it seems to be working.

In other instances, there may be other opportunities to standardize, which we understand obviously is preferable in the long-run and just in terms of ease for all the different entities involved. But the ones that have been working and that have had these -- could have detrimental effects on women, we don't want to see those changes. And we don't want to see sort of derivatives of those drugs.

The REMS standardized to reduce any of the risks that -- the potential benefits that we have now. So we are sort of happy with ones that we know. We don't want those changed.

MR. EMMETT: Now I would add that it is important to look at REMS standardization for new drugs as well as existing drugs. I think that a lot of lessons learned from existing REMS programs can be applied to new REMS programs as new drugs are approved. And to the extent that stakeholders and the provider and pharmacy in patient communities are suggesting that certain REMS elements may be a burden on the healthcare delivery system. I think it is important that we do assess that for existing drugs.

MR. FETTERMAN: I would just add three quick points. First of all, it is a foundation of every quality process that there needs to be continuous quality improvement, that the lessons of the past are incorporated

into the revisions of the future.

And so that clearly needs to be applied to existing REMS programs, as well as REMS for new molecular entities.

Secondly, another principle that is applied across quality programs is prioritization. So that doesn't mean that every program has to be updated immediately. There can be a prioritization of which ones should receive immediate attention and which ones can be staged at a later time.

And thirdly then, that could itself be informed by reassessment of the benefit-risk profile because benefit and risk is a characterization at a point in time and that evolves over time. And so that it is possible that updated benefit risk assessment may be one of the prioritization methods by which you would determine which ones that exist come to the top of the queue.

MS. TOIGO: So I have a couple of questions but I will just ask one. I think

JoAnn you laid out some SOPs that UIC has in place. And so when we think about looking at burden and making decisions about REMS, what kind of things are either features or processes are in place within your healthcare system that would enable you to safely administer drugs without a REMS?

When we think about formulary systems or the guidelines and training within your institution, you have pointed out where you have worked REMS into your SOPs. So, have they added to your SOPs? I'm trying to -- when we think about burden and where the healthcare system takes care of the risks versus where it doesn't. And those factor into our decisions about whether or not a REMS is necessary.

So do you have those kind of discussions I mean when you are writing those SOPs?

MS. STUBBINGS: Well, we are actually having a lot of discussions on

managing safety, especially in the outpatient side because safety is an important part of inpatient care with safety committees and the safety officers and the inpatient. And we are starting to have a lot of discussions. And we have a presentation tomorrow that is going to elaborate on your question actually and how to incorporate safety management into the outpatient setting because high-risk drugs are being increasingly used in the outpatient setting.

And I am not sure -- I know there is a lot of discussion about burden. But I don't really perceive it as a burden because I think you start with a high-risk medication and the first step is either a guideline or a policy and procedure. And then that helps to inform exactly what needs to be done in terms of either a rule built into the electronic medical record or into the order entry or something that has to happen at the point of dispensing, some kind of check. And because

we have so much integration between inpatient and transitions and discharge and outpatient and we have the ability to go for anyone at any point to check the medical record and to verify things without it being an undue burden, they don't have to call anybody. They just check, the medical record to verify a lab or verify a diagnosis.

So I think that it starts with the policy and procedure, to answer your question. And then the steps that are required after that are defined based on the circumstance. I don't think it could be standardized. I don't think it is going to be like every REMS is going to have the same kinds of things that need to happen.

MS. TOIGO: Okay, thank you for that. So if you could consider maybe in looking at the different processes that you have put in place and if you would be willing to comment to the docket.

Because the question is if you put

those processes in place, just by looking at a prescription drug label versus a REMS, so trying to help us think about decision-making of when a REMS is necessary and when labeling is sufficient. So if the processes that you have described, if the REMS helped you put those in place because they described what was needed versus why did FDA do this, we can just read the label and have done this all ourselves because we are sophisticated and could develop these SOPs.

So to the extent that you have had those discussions or could think about that and share some of that feedback to the docket, that would be helpful. Because while not particular to this meeting, but we are thinking about those issues as well. And when you see presentations when people have pretty detailed SOPs, it stimulates that kind of question.

So thank you, if you would willing and anyone else who might be willing to think

about that question.

MS. STUBBINGS: Are you asking for a comment now or comment later?

MS. TOIGO: You can comment now.

MS. STUBBINGS: I think the REMS is definitely an important driver in developing SOPs but it is not the only driver.

We have an example of another category of medications that do not have REMS that we have implemented guidelines and similar processes where we do checks, we do lab checks, we work with the prescribers and the patients to make sure that labs are done. And they are actually not -- they are not REMS requirements.

So there is a lot of discussion and it is not entirely driven by REMS.

MS. TOIGO: We used up an extra time there for my questions. And we are getting close for lunch. So go ahead with your question.

MR. KROETSCH: Okay and I am

afraid that this is a two-parter also but I will try to keep it quick.

Related to this idea of building policies and procedures, I think one question we might have is what can REMS do and I talked about SPL as one avenue of helping clarify what the requirements are, what are the things that REMS programs can do to make it easier to build these policies and procedures as a health system? What are some best practices when we are building REMS so that you don't have to try to interpret what the REMS documents are saying but to actually move straight into integrating it into your system?

And the other question is, and this would be for everyone, is there a forum or a method by which you are able to -- we could learn about what best practices are being done? What kind of policies and procedures are being created? Because it sounds like these are ways of really taking REMS to the next level and actually putting

them into practice. And we are very interested in learning ways, effective ways to do that and sharing those as widely as possible.

MS. STUBBINGS: I think just briefly the things that we have appreciated the most that have offered the best opportunity for integration have been REMS tools that are online and that could be available through links. And also REMS tools, I think it is the TIRF REMS that are a part of outpatient dispensing. So it integrated into the outpatient dispensing system. And those have been the most appreciated.

The second one, the question was about a forum. That would be -- that is for the whole group. Okay.

MR. KROETSCH: Yes, what might be a good forum to help share these best practices? And have you discovered similar best practices in your involvement in REMS that we could be learning from? I'm

acknowledging that we don't have a lot of time.

MS. TOIGO: So Jeff and then JoAnn.

MS. STUBBINGS: I'm not aware of a forum, aside from our professional meetings that we have. We have -- there is a University Hospital Consortium that is made up of academic medical centers and we do speak at length about REMS and we are working on ways of sharing practices. And actually there is several people here from health systems. So I am really looking to forward to hearing their presentations on how they work with REMS as well.

MR. FETTERMAN: There is a forum of risk management professionals that has been meeting for nine meetings now in regional meetings and now one national summit. And the group is called TERM. And there is information at termcommunity.com that provides additional information about ways that there

is some best practice sharing and new insights from a variety of stakeholders that goes beyond pharmaceutical-specific but academia and other stakeholders as well. It is one forum.

MR. KROETSCH: Thanks. And I would encourage, since I know we are out of time for this conversation, if you are aware of those sorts of best practices to please feel free to submit examples to the docket.

MS. TOIGO: Okay, well in the interest of keeping us on schedule, thank you very much to the panel for your thoughtful presentations and for the dialogue and the question and answer session. And I would encourage you, if you could submit your slides to the docket because we can't put those on the FDA website but we can get access to them if you put them in the docket.

And for those who have asked about the FDA slides, yes, we can put those on the FDA website and we will shortly after the

meeting.

So we will see everybody back here at 12:55. Thank you.

(Whereupon, at 11:52 a.m., a lunch recess was taken.)

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

(12:53 p.m.)

MS. TOIGO: Okay, welcome back. Hopefully you had a chance to enjoy the glorious weather that we are having. This is a gift. We don't get this kind of weather in the end of July very often. So, hopefully you got a chance to walk outside at lunchtime.

So we are back for round two of the general standardization comments and we have six speakers for this panel that are going to share their perspectives on general standardization issues and some other things, based on the comments that we got. But we put all of these gentlemen on the standardization panel.

So we are going to start with Gary Appio from Novartis Pharmaceuticals. And Gary, you are up.

DR. APPIO: Good afternoon, everyone.

I head the U.S. Safety Risk

Management area at Novartis and coordinate the REMS processes. What I am looking at today is REMS submissions to better standardize those, especially with the a new indication, an existing or released REMS and what is next. So this is something I am going to go through.

I want to thank FDA for allowing me to speak and share my views. And as my disclaimer says, these are my views and not necessarily those of Novartis. So make note of that.

So question one. So if a product has an improved REMS, an sNDA or another indication is being submitted, is a REMS submission necessary? So this one is pretty straightforward, I think. You could maintain the existing REMS, maybe modify it to accommodate any new risks that may be in a different patient population. And another potential solution could be that when if you are doing a REMS assessment and you saw that the knowledge rate was only moderate in your

first assessment, then that may be a reason to continue the REMS and, in this case, a new like say prescriber population that may not be as aware of the risk.

So this one is pretty straightforward but I think we have a greater opportunity with this next question. And in it is, in evaluating a new indication for a product that had a REMS and was released, say, what does FDA consider in determining if a REMS is necessary for the new indication?

So one example I cited here was a product was approved for rheumatoid arthritis. It had a REMS. The REMS was subsequently released and after that point, the product did gain an additional approval for moderate to severe colitis. Now a REMS was not required at that point.

So I guess the opportunity here is, is there any way we can standardize as again new indications are coming onboard and not looking at it as again a unique risk-

benefit situation every time you have a new indication. So there could be some factors that the Agency could consider. And again, looking at the prescriber population, is it completely different or would they be aware of the risks from earlier use?

Again, looking at the patient population. So certainly if the risk in the first patient population isn't as great as a second one, that would be a consideration to either reincorporate the REMS of some type. Or the third potential could be that the physicians and patients are well aware of the risk and it could be considered that the safety profile is well-established. That may not require a REMS.

So these are some things to consider. And we are thinking that some of the potential solutions could be that if the REMS was released, to have the sponsor continue like posting the REMS say on a website, like similar to the LABAS. We had a

LABA and the REMS was released but the Agency asked us to continue to have the risk messaging on our website. That is something that could be a potential solution.

And then another could be is to do another risk awareness testing, like in this case if it is a new prescriber population. And then really ascertain if they have enough knowledge about the risk and that will dictate if a REMS would be necessary or would need to be restored.

So looking at recommendations and benefits, we strongly recommend that FDA develop guidance. And I believe that is why we are all here today and really try and just give some more input during the pre sNDA or SBLA type meetings so we can get a better understanding if a REMS will need to be incorporated with a new indication.

And the benefits I have listed here are pretty straightforward. We believe it would be standardized and streamlined

submissions for drug sponsors and FDA review to continue forward and that certainly would help the process. It would really ensure prescriber awareness of just the important safety risks and really not having any REMS programs diluted if either there is too many of them or redundant programs out there.

Decrease the administrative burden on the healthcare system with repetitive REMS programs. We see that would be another benefit and certainly would increase the transparency between drug sponsors and FDA.

And I believe that is my presentation. Thank you.

MS. TOIGO: Thank you, Gary. Our next speaker is Jim Devita from CVS Caremark.

MR. DEVITA: Well, good afternoon. On behalf of CVS Caremark I would first like to thank the FDA for the opportunity to provide further information on the development and standardization of REMS programs.

My name is Jim Devita. I am the

Director of Quality Assurance in Patient Safety for Retail Pharmacy Operations at CVS Caremark Corporation. I am responsible for the safe production and dispensing of medications to our patients at retail.

My goal today is to provide the committee with comments from the perspective of a pharmacy services provider that manages REMS programs with a broad and integrated approach through retail specialty and mail service pharmacies. CVS Caremark is the largest provider of prescriptions, pharmacy care and specialty pharmacy services in the nation. We fill and/or manage over one billion prescriptions annually. We employ over 26,000 pharmacists. We have over 7,500 retail pharmacy stores, 43 retail specialty pharmacy stores, and six mail order pharmacies.

Since the implementation of the Clozaril Patient Management System in 1990, our pharmacies have gained over 20 years' of

experience developing, implementing, and managing FDA-mandated drug safety management programs both simple and complex. Today CVS Caremark manages over 70 REMS programs.

So as we have submitted detailed written testimony, I would like to use this time today just to focus on three key points. The first one is that REMS programs should not only be standardized, they should be integrated with workflow. Today many REMS programs create unnecessary burdens, impractical impediments to their implementation, regardless of pharmacy channel. Additional steps outside of workflow processes can impede timely and effective patient access to drugs and valuable focus on patient care.

REMS programs should be user friendly, standardized and system-based that integrates into the workflows for not only pharmacists but prescribers as well. These are keys to delivering consistent results and

facilitating access to information.

So standardization and efficiencies can be achieved in a number of ways. First, creating consistency in training, enrollment forms, and medication information, establishing REMS level identifiers, establishing a central database for REMS information, and leveraging prescribers' electronic prescribing system and electronic medical records.

We recommend creating a focus group of stakeholders that includes prescribers, pharmacists, ePrescribing software vendors and others to create standardized REMS level identifiers within the structured product labeling. Medications of similar risks should be grouped together and share the risk mitigation components that trigger specific workflow processes.

So for example, a REMS level one may be indicated for medications with relatively lower risk and require a MedGuide,

whereas, a REMS level two could be for medications with higher risks, such as teratogenic risks and could require a MedGuide, a negative pregnancy test, and a completed patient prescriber agreement before the drug distribution occurs.

The goal here is to minimize unique drug-specific solutions and develop uniform language that can be used by all participants while standardizing and automating manual administrative processes.

We also recommend creating a central REMS database for all approved REMS. This concept is currently being used and being used successfully for the transmucosal immediate release fentanyl medications or TIRF medications. This limited central database is a real-time REMS administrative solution that nicely aligns with pharmacy workflow.

We should learn from this success and create a database for all REMS drugs, which could contain the REMS level identifier,

the REMS requirements including the elements to assure safe use, and it could be a training and enrollment portal as well that could check for enrollment status for prescribers, patients and pharmacies, and also facilitate reenrollment.

This database could be accessed by ePrescribing and claimed adjudication systems, supporting both prescriber and pharmacy workflow processes. This would streamline the delivery of medication to the patient by informing each provider of their REMS responsibilities at the point of care.

This database could also be leveraged in the future in conjunction with NCPDP standards to share critical information and allow for real-time communication between the prescriber, pharmacy and others who contribute to the patient's electronic medical record, making medication history, lab values and coverage information available to the prescriber at the time of dispensing.

The second key point is that not all REMS requirements integrate well with existing retail pharmacy dispensing systems. With over 65,000 pharmacies in the distribution chain, standardization of REMS will significantly enhance the effectiveness of REMS programs for the many drugs where there are similarities in risk profiles. But experience tells us that there will be product-specific situations where the management of non-dispensing elements to assure safe use might pose challenges for providers, including community pharmacies.

REMS requirements that include expanded or drug-specific counseling, drug therapy management activities, and non-dispensing interventions, such as lab testing documentation, also often contain requirements not supported by ePrescribing or claim adjudication systems. By their nature, they require partial if not total manual intervention.

For example, some programs fit better in the specialty environment due to the burdensome time-consuming requirements such as providing consultation on every fill, manually obtaining and maintaining confirmation and authorization numbers, tracking each dispensing to adhere to quantity restrictions and ensuring appropriate documentation is received.

As specialty therapies become more targeted and focus on modification of biologic responses, we can only assume that the prevalence of REMS will increase and include more restrictive tiers, more REMS components, education, and processes.

Drug products which meet these safe use conditions should be labeled as such through the REMS level identifier, allowing pharmacy systems to determine if their workflow provides appropriate levels of support. At CVS Caremark, our specialty pharmacies dedicate the necessary educational

and administrative time necessary to excel in managing intricate and customized REMS programs, filling the gaps beyond the scope of retail pharmacy.

And the last key point is that the FDA should require increased transparency in REMS development, modification, and surveillance. Prescribers and pharmacists undertake a major responsibility in implementing REMS and are on the front line of facing the associated challenges. It is only logical, therefore, that REMS applicants should be required to consult early in the design, development, and modification processes with the pharmacies, pharmacists, and prescribers who will be responsible for implementing and complying with these new REMS requirements.

Additionally, the FDA should require that drug manufacturers set up a mechanism to obtain ongoing feedback from healthcare providers, practitioners, and

particularly pharmacists to ensure that REMS programs are effective and adds no unreasonable burden to the provider community, nor does it impede patient access to these medications. We consider transparency to be a key success factor.

So in closing, CVS Caremark is committed to the success of REMS programs, including both existing and proposed REMS. We look forward to being a partner in the REMS program development, standardization, implementation, and evaluation process in the future. We thank you again for the opportunity to comment.

MS. TOIGO: Thank you, Jim.

Next we will hear from Stephen Goldman.

DR. GOLDMAN: Thank you, Terry.

I am going to provide a little different perspective as an academic physician, former regulator, former industry physician, and for the past 12 years,

independent consultant internationally on drug safety and pharmacovigilance.

I would point out that I was honored to serve on the 1999 Task Force on Risk Management, which established the concept of a pre- and postmarketing continuum when it came to risk management.

One thing that has been missing from the discussion so far today is where REMS fit. REMS are an end product of an entire program of premarketing clinical safety and postmarketing pharmacovigilance. They are not an end unto themselves. They are part of that continuum.

Secondly, the aspects of the context for a REMS is case review, signal detection, both national and international compliance, and labeling which was mentioned this morning, within an entire system of assessment of product safety and risks management. That is imperative for the evaluation for the revision of REMS.

The system is designed within any company to be designed to generate high-quality safety data from all the varied source of information we get, starting with the animal data which leads to submission of the IND; clinical trials, both pre- and postmarketing; the underlying epidemiology of disease states, which are becoming more and more critical; spontaneous reports; observational studies. REMS do not arise de novo. They arise from the perceived need of this type of data as to where the benefit and risk are associated and the fact that benefit must continue to outweigh risk.

To have optimal REMS evaluation, you must have regulatory standards that are reflective of the state of the art medical product safety to enhance both the quality of the data, compliance with requirements both national and international, and the ongoing evaluation of benefit-risk. Regrettably, in the United States we do not have a state of

the art postmarketing standards. The proposed rule remains a proposed rule since 2003, unlike the IND reporting rule which was recently revised. This is an ongoing problem, particularly with Europe doing a complete rewrite and change on the pharmacovigilance regulations and modules.

Secondly, safety is global, just like REMS are. Therefore, what happens in the United States has an effect on what happens in Europe, Japan, the product being used anywhere. The drug is exactly the same whether using it in Brooklyn or Australia. Therefore, safety is global. REMS are no different.

E2E is the true philosophical viewpoint of how one does safety. It was operationalized as a finalized guidance in the United States but, unlike Europe, there is no requirement for sponsors to submit either a safety specification on pharmacovigilance plan with new dossiers. That is the state of the

art but it is not required yet in the United States. It is required in Europe and Japan in relation to that.

It is interesting that it is not required in the United States, considering the FDA in the past two years has now begun to utilize the philosophy of E2E and for example the DSUR, the Developmental Safety Update Report, which can now be submitted in place of the IND annual report, which is based on the E2D philosophy. And just this past year, the FDA actually just in the past couple of months, has stated that you can provide, you can do the new Periodic Benefit-risk Evaluation Report in place of the traditional Periodic Safety Update Reports.

It is hoped that the FDA will see the way to standardize E2E in relation to submission of a pharmacovigilance plan and a safety specification to show where REMS arise from in the premarketing arena or in postmarketing.

We were here three years ago talking about where we are with REMS. And one of the things that was mentioned was consultation with prescribers, pharmacists, patient groups, and others and to reduce the burden to integrate REMS into the existing healthcare systems. And again, this is one of the stated objectives was to standardize REMS. I am cautioning against standardization versus a lock step because all REMS are not alike.

Why is that a concern? I spent the year working with the American Society of Health System Pharmacists with pharmacists. I can tell you there was a lot of anger in the first several months from pharmacists who were working with some of the REMS and I was the recipient of some of that anger. It was understandable because one of the things that happens is you are usually involved with one REMS, not multiple ones, and that will often be the reason why you feel the way you do about REMS in general but all REMS differ. I

can tell you that one of the things that became clear the longer I did this was if people understood that the products they were concerned about would not be on the mark without a REMS, their view of that did change. That was mentioned this morning in relation to that. It can't be emphasized enough.

There are many reasons why REMS are accepted or not accepted in relation to their perceived necessity, the administrative burden, the treatment setting, and of course its clinical relevance.

This is from the FDA draft guidance on REMS and it talked about using relevant information. But again, a caution. The relevance is dependent on the particular disease state being treated, including its potential lethality. The particular patient population, the perceived benefit, the perceived risks that need to be mitigated, accumulating knowledge, and where the healthcare delivery system is being delivered,

as we just heard concerning CVS.

The idea of consultation is obviously a good one but with whom are you consulting? And it really should be broadened to include those who work in safety, quite frankly, those who work with risk and disease-specific experts. You cannot have a REMS that focuses on a particular disease population if you are not going to talk with the clinicians who are going to see those patients or the nurses or the pharmacists involved with that. This is no different than what the FDA requires for looking at packaging, naming, and labeling in relation to looking at possible risk factors. It should be exactly the same with a REMS in relation to that.

I would advocate for clinically-relevant patient-accepted evidence-based variables. Think of it like a large simple trial. No surrogate markers. The way that you look for the effectiveness of a REMS was to have direct clinical relevance, must be

directly relevant to patient care, and if possible to the greatest extent, have those tools be used at the point of care.

Other aspects I would point out, there is clearly a need for greater understanding of healthcare professionals about the relationship between labeling and REMS. In particular, box warnings and other significant safety-related changes, particularly with recent Supreme Court decisions, particularly with the relatively new package insert information, the terrific new form that we have in the format and information. People also need to understand where REMS fit with the ongoing assessment of pharmaceutical benefit risk and a greater understanding of how a REMS is determined to be necessary. I have to push this back to again the E2E, the determination of whether you are going to need ETASUs. When you are going to need additional things than "routine pharmacovigilance."

Let's be honest. No matter how well a REMS is designed, it is going to add to the workload of the healthcare professional. But the benefits of that participation must go beyond the simple need in relation to the pharmaceutical simply being available. MedSun, the program that is utilized in medical devices, has a great two-way communication. One of the complaints that I heard from pharmacists and physicians is not getting feedback, exactly the same complaints that we heard about adverse event reporting in relation to that. Timely feedback on an ongoing basis, I believe again was mentioned before.

Utilization of the data for quality assurance, this is a P&T Committee, peer review and accreditation, and treating your participating healthcare professionals as partners. If REMS are going to be accepted as they need to be, there has to be made clear what the benefits are not only to the patients

but the healthcare professionals and administrators involved in their utilization.

Thank you.

MS. TOIGO: Thank you, Steve. Next we will hear from Paul Seligman at Amgen.

MR. SELIGMAN: Good afternoon. My name is Paul Seligman. I am the Executive Director for U.S. Regulatory Policy at Amgen. Thank you for the opportunity to address the panel and for FDA's leadership in convening this hearing to gather stakeholder input on standardization and assessment of REMS.

Amgen looks forward to participating with the FDA in risk management efforts, with the goal of achieving safe and effective use of medicines.

Prior to the FDA Amendments Act of 2007, which legislatively established REMS and FDA's role in the process, how to effectively manage the risk of medical products has been an important and sometimes vexing issue for the Agency and the U.S. healthcare system for

years. I had the privilege to work at the FDA in postmarket safety for eight years during this period and have the profoundest respect for the challenges and struggles in crafting programs to effectively mitigate or minimize safety concerns.

Now in my current role, I have the opportunity to draw upon an view Amgen's significant experience with REMS since their inception in 2008 and to share our views on what we believe are the five key elements required for a successful REMS program, as the FDA and all stakeholders look to create more effective and efficient ways to manage risk.

These five elements for success include: 1) setting a clear measurable goal as linked to achieving a desired behavior; 2) embedding the risk management processes into the healthcare system to attain these goals; 3) carefully and thoughtfully incorporating the significant experience gained in the past five years in the nearly 70 REMS programs,

particularly the 27 some-odd that have specific elements to assure safe use or ETASUs; 4) using the information technologies now available to create an integrated and, if possible or practicable, a universal platform for managing and monitoring these REMS activities; and finally 5) harnessing the leadership role the FDA has so successfully played in many critical drug development areas in convening stakeholders to address and guide implementation of the aforementioned element.

The first key to success requires setting a well-defined public health goal. Such a goal should be based on a risk that can clearly be identified, a risk that is preventable or can be mitigated or reduced in frequency or severity. The risk management goal should be explicitly stated in the REMS document and the conditions for safe use articulated on the label. It is a goal that should be capable of being monitored by a measurable metric, such as a laboratory value

or appropriate use of the product.

The goal must be tied to achieving a desired prescribing, dispensing, monitoring, or utilization behavior, rather than being linked to knowledge acquisition. REMS should not be used to address risks that cannot be prevented, mitigated or reduced.

In general, while training and education are important and vital parts of a continuous running system, they are not entirely reliable indicators of the ability or willingness to incorporate learnings into medical practice. Similarly, current paper-based systems of certifications and attestations, the use of stickers on prescriptions all add burdens to the healthcare delivery system without adding clear, demonstrable benefits to patient safety. Conducting surveys of and demonstrating knowledge acquisition is not, per se, an accurate indicator of REMS success.

A second element for success is to

embed REMS processes into and across the healthcare system. To do so requires both a clear articulation of the roles that key stakeholders play and an understanding and commitment by all to actively engage in the management of pharmaceutical therapies.

The focal point of risk management of marketed products needs to be shifted permanently and decisively from the FDA and sponsors to those who administer and deliver healthcare, namely, dispensers, hospitals, HMOs, ACOs, physicians, nurses, and pharmacists.

One of the challenges is how to move from the one off, product-specific or product class-specific programs that involve sponsors working directly with the FDA to generalizable models for managing risk, depending on the medical care setting patient populations or the practitioners who prescribe or administer the medication of concern.

The role of the regulator should

be to highlight the risk to mitigated and the goal to be achieved. The sponsors and the Agency can then work together with the medical community to determine the best risk management model to implement and the nature of the regular assessments to be conducted. Such an approach will allow each stakeholder group to focus its efforts on those efforts within its control and expertise.

A third element for success is incorporating past experience. FDA has gained significant experience across a variety of REMS programs which should be integrated with the experience of external stakeholders. This combined experience should be a mine to identify the situations, tools, and processes that represents best practices, as well as to characterize predictors of success.

It would be useful in identifying what hasn't worked to date and in pinpointing those areas that need further study or piloting; for example, when a risk has not

been successfully mitigated.

The data from the assessments of these programs need to be analyzed and the result of these analyses made public. Without the synthesis of experience from this public health experiment that has been conducted over the past five years, there is simply no way to know what works, what doesn't, and how to proceed to create a more efficient and effective programs that are embedded inside the healthcare delivery system. At present, only the FDA has this information. Everyone else, all the stakeholders represented here, are looking at REMS based on their unique experiences and vantage points, blind to the experience of others.

A fourth element for success is to adapt REMS to reflect a current and anticipated realities of information technology, increasingly centralized drug dispensing, electronic prescribing, electronic health records, and the push towards greater

accountability in healthcare organizations.

Currently, information systems and tools are developed for each product and are not aligned across REMS, resulting in an increased implementation and operational costs. As a result, clinics, hospitals, and pharmacies in particular, find themselves supporting multiple REMS programs. One remedy to consider would be the development of a single risk management system that would be integrated, consolidated, and universal. It would include a cloud-based platform with dedicated portals for each stakeholder group. For example, patients, healthcare providers, hospitals, pharmacies, and distributors, with all the tools essential to manage risk tailored to each stakeholder group.

The distribution portal, for example, could provide real-time approval to distribute a medicine for the products that require monitoring and/or limited distribution. Such a system would be used for

all products determined to need risk mitigation tools, regardless of the medical product sponsor.

And finally, the fifth element for success is to foster the engagements and collaborations necessary to create such a systems approach and withstand the test of time. By exerting leadership as a catalyst and a convenor of diverse stakeholder groups in such areas as the Critical Path Initiative, Quality by Design, and the Sentinel Initiative, FDA has demonstrated its ability to advance important public health issues that go well beyond its circumscribed regulatory function.

Risk management of products that require specific elements to assure safe use offers FDA just that opportunity to leverage its knowledge and creativity across the entire healthcare spectrum to improve patient safety.

The convening of key stakeholders, of which this public meeting is certainly a

part, will help all stakeholders focus on developing solutions that can be embedded into and integrated across the healthcare system, particularly in a world increasingly reliant on web-based information systems and electronic records.

Thank you for the opportunity for allowing Amgen to share its views today. We look forward to working with the FDA in making the management and minimization of risks an integral part of the way we collect and we strive to improve healthcare and patient safety.

MS. TOIGO: Thank you, Paul.

Our next speaker is Brian Malkin, a partner at Frommer, Lawrence, and Haug.

MR. MALKIN: Hello. Good afternoon. My name is Brian Malkin and I am a partner at Frommer, Lawrence and Haug here in D.C. I also edit a blog, FDA Lawyers Blog. And just by way of quick background, I used to work at FDA in the Office of the Commissioner

in the Center for Drugs from 1991 until 2000. And I have been in private practice since then, except for a stint for about two and a half years when I went back to school to get a biochemistry degree so that I could combine my FDA law background with IP. So I am both an FDA and IP attorney.

Now there are some disclaimers which folks have been doing in this panel, which is good. I definitely have to say here I am speaking on my own behalf. I am not speaking on behalf of the firm or any client or potential client. And I also reserve the right to take a contrary position, which is what attorneys do from time to time.

What I am going to be taking a position here on in terms of the overview is that I want to talk about what are the expectations of shared REMS operation. What have I seen over the years? And I am talking about years probably from 2000 to current time when there were risk management programs and

then RiskMAPs and now REMS. So what has not been working in terms of these programs being effectively shared. And then some sort suggestions to improve and things to think about that maybe FDA could take up in a subsequent meeting.

So what are the expectations for a shared REMS operations? So just a little bit of background. Just because haven't we really talked about it earlier today, where the whole concept of sharing a REMS sort of come from, it came from FDAAA. And here it talks about if they are ETASU, which we know what they are, here in terms of Element to Assure Safe Use, that it stipulates that the brand name and the generic manufacturers should work together on coordinating a single share of REMS program, unless one of these two situations occurs that FDA determines that the burden of creating a single shared system between competitors outweighs the benefits of the shared system or an aspect of the elements

to assure safe use for the applicable listed drug as claimed by a patent that has not expired and the applicant for the ANDA certifies that it has sought a license and that is was unable to obtain a license.

And one of the programs described earlier today from Celgene is protected by a myriad of patents that is an example of a program that would fall maybe into that category.

Now for an ANDA REMS, what FDA has sort of explained before, that they do not necessarily need to have their own sort of unique communication plan. FDA has described before that they will undertake the communication plan for both the NDA and the ANDA and that means that the Medication Guide, the patient package insert, the communications and documents, they should all be aligned and same.

The ANDA REMS are supposed to share a single system and the way that my

understanding of how that program has worked in the past, is when they are multiple ANDAs that have applied for a drug that is now covered by a REMS with ETASU. The ANDAs will all receive a letter that tells them that they now need to come up with a shared program, talk to the innovator of the reference listed drug and see if they can share into the system. My understanding is that the innovator does not always get that letter. And it only goes to the ANDA applicants and they are now supposed to go back and make that communication and there also is an understanding that I understand from FDA that FDA then maybe will take a chance to try and negotiate, if it doesn't work out by the ANDA negotiators.

But the statute also notes that -- and if at that point if it fails then there is the potential for a waiver, which we will get to a little bit later.

The statute also notes that no

holder of an improved or a covered application should use their -- this is sort of the ETASU required for any REMS to block or delay approval of an application under the 505(b)(2) or the (j) the ANDA mechanism to prevent application of such element for the purpose of them getting approval when they are talking about the ANDA.

So this is a list that is from FDA's website of the products that right now have shared REMS programs. As you will notice by the asterisk, all of those are both the brand and generic manufacturer programs. And isotretinoin was one of the first ones that started that was not protected by any patents. And the subsequent programs that you look here that they are all programs that don't really fall into having a patent sort of issue. And when it came to buprenorphine, there was not a patent issue but as sort of described later, there was an issue of the generic applicants and the innovator coming to agreement for a

unified plan so, ultimately, FDA permitted a waiver.

So what are some of the shares REMS, the dysfunctions that have come up? And so and this abbreviation is just meaning FDA and FDAAA, sort of giving an example of what goes on here, that it does not really define what is meant by a single shared REMS. I mean it talks about that the elements are supposed to be shared but there are some significant things that have come up at least in the past as described in public documents about what are the costs to develop and maintain, assess, and amend the REMS and what might be some of the liability costs for failures. So these have not been described or explained, other than that they are supposed to share the elements.

The FDA and the FDAAA do not provide any guidance about the negotiation process between a generic and brand name and how that is supposed to work. And how that is

supposed to work when there is concurrent patent litigation and when some of the litigation that could be going on could be including some of the patented elements of the REMS program.

And currently FDA and FDAAA do not provide guidance about how the reference-listed drug manufacturer and the ANDA are expected to cooperate and share these elements of the REMS and also another point of it is that the samples for the reference-listed drug which has been again, mentioned in some of the citizen petitions which has been difficult for the generic drug manufacturers to obtain at times, because of the restricted distribution by the nature of the ETASU. And they also do not explain what the ramifications would be for failing to cooperate on either side, once FDA notifies the parties or maybe in the case of just the ANDAs, that notifies the parties of the need to come up with a shared program with the innovator.

To date, FDA also has provided the reference-listed drug manufacturer, the innovator with really no incentive of why they should be sharing their program. I mean it is something that just says in the statute you are supposed to share but it doesn't say what you get sort for sharing. And is there something like the royalties or exclusivity in the past? I believe Celgene was provided royalties for their patented elements in order to design new iPLEDGE program. But similar kinds of royalty agreements have not really been crafted by FDA. And exclusivity, there are no provisions for anything about that right now.

FDA has provided the reference-listed drug, according to the OIG's report which has been alluded to earlier today, that the reference-listed drug manufacturers have been providing limited assessment information, particularly the REMS programs that have ETASU, which makes it difficult really for the

innovator and for the generic drug manufacturers to understand what are the essential risk control elements of those ETASU, which just says you share all the ETASU. But does everything have to be shared or what does that really mean?

And again, I want to mention that the public documents really provide little guidance about how other parties are supposed to negotiate a shared REMS and what elements of the REMS are working. Because theoretically some of the iffy elements are not really working in the ETASU, that may be a time when the generic is coming in to share the elements that FDA may say okay this element is discretionary. You don't have to implement it anymore. Maybe that would be the time to decide what the elements are.

Most shared REMS programs that I showed in the prior program, as I mentioned before in the prior slide is that there are class-based REMS and they were all developed

after all the products were already approved. So it was not done in the process where you had the innovator's product approved and how the generics are trying to get approval but they need to have a REMS and it hasn't been really conducted in that process, except for the buprenorphine group which, at this point, appears to be the first time that FDA granted a waiver for the shared REMS, meaning that the generics all have one program and then the brand has another program, which are all for the same products, in theory. But FDA provided at this point not substantive explanation for how the criteria were met, other than there were a series of meetings, the meetings didn't work out, and ultimately they allowed a waiver.

And then that same decision letter for the petition, FDA mentions that they forwarded this over to the FTC for an investigation because it appeared that there were some -- that the innovator was not

sharing appropriately, was not working the negotiations appropriately.

So I was thinking about what could help in this situation where we are thinking about shared REMS and trying to offer something that might be considered in future meetings just to sort of get that thought process going.

And one thing that occurred to me is that in terms of we are really talking about sharing, there is a proprietary right that the innovator has to the program that they have developed. They put a lot of money into it and a lot of time and effort. So necessarily when it comes to the point where the generics now come and knock on their door and say we want to share into your program, there is a understanding there would be some hesitation, that there is not really anything that has been provided to them to understand what are they to gain from working in this process and what are some of these costs and

other things that have been developed along the way that would be shared.

So what I would suggest is that there might -- I know there are some comment rulemaking or procedure that goes on where all parties can participate and where FDA could then ultimately provide guidance to what the -- the goal for this rulemaking procedure would be to have expectations that would be spelled out to the innovator and to the generics for how you are supposed to negotiate and work for a single shared REMS program.

Talk about what would be sort of reasonable shared control or access to data; how they would share the cost for the development of a program or the maintenance of the program; who is going to pay for the assessments that go along the way and what happens when there are amendments to the process. And if there is some liability or insurance costs that are involved with the program, how those could be shared,

potentially.

And then if there is an opportunity for royalties or exclusivity to make the process work, that would be another option for it, an example.

Okay, this is my last slide. And the last slide is the second idea is we have talked about this earlier today about having a database. So when FDA is approving the REMS, that FDA would create a public database of the current elements for the innovators REMS program and the assessments and also provide some sort of public accounting of what those assessments have been so there would be an understanding of what the essential ETASU elements are that must be shared, which would be agreed to by the reference-listed drug at approval. They would understand what those are and how they could be modified over time, based on the assessments provided and what the ramifications would be for failure to provide such assessments.

Thank you.

MS. TOIGO: Thank you, Brian. And our last speaker on this panel is Bill Martin from Express Scripts.

MR. MARTIN: All right, good afternoon. I am Bill Martin. I am the Vice President of Business Development with Express Scripts. And Express Scripts is the nation's largest pharmacy benefit manager. We manage over a hundred million lives. Our specialty pharmacy, Accredo Health is the largest and most comprehensive specialty pharmacy in this country, providing life-sustaining as well as life-enabling medications to Americans with chronic conditions. And as of our last count, we directly dispense 81 of the roughly 88 drugs that are known to have REMS programs, including all 27 with ETASU requirements.

Express Scripts currently fills over 115 million prescriptions a year and we have significant experience in assisting the pharmaceutical companies, as well as the

patients adhere to these REMS programs. And we believe that REMS programs have been a plus for patient care, as well as safety.

The additional safeguards have allowed for the approval of drugs that might otherwise not have been approved and we believe they have undoubtedly prevented many adverse patient events.

A point that we would like to make is simply this. The REMS system today works. And we ask that you please view any changes being made to this system through that lens. REMS exist for the purpose of ensuring patient safety, not provider or pharmacy convenience or ease of administration. Certainly steps can be taken to improve the ease and the workability of these programs but we believe that any changes made must not have a negative impact on patient safety.

In our specialty pharmacy, Accredo, we dispense literally hundreds of thousands of prescriptions for drugs with REMS

protocols. And we have not found these requirements to be unreasonable in practice. We do believe, however, that some enhancements can be made to this current process.

First, we believe that the patient education portions of REMS would be well-served by a greater involvement of allied health professionals such as nurses and pharmacists. At Express Scripts, we have organized our health professionals into disease specialties. For example, oncology. This specialization coupled with our large volume means that our specialized oncology pharmacist likely counseled more oncology patients per pharmacist than anyone in the country.

The same statement applies to the other disease specialties which we serve. FDA should encourage pharmaceutical companies to look to resources beyond the physician's office when developing their patient educational components.

Secondly, access. When access is mentioned in the industry, it is often referring to pharmacy access but we believe that was is really important is patient access. Patient access in today's era is much more involved than simply expanding the number of pharmacies that stock a drug. Patient access in the United States is more often a factor of insurance coverage, patient authorizations, and completing the ETASU protocols, for example.

Pharmaceutical companies should be encouraged to do more to provide education to physicians, as well as pharmacists in how to best access their drugs and/or establish patient hubs to help manage that process.

Third, we ask that the FDA require early and better monitoring of REMS for effectiveness. In recent years the level of required monitoring appears to have declined and we would like to see more vigorous early monitoring done in a scientific manner and

then see those findings lead to improvements in the existing REMS protocols.

Last, to address the question of standardization, we would be in favor of more standardization of the process and the general structures of the required REMS. For example, standardize the level of risk that would require a patient registry versus physician training. That would speed the approval process and to provide a more similar REMS protocol design for drugs for similar safety profiles. We believe that the absolute or total standardization of REMS protocols themselves, however, would not be effective, given the differences in drug profiles.

Thank you.

MS. TOIGO: Thank you, Bill, for those comments. And thank you to our panel members. And we are staying right on time.

So now it is time for questions from the FDA panel. Who wants to get us started? Mwango.

DR. KASHOKI: I'm still looking through my notes so I am going to do my best to be articulate here.

This question is for Dr. Seligman. You raised several points in your presentation and you suggested that we focus the REMS efforts on risks that can actually, as you are describing them, be mitigated and I believe you said that those kinds of risk would be those that could be reduced in frequency or severity and could be measured in some shape or form.

And you also went on to talk about perhaps in terms of defining our goal, removing some of the things that may not be helpful in achieving REMS effectiveness, such as some of the processes or tools that we use. And later on you then said as we worked towards standardization, we should try and identify those processes or tools that do work.

So starting with the last point,

in order for us to do that, we would have to figure out what success means. Like when we say a tool works or is effective, how were we measuring that?

And so getting back to your initial point about that we should be focusing REMS efforts on risks that can be mitigated, are you then saying that a successful tool or process would be one that directly has such an effect?

I am asking this because some of the tools and processes that we use enrollment forms, enrollment process for example, are necessary steps in order for us to get to the ultimate goal of reducing a particular risk.

So if you could just explain your thought process as you went through those concepts.

MR. SELIGMAN: So there are certainly important and legitimate steps to achieve the goal. I think that the ultimate thing that we are trying to focus on is for

example in the area of fetotoxicity, where the

goal is to prevent exposure to the developing fetus and where the risk mitigation and management steps are ensuring that the patient is not pregnant at the time the product is either prescribed or doesn't become pregnant during the course of therapy.

To me the performance of those tests to ensure that there is a negative pregnancy test, ensuring that there has been adequate prescribing of either birth control or some other means to ensure prevention of an unwanted or unforeseen pregnancy, those to me are the essential things that should be focused on and the goal that should be -- the metric that should be used to judge the success of the program.

So I think that clearly there are lots of other important elements or things that go into ensuring that prescribers do the right thing, that patients do the right thing.

But at the end of the day, I tend to look at the bottom line and I think what I am indicating in my presentation is that kind of sort of bottom line approach to judging the success of a REMS program is something that should be focused on and that those programs that can't be defined by essentially bottom lines really we should take another sort of hard look as to whether they are adding value.

DR. KASHOKI: Can I follow up?

So with regard to the programs that we have where it is primarily an information- or education-based focus for the user risk that we may not be able to intervene. We might need to have both patients and prescribers aware of the likelihood of exposure, likelihood of adverse outcome by using the medication, are you saying in those circumstances a REMS program may not be appropriate indicated because there is no measurable outcome. Are you saying that?

MR. SELIGMAN: Yes.

MS. TOIGO: Sir.

DR. GOLDMAN: I published a paper recently, I guess a few years ago, saying how effective is effective enough. That is the question you are asking.

Before there were REMS, there were RiskMAPs. Before the RiskMAPs there were programs like the clozapine program.

The point is that the data for example on the original terfenadine notification showed that co-prescription went down significantly but it didn't go to zero. We are going to have to determine what the effectiveness is in relation to what we determine to be effective. Otherwise, you have to take something off the market without even trying in relation to that.

There is significant data on notifications. The question is why people haven't looked at that information. Because not only is there effectiveness data, there is

data on how the notifications are written, including the very format they utilized. Qs and As are month the most effective that we can utilize in terms of that. There is information out there and it certainly goes to the point that we are making, Paul and I were making about how you determine what effectiveness is. But going in, you have to have the flexibility within the REMS to not only look at the data you are looking at, looking at the behavior you are trying to change and realize that all risks are not the same. Teratogenicity is not nearly the same as trying to prevent someone co-prescriptioned or someone using something off-label. They are very different risks. Their behavior is going to be different. The solutions may well be different, even though they may share some things in common in relation to education by the patients or prescribers or dispensers.

MS. TOIGO: You mentioned that there is a lot of data on notifications. If

it something you are willing to the docket that we may be haven't --

DR. GOLDMAN: I will send you my preprints.

MS. TOIGO: -- seen yet, then please consider including that with your slides.

DR. GOLDMAN: Sure.

MS. TOIGO: Claudia and then Elaine.

DR. MANZO: My question is for Jim. You mentioned that there were certain REMS requirements that didn't integrate well into pharmacy systems. And I wondered if you could I guess again describe sort of the requirements that you think might be best integrated into retail settings versus maybe specialty pharmacies or mail order pharmacies.

MR. DEVITA: I think for the retail community pharmacy environment that the requirements that fit well into workflow that leverage the technology that is available, the

ePrescribing systems, the physicians' health record, electronic health record, and the claims adjudication system as well. Like the TIRF program is really working out well. There is really no manual process associated with that. It is part of the normal workflow and we get information on eligibility and so forth before the prescription is even filled for the patient.

So things that work into the workflow work best for retail that limits the technology.

The other REMS requirements that are more complex that are more time consuming such as extensive counseling for patients may fit better outside of community pharmacy.

MS. TOIGO: Thanks, Jim. Elaine?

MS. LIPPMANN: Yes, thanks. I have a question for Brian.

You seem to be suggesting that FDA should be involved in the process of determining some of the more logistical

aspects of the single shared system. Like you mentioned liability and insurance costs and shared access to data, that sort of thing. I just want to get a better understanding of how you see, how you envision FDA' role in those kinds of decision-making in the development of the single shared system. How far you think that the role should be extending into those kinds of decisions.

MR. MALKIN: So I would imagine this would come through in a notice of rulemaking comment sort of procedure where both the reference-listed drug, the innovators, and the generic drug manufacturers sort of talk about these different costs and the controls and what is entailed and what would be an expectation.

So for example, if there is a particular development cost for a REMS and that is -- it is able to be quantified by the innovator that the generics agree that they are going to all pay into that, that there

would be this pot of money -- that whatever that cost was, depending upon how many members are now in that program, they all sort of share the cost for that development cost or the maintenance costs for the program or what additional costs that need to be run into it in order for it to make sense, for them to share the program, versus having two independent programs which, as we were talking about earlier today, just makes things more complicated. I mean and now there is a situation where there is going to be innovators and the group of generics having the buprenorphine program that is more complicated. There are two programs to keep straight versus there being one program.

MS. LIPPMANN: Thanks.

MS. TOIGO: Thank you. Anyone -- Adam.

MR. KROETSCH: Hi. A couple of you mentioned that or suggested that we look into using real-time portals, web-based

portals, shared databases that could be used, I think, to track things like certification and provide real-time approvals to distribute drugs, for example. And one of the questions that we asked in the Federal Register Notice is who you might envision implementing something like that and how exactly it would work across a range of different REMS. So did you have any thoughts on that?

I can mention I know Paul, you were one of the people on that.

MR. SELIGMAN: Since I mentioned it, I should actually reply.

So I think there are a number of options to consider. Clearly, the first organization that comes to mind, of course, is the FDA or an organization on contract to the FDA. Particularly when it comes to developing a shared resource for access to various prescriber and patient tools, I think that would be a great resource.

I think you heard very cogently

this morning from the University of Illinois Hospital System how they effectively manage healthcare using their own internal information systems. And again, I think that a resource either at the federal level or a contract managed at the federal level would provide those kinds of tools to, for example, other kinds of healthcare systems that want to effectively manage their risks I think would be probably the best place for that, best locus for that kind of system.

MS. TOIGO: Thanks, Paul. Megan.

MS. MONCUR: I have a question for Dr. Goldman. In one of your observations you mentioned how the perceived burden of REMS or a REMS program, a particular REMS program changes when there is an understanding of the rationale for the REMS and what it makes possible in terms of availability.

Why do you think that that is something that isn't more well-known and how can we make that better understood?

DR. GOLDMAN: Do you really want to know?

(Laughter.)

DR. GOLDMAN: Sub-optimal education by the FDA, by the industry, by the healthcare professional groups across the board, quite frankly.

As a physician, I would say physicians are among the ones. Pharmacists can be more tuned in in relation to that. I was doing work with ASHP. I think that tells you something in relation to that.

I think I was encouraged over the year that I did the work because healthcare professionals advocate for their patients. That is why we are here. I am first and foremost a clinician. And when you explained first of all the rationale for REMS, the fact that most drugs don't have REMS as we talked about, and again, that is why I advocate for the safety specification pharmacovigilance plan because most drugs are not going to

require that.

When I actually explained to I think these were pharmacists around the country, explaining why you have to have this; how the data was being used; the fact that it was feeding into a system that would then possibly revise the plan in relation to that; that is exactly the kind of work we do when we talk about post-marketing surveillance and adverse event reporting.

So I think -- and again, I appreciate your questions because it is obviously one I have thought a lot about. It has to be a coordinated effort. And it is not just one group. That is one of the things we said in 1999. There is a lot of stakeholders when it comes to risk. It is not just a regulator. It is not just a regulator industry. It is healthcare professional groups. It is patients themselves in relation to that.

But you have to explain. You

can't roll out a program that is going to be administered by healthcare professionals without first of all talking to the healthcare professionals themselves. You have got to look at the disease state in particular. And again, I have been involved with several different REMS and risk matters, and they are very different. And the behaviors are very different and the goals are going to be very different in relation to that but the bottom line is all the same. Keeping a product that is effective but that poses particular risk on the market, making sure that patients still have access to it.

If you make that clear from the beginning, I think people will accept more of a burden in relation to that because that is what they are said to do. That is what they sign on to do when they go to medical school, dental school, and nursing school and pharmacy school. You accept that going in.

I think if we made that clearer I

think there would be a lot more acceptance, frankly, of REMS.

MS. TOIGO: Go ahead.

MR. SELIGMAN: Actually I have a really comment to the previous question that Adam raised. In your presentation you talked about the structured product label and the DailyMed. There is another potential place for such access to that information.

Sorry about that.

MR. KROETSCH: Yes and one of the -- I agree completely. But I think one of our concerns is that that is a source of information about different REMS programs and what the requirements might be. But it sounds like what I hear regarding portals is this idea of some sort of shared database two-way communication which is beyond, I think, what SPL would be capable of doing.

DR. GOLDMAN: May I make a point about labeling? Because Paul, that is a very good point.

The issues about changes being affected as opposed to approved labeling is obviously a major concern that people have.

You know I was the Medical Director of MedWatch, the first one we had. And we spent a lot of time changing labeling, posting labeling revisions which now has been an ongoing program, knowing where to the find the data on the DailyMed and others. There are things separate from REMS that are clearly risk mitigation. And again, it goes to the label. It goes to knowing about the latest labeling and those aren't labeling changes.

If I were to advocate for looking at that, perhaps even separate than what you do with a REMS, might be helpful in terms of trying to determine what it is that we are trying to get across and how peoples' behaviors are changed based on the fact that they know what the latest safety information is. I do think it is part of the mix.

MS. TOIGO: Megan, did you have a

follow-up? And then that will be the last for this.

MS. MONCUR: Okay. It is actually not a follow-up question. It is a question for Jim Devita. And you mentioned that the TIRF program is working well for you and in particular because it is an automated program. But one aspect of that program that is not automated and we have referred to it before, if for some reason certification cannot be verified, if somebody hasn't enrolled.

Do you have any best practices or have you received any feedback on how that can be handled more efficiently?

MR. DEVITA: I haven't received any direct feedback to that nature. The feedback that I have received about TIRF is when the pharmacist compared to essentially all the other REMS programs, which is multiple manual processes and they are very different in obtaining a stick or there is a form you have to fax that you have to call. Another

one is you have to access a website. They are all very different. And relying on pharmacists remembering to do it correctly, although they are being trained, it is still relying on them following the process the way they were trained and it could be months later.

The TIRF program is integrated into the system. It goes out through the claims adjudication process. And if there is an issue they get a claims rejection with a message as to what the specific issue is and they can address it from there.

MS. MONCUR: Okay.

MS. TOIGO: Thank you.

MR. DEVITA: You're welcome.

MS. TOIGO: So thank you to our panel members. And again, if you are willing to submit your slides to the docket, that would be great. We heard the references to suboptimal communication. If you have some examples of optimal or even better than

optimal communication or things that have worked well and you want to share those examples, I would encourage you to do that in the docket as well.

So thank you very much. And we will line our up our next panel, which is prescriber and patient directed tools. So we have Ann Karty, Murray Kopelow, Andrew Kolodny, and Natalie O'Donnell.

Hopefully the temperature is better in here. We heard a lot of complaints. We have been trying to adjust the temperature to the extent that we can in this room. So hopefully those that were cold are okay. And if not, tomorrow please bring a blanket.

Okay, so our first speaker for this panel is Ann Karty from the American Academy of Family Physicians.

DR. KARTY: Hi. Good afternoon.

I am Karty and I am the Medical Director in the Continuing Medical Education Division at the American Academy of Family

Physicians. I am a family physician. I maintain a clinical practice and I see patients in an outpatient clinic.

On behalf of the American Academy of Family Physicians, about 111,000 family physicians and medical students, I appreciate that the FDA is holding this two-day meeting to discuss issues and challenges associated with standardization and assessment of Risk Evaluation and Mitigation Strategies.

The AAFP has submitted written comments to the FDA in response to the Notice of the Public Meeting from the AAFP Board Chair, Glen Stream, and I have copies that are also available but they have already been provided.

I represent the AAFP as a registered speaker for this meeting and the displayed link actually goes straight to the written comments that were provided to the FDA.

Because this is the first REMS

that has continuing medical education integrated into it and it also -- my approach to these comments is actually as a case study to demonstrate that there really is a broad-based approach to many multiple medical issues and just to remind everybody that when this first CME introduction happened, there were many administrative initiatives that were happening in parallel. And they were related to not just administrative issues but other medical issues that we had also self-identified that were necessary for our patients.

Pain management and opioid abuse are serious public health concerns and the AAFP shares with the FDA commitment to making sure that patients continue to have access to appropriate pain medications and that all opioid products are used safely and effectively.

The AAFP remains dedicated to finding solutions to the crisis of pain

management and opioid abuse and released a position paper titled pain management and opioid abuse, a public health concern.

Integrated into this position paper there are several key recommendations, including advocacy, clinical improvement, and maintenance of function for patients, evidence-based physician education, and collaboration with other organizations. As such, the position paper urges states to obtain physician input when considering pain management regulation and legislation; urging all states to implement prescription drug monitoring programs; opposition to mandatory CME as a prerequisite for DEA or other licensure; supporting the development of education to ensure the safest and most effective use of long-acting and extended release opioids; and to increase national funding to support research into evidence-based strategies for optimal pain management and incorporation into the patient-center

medical home model.

Again, this hyperlink directs to the position paper and I have extra hard copies that I can share.

The AFP is also pleased that the FDA and the White House Office of National Drug Control Policy continues to address this ongoing public health crisis, resulting in the latest report titled "Epidemic: Responding to America's Prescription Drug Abuse Crisis."

Family physicians and other primary care physicians and clinicians play a vital role in effective pain management, which includes prescribing opioid analgesics. The AAFP remains concerned with any policies that would create additional prescribing barriers for primary care physicians, since professional judgment and clinical experience determine, along with patients, the need for pain relief.

The AAFP fully supports voluntary participation.

In particular, the AAFP is a continuing medical education and national CME provider. We continue to be involved in conversations with the FDA and REMS program committee, other credit systems and other CME provider organizations. We are pleased to support CME that addresses educational goals identified in the FDA CME/CE extended release long-acting opioid REMS blueprint. And the blueprint details core messages to be covered in educational offerings for prescribers of the ER/LA opioids.

Education is foundational to family physicians striving to perform the best patient care possible and to educate family physicians about this growing epidemic, the AAFP continues to offer dedicated CME.

The AAFP is developing live online and self-study CME activities that align with educational goals set forth by the FDA blueprint. The CME offerings are in compliance with relevant accreditation

guidelines and they ensure validity. And again, the AAFP would not support mandates that require physicians to complete the CME because the AAFP believes that voluntary education helps to address the growing problem of prescription drug use and misuse.

The AAFP also offers CME opportunities beyond information that area actually embedded in the FDA blueprint. We have an upcoming webinar called Chronic Pain and the Safe Use of Opioids that focuses on educating family physicians about chronic nonmalignant pain and encourages physicians to talk with patients about past or present risk factors. It is important to note that the curriculum that this particular upcoming program is based on is from information gleaned last fall at one of our annual assembly meetings. So it is always to build your education on outcomes-based research when you are developing new programs.

There are future programs for CME

about REMS that will be integrated where appropriate in the development of educational plans. And the intent also is that there will be additive activities to extend educational experiences to impact and improve patient outcomes.

I have a few summary bullets. As a family physician, it is important to address the dual issue of the pain crisis with appropriate pain management for patients and opioid abuse. Voluntary education is preferred, not to make mandatory additional restrictions to impact the ability to practice medicine or licensure. The AAFP supports meeting and exceeding the FDA targets for this training.

The AAFP as a credit system openly supports the CMSS code and the ACCME standards for commercial support and is successfully working with the RPC and the IWG Industry Working Group to make sure that these REMS work within the rules and follow within the

rules of all of the credit systems.

Within the broad scope of medicine, and specifically family medicine, there continue to be recommendations that the FDA hopefully consider when there are other considerations for CME.

Prescribing is already integrated into physician education when discussing specific clinic topics and CME is designed on evidence-based needs assessments and formal gap analysis. Therefore, gaps in knowledge, practice, skills, and attitudes also exist in new technologies, innovative drug treatments, changes in treatment algorithms, and actually practicing hands-on procedural skills acquisition, as well as important patient-based skills, including communication, cultural competency, attention to health disparities, and end of life issues.

When CME is being considered as a REMS, it may be important to consider reading recommendations of specific topics or formats

to those subject matter experts actually preparing the content and the formal educational design of the activity to those with some adult education experience to meet the specific outcomes of the training. And that goes back to the earlier conversation about knowing the metrics on the front end. That really would depend on what the issue is, what the topic is, and what the outcome is.

Continuing to encourage technology, including integration of electronic health record data, to add patient outcomes and garner information for CME activities, one format which includes performance improvement CME, which is already in existence for measuring physician pre-assessment intervention and post-assessment data, which is a required component of board certification and most states' licensure.

It is also important to remember that PICME or education at this level, it takes time to show change. It is extremely

expensive. And pulling the de-identified data reports and publishing it, again, will take time.

Thank you.

MS. TOIGO: Thank you, Ann. Next we will hear from Murray Kopelow from the ACCME.

DR. KOPELOW: Thank you, very much. It is an honor to be here. I speak in support of accredited prescriber education and in support of REMS. The Accreditation Counsel for Continuing Medical Education was created by the National Organizations of Medicine in 1980 and we accredit the continuing medical education enterprise on their behalf.

The scope of the accredited continuing medical education enterprise that is available to the FDA in the REMS programs for prescriber education is massive. There are 24 million registrants in accredited continuing medical education within the ACCME system in 2012; there were 133,000 activities;

almost a million hours of instruction. There are 2,000 accredited providers between our system and the state medical society's system that covers the country and that is available to the initiatives for prescriber education.

The system has a long experience with population in a community health-base needs. Our system addresses regional variation. It addresses variation within medical problems and their care as described by McGlinnis in 2002 in the New England Journal.

Our system addresses the racial disparity issues as is manifest in the issue of the disparity in healthcare. Survival between black women and white women with breast cancer, for an example. And we have for several years, our system has been addressing the issues that this long-acting sustained release opioid REMS has addressed.

When you look at the factors that predict or increase the probability of change

through education, our system creates the facilitating conditions for change through predisposing, enabling, or reinforcing the professionals to practice.

It is our system's simple requirements are that the education needs to be based on professional practice gaps. We need to understand the needs that underlie those gaps. They need to address a specific competency within the framework of medicine. They need to use the appropriate educational format and they need to measure for success in change. Those are the constructs that come along with accredited continuing medical education.

Tom Frieden, the Director of CDC has acknowledged our system's responsiveness to addressing public health issues, the same kind of public health issues that the REMS address.

Now with respect to integration of REMS into the healthcare system, it is

important to recognize that education developed and delivered by manufacturers is outside the professional practice systems of physicians and is avoided by physicians.

A prescriber education developed and delivered by manufacturers does not meet the medical profession self-regulation standards for independence from ACCME-defined commercial interest as articulated in the ACCME standards for commercial support.

So we say stay the course. Use accredited continuing medical education for prescriber education in your REMS.

With respect to standardization, it is important to recognize that an option is the standardization of process, not the standardization of content as to be delivered in the education, that our process ensures that the basis for educational content is the needs that underlie the professional practice gap. We ensure that the scope of evaluation of effectiveness is always the change in

competence performance or patient outcome and all of our providers measure change in these parameters. And that the data system or the data set describing accredited CME is standardized by the accreditors a priori.

In addition, there is a rigorous management of the boundary issues created by the presence of manufacturers and their funds in the process. The ACCME standards of commercial support that were first articulated in 1992 and then revised in 2004 provide for independence, provide for the resolution of personal conflicts of interest, ensure the management of commercial support is appropriate, that there is a separation of promotion for education, that there is absence of bias, and there is the disclosure to learners of relevant financial relationships in the presence of money.

It is ironic that these parameters were created by the Food and Drug Administration in your guidances to the CME

industry in 1997 and these are manifestations of the CME system's implementation of what is important to the Food and Drug Administration.

A way to standardize contents, one is through blueprinting. But blueprinting may be the enemy of integration, as prescribers are living in a world of practice-based learning and change and of reflective self-assessment. Continued professional development systems that REMS prescriber education wishes to integrate into are now based on the individual's own knowledge, their own confidence, or their own performance.

Variants in the overall content is a strength of the CME system. And doing the same continuing education over and over again to every audience is somewhat like a watch that doesn't move. It is perfectly accurate twice a day but otherwise, it is not very useful.

Prescriber education that is defined and based on the individuals' needs

reflects the true variation of the needs within the physician community. The physician community is not a homogeneous group. Physicians are at various stages of either knowing or at various stages of changing. And the continuing medical education enterprise and the evolving and emerging continuing professional development systems like maintenance of licensure and maintenance of certification are based on understanding that individual variation and having the education be responsive to it.

So if you want education that goes beyond the requirements of the drug prescriber information, we can do it if accredited education is left to be responsive to the information on professional practice gaps, the needs that underlie these gaps. And the FDA and the FDA's processes would be a great source of what those gaps are.

Does the accredited prescriber education teach us how to manage serious risks

associated with the drugs? Yes, if the accredited CME is allowed to be responsive to the stage of change and levels of knowing that the people in the room and not dealing with all of the physicians as a single homogeneous group.

The less the FDA dictates the content, the further beyond the requirements of the drug information the CME system will probably go and the more likely we will be to address all of the individuals' needs who are taking care of patients.

The prescriber education -- the effectiveness also could be measured simply by its effectiveness in promoting access to education for physicians that didn't have before. By mobilizing the education community to an issue could be an effectiveness of REMS. And drawing the profession's attention to the problem would be another parameter through which the effectiveness of REMS could be measured.

Going forward, we think we should be promoting the integration of REMS into the fabric of accredited continuing medical education. We should value addressing many people's measured and individuals' needs and that could be the focus. We could value the evidence of change and not just the evidence of reach to the learners. And we could promote reliable recognition of prior learning that if people do know what the risks are, if people do know how to use it, then maybe those people don't need to have additional education.

And the other is that perhaps the route to safety for the patients is not solely through education to the prescribers but maybe to the physicians who are not prescribing these products.

Thank you very much.

MS. TOIGO: Thank you, Murray. Our next presenter is Andre Kolodny from the Physicians for Responsible Opioid Prescribing.

DR. KOLODNY: Thank you. It is a pleasure to be here today. My name is Andrew Kolodny. I am president of PROP, Physicians for Responsible Opioid Prescribing. It is an organization with a mission to reduce morbidity and mortality from opioid analgesics and to encourage more cautious prescribing of opioids. I am going to share with you our organization's perspective on the ER/LA opioid REMS.

The United States is facing an epidemic of opioid addiction, opioid analgesic addiction to be specific. The epidemic began in the late 1990s and this rate shows you rates of people seeking treatment for pain killer addiction in the late 1990s, just when the epidemic was beginning. And what you see is that states that are showing up as red or maroon are the states with the greatest rate of people seeking treatment for pain killer addiction. I would like you to watch what happens to the color of the map as we go

forward in time. This is 1999. This is 2005 and you can see that much of the map has turned red. Almost the entire east coast has had a sharp increase in people seeking treatment for pain killer addiction. And by 2009, you see that just about every single state in the country experienced a sharp increase in people seeking treatment for pain killer addiction. And this is how you would define an epidemic when you have a sharp increase in the prevalence of a disease over a short period of time.

It is important to recognize that people get this disease in pretty much one of two ways. You become addicted to pain killers either through non-medical use, so for example a young person finding leftover pills in a medicine chest; experimenting with them, enjoying them, and then becoming hooked. Or a patient can become addicted through medical use of opioid analgesics, starting off by taking the pills as prescribed and then

developing the disease of addiction.

One of the unfortunate but common outcomes for people who develop this disease is that many of them die of overdose deaths. And what we have seen over this period of time since the beginning of the epidemic, we have seen a sharp increase in people dying from pain killer overdose deaths indicated in red. We actually have more people dying from pain killer overdoses than dying from heroin and cocaine combined. And for drug overdose deaths in general, we now have more people in the United States dying from drug overdose deaths than dying from car crashes.

This is a CDC slide and the CDC has been showing this slide to try and be as clear as they possibly can about what they think is causing this epidemic. The green line represents cells for opioid analgesics, basically the increase in consumption of opioids. And what the CDC is arguing is that the sharp increase in prescribing of opioid

analgesics beginning in the late 1990s is causing this epidemic and it is leading to parallel increases in overdose deaths, represented in the red line and in addiction or people seeking treatment for addiction to pain killers represented by the blue line.

As you look at this graph, one thing that is important for you to recognize is that this change in prescribing practices, what caused this green line to shoot up was not some new evidence that opioids were safe and effective, what caused the change in prescribing practices was an industry-funded campaign that misled the medical community to believe that the risks of opioid analgesics were far lower than they actually are. In particular, we were misled to believe that we shouldn't worry about addiction. And the benefits of opioids, particularly for chronic non-cancer pain were exaggerated.

The opioid REMS, FDAs plan to have an opioid REMS was released in February 2009.

And when there was the first announcement that FDA was planning to do this, there were many in the advocacy community who had very high hopes for this REMS. And some of the early communications about the REMS led us to believe that FDA might be interested in having a registry for chronic pain patients who were on opioids that could ensure that the patients are being properly monitored, that could ensure that they are not doctor shopping, or even reduce the risk of diversion of pills to the black market. We were also hopeful that FDA would be introducing mandatory education so that prescribers of opioid analgesics might be required before prescribing opioids for low back pain, for common chronic conditions long-term that you might require some mandatory education for prescribers like we have for buprenorphine when used for addiction treatment. And we understand that buprenorphine has a significantly lower risk of addiction and abuse potential than the

other opioids.

Between the first announcement of an FDA opioid REMS and the plan that was presented to an advisory committee in July 2010, there were multiple meetings and multiple opportunities for stakeholder input. And on my slide I put stakeholder in quotes because I think that FDA was most influenced by organizations that I probably would not characterize as legitimate stakeholders.

So for example, the American Pain Foundation, which is an organization that closed down last year when the Senate Finance Committee announced an investigation of its influence on opioid prescribing, that is an organization that had received about 90 percent of its income from opioid manufacturers. That organization which presented itself as a grassroots organization representing the interests of patients in pain but probably better characterized as an AstroTurf organization, artificial meant to

look like grassroots, the American Pain Foundation told the FDA that patient registries would stigmatize patients, would be bad for pain patients. And other organizations, along with the American Pain Foundation, convinced FDA to gut the plan that had initially been proposed.

When the final REMS was presented to an advisory committee in July of 2010, the committee voted it down 25 to 10. And what they said was that this REMS has no teeth in it. This was the coverage of that meeting in the press, FDA News. Class-wide opioid REMS lacks teeth to tackle abuse. FDA advisors reject Agency plan to control opioid use as too soft. FDA panel rejects REMS for opioids says current plan inadequate.

Why did FDA listen to the American Pain Foundation and to the other organizations? And why did we wind up with such a weak REMS program? I think if we would give FDA the benefit of the doubt, I think

that they bought this argument and this is the argument that pain organizations made. They argued that there are millions of pain patients who need ready access to opioids because they are being helped by them and then there are the drug abusers who are being harmed by opioids and they said don't have a REMS that is so strict that you are trying to stop drug abusers but making pain patients pay the price for the bad behavior of drug abusers.

But that is really a false dichotomy because what we do know is that we don't have two distinct populations. We don't have pain patients who are all being helped and drug abusers who are being harmed. We know that abhorrent drug use behaviors are extremely common in pain patients.

We know that 35 percent of patients on long-term opioids meet criteria for opioid addiction. And in a recent study of overdose death victims that came out of

Utah, they found that 92 percent of the people dying of opioid overdoses were having opioids prescribed to them for a diagnosis of chronic pain. Probably many of them were addicted but they were having opioids prescribed to them supposedly for legitimate pain.

After the FDA plan for an opioid REMS was voted down, we had the release of a blueprint curriculum for voluntary education programs. And then finally in April 2013, FDA issued the final curriculum and there was the final plan for the opioid REMS, which was the exact same plan that the advisory committee had voted down.

When comments to the draft curriculum were sought, my organization submitted a letter to FDA expressing our concern about the curriculum that was going to be used for voluntary education programs sponsored by industry. And I suppose to many of you this is just a list of names but this list includes some of the most prominent pain

specialists in the world. Some of the experts on opioid use. It includes some of the leading experts in the country on addiction, including the former Deputy Drug Czar. It includes leaders in the field of public health, including health commissioners who signed this letter.

What we told FDA in our comment on the curriculum that was being proposed was that we were worried that the curriculum would potentially cause more harm than good, that the curriculum would suggest to prescribers that opioids are safe and effective for chronic pain if certain rules are followed. What we wanted were education programs that would present what the medical community is beginning to realize, which is that when you treat chronic non-cancer pain with opioids, with long-term opioids, that you are harming far more chronic pain patients than you are helping. What we wanted was an education program that would communicate to prescribers

that treating chronic pain with opioids is often a very bad idea.

Instead, what we have is a curriculum that teaches what the industry would call the new paradigm and what I would call the emperor's new paradigm because I think in many ways it is a hoax. Instead teaching that opioids are a poor choice for fibromyalgia or headache or low back pain, which is about 90 percent of people with chronic non-cancer pain, instead what is taught is that if you use certain risk assessment tools that will help you identify somebody's risk of becoming addicted and then you stratify them on the basis of that risk and monitor them closely, that somehow this turns the treatment into something that is safe and effective, which we know is not true.

So the opioid REMS included more than just the education which we were opposed to because it was voluntary industry-paid-for education which is what caused that green line

to shoot up in the first place, but also there were other elements of the REMS which could have been effective if done properly.

What I have just passed out would be what is called the Patient Counseling Document. And according to the description of the document and FDA briefing materials, the document was intended to encourage a conversation between patients and their prescribers about the risks of opioids that would have been an opportunity for a prescriber who he or she himself may not be well-informed about opioid risks to go over some of these and provide a patient with informed consent.

If you look at this document -- I am going to finish up here -- but what is missing from that document is any counseling on the risk of addiction with opioids. And according to the FDA, there was no mention of risk of addiction because they prefer to have blank space on that document where doctors

could put in information specific to their patients.

I am going to wrap up here. What we wound up at the end of the day was an opioid REMS that would in no way jeopardize this green line from continuing to go straight up, which is exactly what the industry wanted.

And unless we begin to see that green line begin to come down, it is unlikely that we are going to be able to have an impact on this epidemic.

Thank you.

MS. TOIGO: Thank you. Next we will hear from Natalie O'Donnell from United BioSource Corporation.

MS. O'DONNELL: Hello. My name is Natalie O'Donnell and I am the Director of Risk Management at United BioSource or UBC. UBC has been working in the area of risk management since 1999. We have been involved in many RiskMAPs and REMS. Today, I am going to be talking about patient-directed REMS

tools, which include patient counseling and discussions around benefits and risks of drug or biologic, as well as instructions on how to use drugs safely. I am going to be speaking about this in relation to the patient.

So we have talked a lot about PDUFA V today and the goal to examine the need to reduce burden in the healthcare system. We know the mission of the FDA to protect public health and ensure safety. And when we consider REMS in place to ensure that the benefit of drugs outweigh the risks, all those important factors together are very important and why we are here today.

However, I want to ensure that through this examination, this meeting today, and the docket in the future, that we don't decrease the focus on patients and patient education. I think instead, let's move towards a greater efficiency. It would be efficient to use our existing healthcare system to manage patient safety.

While we believe that REMS has been effective in minimizing risk, we want to continue to expand their role in other healthcare professionals to further strengthen REMS. Although REMS requirements have never prohibited nurses or pharmacists from being key stakeholders, the primary focus has typically been on physicians or prescribers.

I would like to comment today on the need to better recognize the role that pharmacists and nurses play in the education and interactions with patients. In current REMS programs, it is unusual for nurses or pharmacists to be specifically included in REMS training and enrollment requirements. In fact, when reviewing REMS with elements to assure safe use, about only half of them even have outreached to nurses or nurse practitioners.

Currently, there are over 2.6 million practicing nurses, including 250,000 advanced practice nurses and 2.1 full-time

practicing pharmacists in the United States. The nurses are responsible for primary direct patient care in many settings, including medical offices, hospitals, long-term care facilities, and pharmacists are interacting patients in pharmacies, hospitals, grocery stores, other retail and healthcare environments, as we have talked about today.

Considering the timing and frequency of patient counseling, the initial dialogue occurs between the prescriber and the patient. I understand this relationship is the cornerstone of an informed treatment decision. Additional downstream safety nets exist within our current healthcare delivery system. We won't be over-educating our patients by building a model of reinforcement. Data indicates that when patients are provided solid knowledge base about their disease process and treatment, the outcome for patients is more favorable.

After a prescribing decision is

made between the patient and physician, the nurse and nurse practitioner have the opportunity in many of the settings I have already discussed to reinforce, further educate the patient on the risk and benefit of the product. Then the pharmacists has the opportunity to further reinforce early teachings, as well as cross-check medications on the patient's profile.

In particular with many complex REMS involving specialty pharmacy, there is a natural opportunity for pharmacists to serve as the bridge between the patient and prescriber. REMS are a central part of the specialty pharmacy model. Processes in the specialty pharmacy allow for regular monitoring of patients and adherence to treatment regimens. Specialty pharmacies have the ability to identify in real time patients exposed to medications and engage with them directly. In both the retail and specialty pharmacy settings, pharmacy management systems

can provide messaging to the pharmacist about specific educational messages related to REMS while confirming that the appropriate patient is authorized to receive the medication and those who do not meet the REMS requirement do not receive the medication.

There does not seem to be a downside to leveraging the current health system. This does not increase burden but rather redistributes the important components of educating patients.

With the Affordable Healthcare Act on the horizon, it is anticipated that an additional 32 million Americans will have access to healthcare. The timing is right. Engaging more healthcare professionals already key to patient education will help us ensure the goal of the FDA, PDUFA V and REMS. Together, we cast a safety net ensuring the right patients receive the right products. We reduce adverse events and hopefully prevent death.

In summary, REMS required training should and could include nurses and pharmacists. While the decision about the appropriate treatment takes place between the prescriber and the patient, education is an iterative process, building the bridge between the patient and the prescriber with the support of nurses and pharmacists creates a solid foundation REMS can build upon.

Thank you.

MS. TOIGO: Thank you, Natalie. That concludes this panel. And we have time for about ten minutes of FDA questions. So who on the panel wants to start this session?

Gary.

DR. SLATKO: So my question is to Natalie.

One of the things that we have heard from stakeholders is that, particularly those in closed systems and government healthcare organizations, that the specialty pharmacy, they have a barrier to getting

access to products if they are distributed through specialty pharmacy mechanism exclusively.

So do you have any thoughts about a way to make those products that are distributed through a specialty pharmacy also available through these organizations?

MS. O'DONNELL: I should have said I am a nurse not a pharmacist. I don't -- actually our organization has some knowledge about that, it is not my area of expertise. I would be misleading you if I tried to answer that honestly. I'm sorry.

MS. TOIGO: Kate?

MS. OSWELL: This question is for Murray. You had spoken about accredited CME and allowing them to be responsive to knowledge gaps and the stages of change to address individual needs.

Could you expand a little bit about how the knowledge gaps are determined and developed, actually, in the CME?

DR. KOPELOW: Thank you. It starts with a professional practice gap. It starts with the difference between what people are doing either as individuals, communities, or populations, between what they are doing and what they should be doing. That data comes from you, from industry, from patients of those who are observing directly what is going on.

The reason for that is the need, either a knowledge need, a strategy need, a performance need that underlies that gap. The incidence, the prevalence of substance abuse in the population of the United States is 1 in 12 I was taught when I was at ONDCP. The incidence or prevalence of physicians -- of patients in physicians' practices ranges dramatically from zero to 1 in 12.

And the need that underlies that professional practice gap might be that the physicians don't understand or know about the epidemiology of the disease. They don't

understand the use or misuse of products. They don't have the strategies to ask the question. They don't have the ability. They don't know what question to ask. They don't have the expert kind of tools available to them to use to screen.

There is a range of what the needs are that underlie those gaps and they are as heterogeneous as the physician population.

It is limited. We have heard some on both sides that describe some of them. And it is that variation that is the richness of the continuing education enterprise.

Did that answer your question? Thank you.

MS. TOIGO: Ann, did you want to add anything to that? Knowledge gaps, how AAFP may look at when you are developing your educational programs?

DR. KARTY: Our process is very similar. And actually AAFP wears a unique hat because not only are we one of the three

credit systems, the AMA, the AOA, and the AAFP, we are actually an accredited provider of ACCME credit as well. So we have several different hats.

But as far as creation of identification of need assessments and gaps in physician practice, it is a very similar process. I would say opioids are one that doesn't have as distinct a performance measure as diabetes, for example, where there are specific blood tests or specific tools that can be or pieces of information that can be garnered from electronic records to see if physicians are doing them on appropriate times.

And then the whole concept and the notion of peer review and comparing yourself to your geographic location to those in other practices. Sometimes gaps are found based on zip code and practice performance.

MS. TOIGO: Mwango.

DR. KASHOKI: Hi. My question is

for Ann as well. And I don't know if this is what you meant to imply in your presentation but you talked about the voluntary participation in education or training is effective, so to speak.

I know you talked about some of the limitations you have thus far with regard to training in opioids and the opioid REMS, et cetera.

But I was wondering if you have any general information that compares effectiveness of a voluntary education program for any other kind of learning against something that was required, whether it was a guideline or whatever, in order to give some context for how useful voluntary participation in a training is.

DR. KARTY: I am going to give a couple different pieces of background. I think the concept of voluntary education versus mandatory education specifically in family medicine with pain management, it is

concerning that things that are more restrictive on any type of practice has the potential for physicians to choose not to do that in their practice and for physicians that are in rural practices where they may be the only prescriber to be able to write opioids, should they not take the mandatory education, there is the potential to impact patient outcomes. It becomes an access problem.

And so as much as one can encourage voluntary participation, I mean I think that is the preferred route to go. And I am not representing the licensing boards, although I have a few extra comments that I can provide from our meeting earlier in the week, but there are several municipalities from a prescriber and a physician licensing piece that there are over 40 of the 46 states, I think, that actually have CME requirements globally for a certain number of hours, certain number of credits per year to maintain licensing. And physicians on average have

multiple licenses, two to four licenses I think are the most recent statistics I have heard.

So each state has different requirements and may have different numeric of 20, 40, 60 credits globally. And there are I think 16 municipalities that have topic-specific requirements of which I think 14 involve some opioid piece of that.

So you can envision somebody who has four different licenses with many different requirements not only to hit a certain credit number to maintain those licenses, which probably are reciprocal, but if there are multiple states that have different topic-specific CME and now there are REMS-required CMEs, that that really eats into the overall 40 credits per year, whatever that would look like. Because each one is different.

So that whole notion of required versus voluntary for family physicians, it

definitely would be an access concern.

For the question of is there a difference between voluntary education and mandatory education, I am not sure I have that data or that I can provide comment on that.

MS. TOIGO: Anyone else on the panel with a question?

MR. KROETSCH: So I think I have questions about the idea that the training is designed to address these gaps in knowledge and in practice. And that if we were to be able to supply that list of gaps that CME providers could build training that addressed that and customize that training to different prescriber needs. Is that the -- did I get that right?

DR. KOPELOW: Right, that is the current system and we have data to show that when presented with these gaps, the CME system does translate them into education and does translate that into evaluation.

MR. KROETSCH: Yes, and actually

it was that translation that I am curious about. I would be interested in understanding better what kind of evidence you use to track that sort of translation and how you might -- that is how you know retrospectively that that has been successful. And then in the future if we were interested in a REMS to understand how those gaps were translated into say messages that are delivered in the education and then ultimately into behaviors. Do you have systems that can help track how that happens?

And I think even in addition to that, is there a way to track what the baseline level of knowledge was and what the sort of customizations that were made to account for any of the unique needs of prescribers?

DR. KOPELOW: You know, it is okay to ask a one-part question, --

(Laughter.)

DR. KOPELOW: -- especially to

someone old who has trouble remembering.

An assumption in your question is that a knowledge deficit is the cause of a patient outcome. And that is a testable hypothesis.

Our system of accreditation has the data you seek about whether or not the providers have based their education on professional practice gaps because our system does that in the determination. Then have they translated or not translated but deduced what the needs are from that gap? We have that data. That is our compliance data and our providers are operating at an 80 or 90 percent compliance rate for that. That is the process that I was speaking of that you have access to.

We do not have data -- we have the information but we have not pulled it out of the information what the prevalence of education is on the substance abuse issues and that range. We have recently done that for

NIH for genomics to look at the range of education that is on genetics and genetic testing. And we can do that within our system.

So we have that data. We have that information. We do know with the certainty of the accreditation process that the educators can translate professional practice gaps into needs and needs into education and we have a requirement that you use the appropriate format.

The quality of the education is as good as the accuracy of those professional practice gaps. And what Dr. Kolodny talks about about the inaccuracy of what is right and what is wrong, that needs to be reconciled. That needs to be reconciled.

We need to say that having a zero percent of patients in your practice with substance abuse is, in itself a professional practice gap. We need to be able to say that your use of products and your manner of using

them is at variance from what is in the best interest of the nation.

That is the professional practice gap that we need. That is what we need from you because that determines the precision and the accuracy and the reliability of the education that follows.

MS. TOIGO: So I think Dr. Kolodny wanted to add something to that comment, Adam.

DR. KOLODNY: Yes, I see it a little differently from Dr. Kopelow. So I think your question may be assuming that if we teach doctors the right way to treat chronic pain with opioids, for example, if they are taught to use risk assessment tools, stratify a patient's risk of addiction, monitor them accordingly, that it can turn out safe and effective in the end. And there is really no evidence that that is the case. There is increasing evidence that using these medications, extended-release opioids for non-cancer pain long-term is a really bad idea.

And so the real gap in understanding for prescribers is that these medications are highly addictive, not that there is just one small percentage of our population at risk of getting addicted. That is not really true. With highly addictive drugs, if you expose people long-term, a good number of people will develop that disease.

So the gap in understanding is that the drugs are very dangerous and that evidence of long-term benefit is very weak. And in fact, there is increasing evidence that patients do poorly long-term because of tolerance to analgesia.

So the education programs that we have that are getting accreditation are teaching to use these practice tools and this is the safe and effective way to do it but the evidence does not support that.

MS. TOIGO: Well in the interest of time, we are running a little bit over but I wanted to make sure that we had an

opportunity for questions on this panel.

So we will take a break. We will take a full 15-minute break and we will be back at five after three o'clock.

The unfortunate thing is we didn't have enough time during this panel to really explore more about how CME, the process worked with the ER/LA opioids but we would spend a half hour on that. So I can't ask my question. Sorry.

(Whereupon, the foregoing proceeding went off the record at 2:54 p.m. and went back on the record at 3:11 p.m.)

MS. TOIGO: Okay, we're going to get started with our last panel for today. And this is our speakers are going to address REMS tools in dispensing settings. And so we have multiple representatives from diverse pharmacy practice settings that are going to speak to us today about tools and dispensing settings.

And we are going to start off with

Kevin Nicholson from the National Association of Chain Drug Stores.

MR. NICHOLSON: All right, thank you. Good afternoon and thank you for the opportunity to share the perspective of chain pharmacy on the issues and challenges associated with the standardization and assessment of Risk Evaluation and Mitigation Strategies.

I am Kevin Nicholson, Vice President Public Policy and Regulatory Affairs for the National Association of Chain Drug Stores. NACDS represents traditional drug stores, supermarkets, and mass merchants with pharmacies from regional chains with four stores to national companies. Our members operate more than 41,000 pharmacies and employ more than 3.8 million employees, including the 132,000 pharmacists. They fill over 2.7 billion prescriptions annually, which is more than 72 percent of annual prescriptions in the U.S.

We commend FDA for looking for ways to standardize and assess REMS to better integrate them into existing and evolving healthcare systems with a goal of reducing any associated burdens. Streamlining REMS will assure that healthcare providers can focus on the provision of health -- provision of patient care while still meeting underlying REMS goals. We support FDA's work to this end.

From our members perspective there are a number of ways that FDA could work with stakeholders to standardize and improve REMS. We strongly urge FDA to elevate in priority the adoption of a single patient medication information document that is standardized with respect to format and content, referred to as the one-document solution.

The one-document solution would improve the effectiveness of information provided for REMS drugs, enhance pharmacists' ability to consultations on those drugs, and

streamline provision of that information into pharmacy management systems.

Currently, patients are given numerous written materials, including Medication Guides, patient package inserts, and other consumer medication information in myriad formats when they receive their filled prescriptions from their pharmacies.

Patients need a useful document designed and written for them in a manner that recognizes their information needs that provides both concise and critical information. This is especially important for REMS drugs where over-saturating patients with confusing lengthy documents can lead to patient oversight of critical information, which could have severe health consequences.

A single, concise, and well-designed patient medication information document could be used by pharmacies as a tool in their counseling sessions with patients to highlight and clearly delineate any critical

information about a prescription. This document would also serve as an important resource for patients to take away from the counseling session, reinforcing the key information that they learned from their pharmacist about their medication.

Where a patient is interested in more detailed information, this should be obtainable through an FDA-provided or manufacturer-provided consumer-friendly website, which we suggest that either FDA work to create or that FDA develop standards for the creation of websites by manufacturers.

Additionally, patients would be well served by more in-depth MTM services for REMS drugs. Reimbursing pharmacies for providing enhanced MTM sessions would further facilitate patient understanding. To this end, models for pharmacist reimbursement should be considered when designing REMS.

Beyond consolidating the format of written information via the one-document

solution, there are other ways to improve the provision of information to patients to meet REMS requirements. With more patients relying on mobile and other technologies, patients should have the option of receiving medication information in a written document, electronically via email, through a stable website, or through applications on mobile devices.

Additionally patients with low literacy or visual impairment should have the option of toll-free numbers so that prescription information can be orally communicated.

To facilitate these various multiple media solutions, FDA could create or approve source documents for each medication that would be used for the development of electronic and paper media. The source document would serve as the most authoritative reference.

To further improve organized,

standardized, and centralized REMS, REMS information and any associated processes and requirements, NACDS urges FDA to continue to work with the National Council for Prescription Drug Programs, NCPDP, to integrate REMS into the standard product labeling standard known as SPL. And this has been mentioned by other speakers today. So we support that. We support the SPL standard as well.

Integrating REMS into SPL will yield uniform format and content for REMS information that is easily accessible for practitioners, along with other product labeling information in one centralized resource. This is notably in line with the one-document solution that we continue to advocate for. Doing so will facilitate the integration of REMS into the prescribing and dispensing processes via the ePrescribing systems used by prescribers and the pharmacy management systems used by pharmacies, which

will ultimately streamline the process for practitioners to complete any REMS requirements for a particular medication.

We believe that FDA could also improve REMS by establishing a single web portal to act as a repository for standardized REMS tools and materials and to serve as a central information or reference source for REMS stakeholders. We strongly urge FDA to work with a strategic partner with experience necessary to design such a resource for this purpose.

FDA should also work on developing a uniform standard for REMS that include elements to assure safe use, the ETASU. For these REMS in particular, standardization of the now varied approaches that can include patient registries and/or attestation, and special processes for practitioner enrollment and training will streamline processes and minimize associated compliance challenges for patients and practitioners.

In general, the TIRF REMS serves as a good example for standardizing and integrating REMS with ETASU into healthcare delivery systems. The TIRF REMS effectively incorporates training and certification requirements for patients, prescribers, and dispensers into the dispensing process and into existing pharmacy adjudication systems. This approach allows dispensers to effectively ensure that any safe use conditions are met prior to dispensing.

This is a much more efficient approach than the patient registry requirement under other programs, such as the iPLEDGE program. Where training enrollment is necessary for prescribers and/or dispensers under particular REMS, this should be made available online. Doing so provides a convenient and faster way to enroll and meet particular REMS requirements. With respect to certification of pharmacists and pharmacies, in the pharmacy setting, additional

certification for pharmacists would be unnecessary. We are required, pharmacies are already certified and there are trigger points in place operationally to alert dispensing pharmacists if there are any REMS requirements that must be met for a specific medication.

Moreover, by virtue of their education, all licensed pharmacists are medication experts who know the risks of various drugs. So we feel that additional certification for pharmacists would be unwarranted. Notably, it would be extremely challenging for a pharmacy chain to ensure that every single pharmacist is current with their certification. There is a strong probability that this would lead to patient access issues as most likely only certain pharmacists in certain locations would be certified.

Additionally, we believe that a workable certification process can be created for certifying a chain pharmacy as a whole, as

opposed to individual pharmacy locations. We believe appropriate policies and procedures can be implemented to ensure that certification requirements are followed chain-wide.

Finally when evaluating REMS, FDA should consider that certain REMS requirements can make it difficult for authorized dispensers to obtain drugs to meet their patients' needs. For example, REMS that have limited distribution place an undue burden on patient access. Additionally, where REMS requirements are onerous and unique, this, in some case, has caused particular pharmacies not to carry the product, which also impacts patient access. Improved standardization could help address these issues.

Thank you again for the opportunity to speak with you today and convey our members' input on the topic of REMS standardization. I would be happy to answer any questions.

MS. TOIGO: Thank you, Kevin. Next we will hear from Stacie Maass from the American Pharmacists Association, not the American Public Health Association.

MS. MAASS: Thank you. Good afternoon. I am Stacie Maass, Senior Vice President for Pharmacy Practice and Government Affairs with the American Pharmacists Association or APhA.

APhA represents more than 62,000 pharmacists, pharmaceutical sciences, and pharmacist technicians in all practice settings.

Pharmacists, due to their medication expertise, play an essential role in the safe use of medications and effective implementation of REMS programs. APhA would like to take this opportunity to thank the FDA for the significant investment of your time and resources in the improvement of the REMS program. We are especially gratified that FDA's current questions reflect the progress

made and the input by APhA and other stakeholders over the past few years. So, thank you.

APhA continues to support efforts to standardize REMS. With a wide variety of REMS programs, each with its own particular components, compliance can be very daunting. However, moving forward standard REMS programs will contribute to the efficiencies by ensuring that patients not only have access to medications but take those medications safely, while reducing the administrative burden on providers.

As stated by many speakers today, REMS should be incorporated into existing prescriber and dispenser workflows to the greatest extent possible. Leveraging existing technologies and infrastructures, including electronic health records, ePrescribing systems and pharmacy management systems creates the possibility of interoperability among providers, as well as information

sharing, without the necessity of expensive, new information technology.

New options for integration should be evaluated in pilot programs, allowing front-line providers to offer feedback and suggestions for improvement, as well as time for providers to prepare for and adapt to changes.

As the entire healthcare system becomes more coordinated, the opportunities for centralizing REMS and effectively sharing information increases. We urge the FDA to consider centralizing all REMS information, making education material, training, and registration information available on one site.

Further we suggest that FDA continue to examine the possibility of organizing REMS programs based on tiers or levels, perhaps similar to the schedules for controlled substances. The structure of each level could consist of a standard set of

components that may be applied based on the level of risk associated with the medication. Such an approach would offer manufacturers some flexibility in constructing REMS programs but would also provide baseline consistency that would make management of numerous REMS programs easier, as well as decreasing the burden on prescribers and dispensers.

By integrating REMS processes into regular operations, prescribers, dispensers, and patients are able to maximize communication, leading to improved patient experiences, fewer adverse effects, and less time handling paperwork.

APhA appreciates FDA's ongoing effort to improve patient education and the outreach regarding REMS programs. In a perfect world, all discussions of REMS medications would involve a provider intervention. However, the cost associated with such an approach would make it infeasible. As such, we support the

simplification of the education materials so that patients are not confronted with the overwhelming amounts of information.

For instance, each REMS medication could have a one-pager of the risks and benefits, followed up with additional information separate and apart with more of the technical or scientific information.

Further, in some instances it may be helpful to take advantage of technology solutions, such as online learning modules that guide patients through the medication information or a smartphone app that you could push safety reminders, along with reminders to take medications. These innovations, though should only supplement communication with a provider, not supplant that communication.

Patients, like most people, have a limited capacity for taking in and retaining highly technical information. In many instances, medication discussions comes at the end of an appointment, by which point the

patient may have already reached his or her medical information saturation limit. I think that something that probably all of us in this room maybe are experiencing at this hour. And I am sure you are all wishing for a one-pager but sorry.

Thus, APhA recommends that FDA and stakeholders consider solutions that result in face-to-face and telehealth consultations as key elements of REMS programs, incorporating human interaction into the REMS process improves patient safety and allows for a provider to gauge patient comprehension.

For example, many states embraced medication therapy management or MTM as an essential tool for adherence or safe use of medications. We suggest one possible REMS patient education be folded into such MTM programs. In addition to the benefits to the patient, MTM programs provides an opportunity to provide data, relevant data regarding REMS and MTM allows patient monitoring, produces

data on patient usage in adverse events, which could be highly beneficial in assessing the relevant effectiveness and impact of REMS programs on patient medication usage.

APhA believes that with the appropriate application of time and resources direct intervention REMS element would allow pharmacists to improve program effectiveness, patient safety, and the public health.

I touched on earlier the development of a standards repository for REMS-related information would greatly pharmacists. A REMS clearinghouse would allow pharmacists to complete certification education requirements under a single system, rather than across multiple program-specific platforms.

Pharmacists could use a national provider identifier, such as NPIs, to access REMS verification and education requirements as required for certification. Attestation of the successful completion of the program could

be sent electronically and verified through a seamless electronic process claims adjudication process.

Additionally, we believe this electronic verification would cut down on the administrative work for pharmacists and improve communication across the whole healthcare team. This worked well for TIRF products and it could be translated into additional medication that is suggested by others.

APhA suggests that FDA and stakeholders continue to work cooperatively to identify opportunities for effective integration across providers and systems.

In closing, we thank FDA and stakeholders for their dedication time and resources to this effort in acknowledging the essential role of pharmacists and pharmacies in REMS standardization and implementation. While FDA does not regulate the practice of pharmacy, the decisions you make definitely

affect our practice. If appropriate time and resources are invested, pharmacists can further improve public health and education regarding REMS medications. We look forward to working with FDA, manufacturers, prescribers, pharmacists, and other stakeholders to identify solutions, evaluate options for REMS standardization and implementation. Thank you.

MS. TOIGO: Thank you, Stacie. Our next speaker is Carolyn Ha from the National Community Pharmacists Association.

DR. HA: Thank you, Terry. Good afternoon and thank you for allowing me this opportunity to share community Pharmacies' perspective regarding issues and challenges associated with the development, standardization, and implementation of REMS.

I am Carolyn Ha, Director of Professional Affairs of the National Community Pharmacists Association. NCPA represents America's community pharmacists, including the

owners of more than 23,000 community pharmacies, pharmacy franchises and chains.

First we would like to applaud the FDA for making the process that has led to this public meeting a transparent one and we appreciate another opportunity to publicly comment on FDA's efforts to standardize and assess REMS and the impact of such programs on community pharmacists and the patients they serve.

We would like to reiterate, however, that state boards of pharmacy regulate the practice of pharmacy and also would caution that REMS programs have the potential to interfere with that role if they are used too frequently and without coordination with existing regulatory requirements.

Pharmacists take seriously their role as a primary source of drug information for their patients. Pharmacists provide both lifesaving medications to their patients, as

well as critical written and verbal drug information and counseling that allow medications to be used most appropriately and safely.

Recent studies have shown that patients recognize the value of and are willing to receive pharmacist provided care. Ideally, that care is delivered by a pharmacists with whom a patient has had an established and trusted relationship. While other approaches to delivering these services exist, studies continue to show that community pharmacists providing face-to-face patient interactions may have a greater impact on patient behavior and adherence, compared to other methods of service delivery. Such patient counseling services that are based on a medication therapy management model could be utilized to meet the goals of a REMS program.

It is important to note that in the provision of care processes, pharmacists have standard workflow procedures that ensure

prescription medications are safely delivered to their patients. The absence of such standardization of REMS processes creates unnecessary workflow and workload burdens and eventually hinders patient care.

To date, community pharmacies experience with REMS continue to be challenging due to the lack of a common design or platform surrounding such programs. Medication Guides have not provided the solution that some had hoped and that is why NCPA is a strong advocate for the creation and use of a single FDA-approved language document to replace existing written information that is currently distributed by pharmacies.

We greatly appreciate the Agency's movement in this direction and additionally we are encouraged by the Agency's approval of a classified REMS for long-acting and extended release opioids, which provides for a consistent framework for all stakeholders while addressing FDA's REMS requirements.

As previously mentioned, community pharmacies are highly regulated in each state by Boards of Pharmacies and the Drug Enforcement Administration. It is, therefore, NCPA's position that any state and DEA-licensed pharmacy should be eligible to dispense specific REMS products. Not only do restricted distribution programs interfere with patient access to prescribed therapies, they may limit legitimate access to certain therapies as well.

As an example, NCPA does not support REMS for products which are dispensed through a sole channel distribution such as specialty or mail order pharmacy. Based on studies and experience, we know that direct face-to-face counseling is more effective than a restricted programs method of shipment via courier service to the home and counseling those provided by a call center phone bank from an unknown individual. This submits the necessary pharmacist patient contact, which

can lead to greater risk in patient safety.

NCPA contends that many independent pharmacies can meet stringent REMS requirements, such as being on-call 24-hours a day, as this is the level of service many of our members currently offer to their patients, regardless of REMS requirements.

The independent community pharmacists who choose to participate in a given REMS program and can meet all of their requirements should be allowed to do so and not be restricted by a special arrangement between the manufacturer and its specialty firms provider or any issues surrounding the ability of drug wholesalers to only distribute product to specific pharmacies. This is a service that NCPA believes wholesalers have the ability to provide on a daily basis currently.

Therefore, NCPA respectfully requests that FDA verify that REMS elements will not impede patient access to lifesaving

medications by placing products in a restricted distribution program. In instances where products have been placed in such a program, NCPA would respectfully request that FDA study the prescribing patterns for these products where oftentimes prescription volume could significantly decrease, thereby reducing patient benefits from these products. It also limits the ability for the pharmacist to manage the patient's entire drug therapy through multiple dispensing site.

Regarding certification of pharmacists or pharmacies to dispense certain drugs with REMS, the education of pharmacists to ensure understanding of these products, NCPA asserts that self-attestation of completion of education should serve as confirmation of receipt of training. Certification of individual pharmacists is not necessary. Certification at the pharmacy level should be sufficient, as long as there is an authorized pharmacists such as a

pharmacists in charge who, on behalf of the pharmacy, can attest that any required training will occur for all pharmacy staff involved in the dispensing of a REMS product.

If additional education is required, any provider of continuing pharmacy education should be accredited by the accreditation counsel for pharmacy education. Furthermore, this education should be allowed to be provided by entities such as national, state, or local pharmacy associations, or schools of pharmacy who are experts in the development of pharmacy-specific training and certification programs.

For pharmacists to receive the certification of completion awarding CPE credits for home study programs, they must review the content of the activity and successfully complete a post-test before their statement of credit is issued.

Any REMS-related CPE programs offered by an ACP-accredited provider would be

required to follow this process. In addition, the CPE provider could track which pharmacist had completed a given program, if it is necessary to specifically track completion of training.

NCPA cannot stress enough that any REMS system be created using a standardized platform. As stated before, and as many of my other pharmacy colleagues have pointed out, workflow standardization is an important component of safely filling prescriptions. A standardized REMS process that can be integrated within existing pharmacy workflow is critical to the successful execution of the program.

If the need for verification of certain elements to assure safe use does exist, we would urge FDA manufacturers to utilize existing nationwide technologies that provide automation scale and efficiency in the transmission of electronic or hand-written prescriptions, ePrescribing, any registry the

pharmacy management system and technology used to document patient understanding at the point of dispensing, should all work together and be interoperable.

For example, as mentioned this morning by the panel and you will hear more about it tomorrow, there is currently work underway from the National Counsel for Prescription Drug Programs, an accredited standards development organization looking at the development of a template for codified submission of REMS information in a centralized repository within FDA's SPL. Additionally, we would recommend a centralized website with a secure login portal that could significantly ease the process for patients, prescribers, and pharmacies to carry out the necessary registration, enrollment, and certification required for varying REMS programs.

REMS should be monitored and assessed frequently enough to evaluate

effectiveness, as well as to evaluate overall burden on the healthcare system. For example, the number of minutes a healthcare provider dedicates to each component of a given REMS should be captured and evaluated. In certain instances, this information may be collected by online methods, especially as it relates to provider training or enrollment of patients in a specific REMS program.

In other instances, methods should be developed or expanded that will allow for a capture of time spent by a provider with their patient discussing elements that are associated with REMS.

Metrics for determining the effectiveness of REMS should be specified, as has been noted today at the time that REMS are approved on the front-end of the process. NCPA recommends that efforts to create REMS are equally matched by efforts to evaluate the effectiveness and outcomes of a given REMS and its individual components.

FDA must ensure that the components of any REMS are proven to be effective in mitigating the specific defined risks and are also workable for patients, prescribers, pharmacists, manufacturers, wholesalers, and technology-assisted vendors. In addition, FDA should make outcomes information available to required participants of any given REMS program, as this applies transparency to the process, so that participants are aware of their contributions to achieving the agreed-upon goals.

In order to measure the effect of REMS on health outcomes, we recommend that data could be classified into general categories. Depending on the specific product, these categories could be further defined, such as patient prescriber and pharmacist knowledge, behavior such as inappropriate prescribing and non-medical use and abuse, and outcomes such as serious adverse effects and patient access to care.

Though we all admit challenges to trying to measure these outcomes, NCPA believes that through concerted effort to define a set of metrics, REMS will meet the goals of reducing serious adverse outcomes while maintaining patient access to medication.

In conclusion, we urge FDA to leverage the value that community pharmacists offer related to proper use of medications and avoidance of costly errors down the road. NCPA encourages the FDA to request stakeholder feedback regarding different approaches to create a standardized REMS process and to support industry-wide efforts to both standardize the REMS process, as well as harmonizing these activities with agency requirements.

The NCPA appreciates the opportunity to provide comments on this issue and applauds the FDA for recognizing the important role and involvement of independent

community pharmacists in the creation of REMS programs. Thank you for your time.

MS. TOIGO: Thank you, Carolyn. Our next speaker is David Chen from ASHP.

MR. CHEN: Good afternoon. My name, as mentioned, is David Chen. I am the Director of Pharmacy Practice Sections at the American Society of Health-System Pharmacists.

ASHP is the national professional association whose more than 40,000 members include pharmacists, pharmacy technicians, and pharmacy students who provide patient care in hospitals, health systems and ambulatory clinics.

For 70 years, the society has been on the forefront of efforts to improve medication use and enhance patient safety. And again, I appreciate the opportunity to present our views to you here today.

ASHP is a strong advocate for improving patient safety and medication management. The society believes that the

development of consistent evidence-based medication use systems is central to achieving safe medication use. Our members serve as an important patient advocate and the disciplinary care providers helping to ensure the safest use of medications.

While ASHP is pleased that the FDA has expanded authority to ensure the safety of drugs through REMS, we still remain concerned about how REMS are applied in the marketplace, the lack of standardization of REMS, and the inability to operationalize REMS without undue administration burden on the medication use system.

ASHP believes that through REMS, rather than developing a systematic approach to evidence-based medication use practices, we are seeing a separate medication use system that is being created for each high-risk medication.

Before I go into my comments for three facets for dispensing tools related to

REMS, I would like to take a moment to acknowledge and recognize the significant number of improvements made to the REMS programs and the FDA resources, since the July 2010 FDA meeting. For example, the development of the shared system REMS and the release of the guidance documents for Medication Guides, as well as like today the continued interest in engaging with stakeholders that are taking care of our patients and their medication needs.

Our members recognize the potential risk of medications that are inappropriately prescribed, dispensed, and monitored, as well as our own responsibility to provide patients with comprehensible information that is useful both to the patient and the provider. However, ASHP is concerned that current REMS programs are negatively effecting the already limited time that pharmacists have to care for and ensure the safety of their patients. We are also

concerned about the fragmentation of the drug supply chain, since any process encouraging a separate distribution system for particular drugs has the potential to increase risk of error and impact continuity of care.

Again, we appreciate the opportunity and now I am going to speak about three facets of dispensing relating to REMS that we have been asked to comment on today.

Patient education and safety. As noted in the past ASHP comments to the FDA, we believe educating patients is clearly important but there is a lack of research relating to the role, scope, and effect of patient understanding of MedGuides and resulting patient behavior. The usefulness and effectiveness of MedGuides as they are currently written and distributed as tools for counseling patients about serious risks remains to be established through adequate well-designed research.

Additionally, FDA should look at

the elements of REMS to ensure they are well-founded and effective at mitigating risk. As a member of the National Quality Forum, the ASHP recommends that the FDA look at processes that the NQF uses for the endorsement of quality measures. The process is rigorous in consensus building and can be used by the FDA as a model when developing a process to validate the FDA is actually measuring and achieving what we are hoping to attend to accomplish with particular REMS.

Thus, the goals of REMS need to include continued verification and validation that patient knowledge and receipt of information will actually improve outcomes and should include information proving that the MedGuide design is going to reach safety goals and should require the use of established research methods to sample patient populations on behavior modified based on receipt of patient education. This includes the development of appropriate incorporation of

health literacy standards.

Let's talk a little bit about registration processes in verification. ASHP would like to encourage the FDA to continue working with stakeholders to standardize the different elements of REMS and address the concerns we have heard during this meeting, in order to make this monitoring more efficient and generalizable to future REMS.

The core components of REMS are standards. The elements within each component should be analyzed in an effort for standardization. The lack of standardization results in large amounts of duplication within healthcare systems and the lack of centralized or standardized methods of accomplishing the ETASUs collectively for all REMS is a burden. Members share with us that they have had to dedicate specific resources to manage and keep up with the REMS administrative requirements.

So we would like the FDA to take

into consideration some of ASHP's experiences with our REMS Resource Center for front-line needs when looking at components to consider in a centralized database. In 2009-2010 with advice of members, we created this Resource Center to find the answers for pharmacist providers. The litmus test was to ask what was necessary at 6:00 p.m. on a Friday to manage a patient admitted on a REMS drug. The resulting Resource Center attempts to answer -- well actually it answers 12 questions for each drug. And we took the time to go into the source documents to help providers go to the original information.

These questions: Why is the REMS required? Does the hospital or pharmacy have to register? And take them to the according link. Does patient have to register? Does the prescriber have to enroll? Do I have to verify patient/prescriber are enrolled? Do I have to provide MedGuide? Is there specific monitoring involved? Can I order medication

through a usual supplier? What do I have to document? Am I required to complete CE? Are there any restrictions on dispensing amounts? And am I subject to an audit?

We find that this has been helpful for members as they start building their internal SOPs and other procedures to help operationalize the management of patients on REMS and ensuring that they are compliant with all the components of REMS.

So the ASHP encourages the FDA to work towards a centralized, electronic means for all REMS in the various registration, provider education, and patient documentation requirements in an effort to eliminate redundancies that exist and the need to maintain separate paper record-keeping in the thousands of patient care settings. This should include mechanisms to routinely and proactively inform practitioners on changes to the REMS programs.

Most importantly, it is to ensure

stakeholders from all size settings and geographic regions for future FDA work groups as you are developing practitioner tools discuss medication access and continuity of care.

Hospitals and health systems have a unique charge in that we have to provide and obtain all the medications for our patients while under our care. Introducing systems that require patients to bring in their own medications or require multiple supply chain channels to purchase medications introduces a growing number of variables, variables that consume time, raise risks to health systems' medication use systems.

The ASHP encourages the FDA to continue open dialogue with providers, including hospital and health system-based pharmacists and providers and considerations for a stakeholder group that has all health system providers at the table to conduct a critical analysis on how and where patients

initiate REMS medication therapies and the transitions of care that occur where providers need to obtain access to a REMS drug to manage the patient in a particular setting, with a focus on the IT interfaces between these settings to eliminate as much redundancy as possible and enable or create a vehicle allowing the data and the drug to be accessible to all provider settings.

Centralization of REMS information and data needs to become part of ePrescribing systems and means developed to integrate into electronic health records. Additionally, the FDA should require provider input in the development and refinement of existing REMS on a routine basis. This would provide valuable input to ensure the REMS is effective, has not caused undue burden, and addresses the need of the various practice setting REMS drugs must be obtained and administered, while continuing to safeguard our patients.

So in conclusion, ASHP appreciates

the opportunity to comment and participate on the further improvement of REMS programs and we appreciate the FDA's efforts to engage stakeholders in the process.

Thank you very much.

MS. TOIGO: Thank you, David. Next we will hear from Mary Jo Carden of the Academy of Managed Care Pharmacy.

MS. CARDEN: Good afternoon. My name is Mary Jo Carden and I am the Director of Regulatory Affairs for the Academy of Managed Care Pharmacy.

AMCP would like to thank FDA for hosting this meeting today and tomorrow to continue to improve the REMS process. And we are particularly thankful that over the years FDA has reevaluated existing REMS programs, particularly those with Medication Guide only and released some of those REMS because they were overly burdensome. This is particularly important to continue as programs become more complex, based on new medications and

particularly specialty medications that are introduced to the market. And as biosimilar come onboard, we will have as an industry and as patients, to look at those medications and look at REMS and look at other means to ensure safe and effective use. So continuously examining REMS programs and determining their efficacy is continually important. AMCP members play a big role in managing REMS programs, particularly in the specialty area.

Today I will talk about the impact of REMS on the responsibility of managed care pharmacies. This is true of many pharmacies. And, as already stated, there are ways that this can be streamlined, the REMS process, to ensure that workload is appropriate but also to ensure that REMS programs and REMS protocols actually improve patient outcomes and patient safety.

We also provide recommendations for standard electronic processes to ensure consistency when implementing REMS programs.

And finally, AMCP will provide recommendations for integration into the healthcare system. One of the biggest areas that AMCP believes is important for REMS programs is to evaluate actual patient health outcomes and if the REMS program is actually having an impact on positive patient care and overall improvement of healthcare in this system.

We have already kind of discussed the issue of the primary role of pharmacy. Oftentimes, the pharmacist and the pharmacy are the last entity to touch the medication and to interact with the patient. And as a result, the pharmacy has quite a role in interaction with patients and in administering the REMS program. This can result in a burden in some cases if in fact REMS programs are duplicative of utilization management tools that are designed to ensure that patients receive appropriate medications. In some cases the REMS programs may be duplicative of those and, therefore, it is important to

evaluate whether or not the REMS program is actually effective or that other means implemented by managed care organizations and other entities for ensuring patient safety can actually be better.

And of course, as discussed, this results in administrative and financial burdens for pharmacies that should be examined and should be streamlined as REMS programs evolve.

AMCP would like to recommend a standard electronic process for REMS programs but not recommend a single regulatory approach for REMS programs design. AMCP understands and appreciates the need for a streamlined workflow in the pharmacy for managing REMS. However, as mentioned previously, a one size fits all approach for a REMS protocol may not be effective for drugs that we have yet to see and those in the future. And therefore, a rigid regulatory standard would make compliance more difficult as these new

approaches evolve.

I am not going to explain this slide. As Carolyn Ha mentioned, tomorrow there will be quite a bit of discussion on the NCPDP standard. This is an illustration of it that will be integrated into electronic health records and into pharmacy systems that can manage and help manage the workflow and allow pharmacists to interact clinically with patients and better understand the REMS protocols so that they can in fact communicate that information with patients.

And finally, AMCP would like to recommend that managed care organizations that have access to rich data, patient data, as well as access to patients themselves and particularly in the issue of specialty pharmacies to conduct research both that is required by the FDA.

As mentioned previously the Office of the Inspector General has noted that FDA has not completed the federally-required

evaluations for most drugs with ETASUs. AMCP believes that managed care organizations can help in this process and also more importantly, that managed care organizations can take data and analyze it. The data is out there. It is existing. And we can analyze it and look at how REMS programs are affecting outcomes overall, which is very important in today's new marketplace.

So thank you very much. AMCP looks forward to continuing to work with FDA on the REMS program.

MS. TOIGO: Thank you, Mary Jo.

Our next presenter is Lindsey Kelley from the University of Michigan Health System.

DR. KELLEY: Hello. Thank you all for allowing us the time to speak this afternoon and we will try and move you along as quickly as possible.

My name is Lindsey Kelley. I am a pharmacist and an administrator at the

University of Michigan Hospitals and Health Systems as well as Cancer Center in Ann Arbor, Michigan.

I have experienced David's 6:00 p.m. call for we have a REMS drug and how do I get that to a patient. I am speaking to you on behalf of myself in that role as well as University Health Systems across the nation as we look towards how we solve this problem and the best way to move forward.

The impact of Risk Evaluation and Mitigation Strategies as well as their standardization and limited distribution on hospitals and health systems is important. And it is important to the patients we care for. And it is important looking forward into the future at accountable care organizations and how we make those successful.

When we think about academic medical centers and the types of patients that we care for, they are complex patient populations. They are patients who often have

high illness severity and they are patients who are often recipients of specialty medications and the medications that have REMS requirements. And although many of the medications that received those REMS requirements are tested in our university health systems, once those drugs are approved, we do not have access to those medications. We are denied access to provide the care and, as JoAnn spoke to earlier, these medications, even though we have the ability to provide that safe care, we can access the medical record, we have developed protocols within our health systems to ensure that patient's safety, we simply cannot get the drug or we are creating or taking part in a duplicative process just so that we can gain access and provide that care.

These can be due to a REMS program through the manufacturer. It may also be due to payer carve-out contracts because of the cost of the medications. And either way, this

creates a fragmented care system and it makes it difficult for patients to navigate as they try and make their way through.

Academic medical centers are uniquely positioned with a highly qualified and well-trained workforce, including pharmacists and nurses as was alluded to earlier. And we are able to take care of these patients.

When we think about the considerations of REMS, and I want to make sure that we focus on the solution and not too much on the problem, the considerations are a logistical burden in the unintentional fragmentation of care. When I think about what this means on the patient perspective -- we have a cancer center at the University of Michigan. It is a nationally recognized comprehensive cancer center. It provides to patients in a very well-equipped system.

We created an entire program around oral chemotherapy as one example of

REMS and how they impact our care. The focus of that program was to review the treatment that was prescribed to the patient. It was to look at the profile and ensure that it was safe and appropriate, and then to provide education and communication, very similar to what these programs are trying to do themselves.

When we looked at what quality that was impacting, we looked at adherence. We looked at patient knowledge. We looked at communication. Most importantly, we looked at safety to our patients. We put together a proposal to do this in a standard way for all of the patients coming into our health system. We took it forward. We got it approved. And at the end of day when that program was approved, we were spending seven hours of every workday working through the access components for those patients. Seven hours of every workday, a pharmacist was figuring out how to gain access, how to get a patient able

to provide it or pay for it, and simply just getting access to the drug in a way that didn't delay therapy.

To me this is troubling and so when I look at this, I want to focus on solutions that solve that problem for our patients and for our providers and health systems.

When we think about the logistical burden, additional record keeping and storage is something that we have talked about and I fully support any electronic method or centralized system that would decrease the burden this puts on our health systems.

When we think about the requirements that our colleagues of NCPA have talked about in terms of state requirements and the national requirements that we are already encouraged to meet and forced to meet, the additional record keeping can be burdensome.

When we think about the

certification of pharmacists, I agree with my colleagues that we are already medication experts and that there really is very little role to certify an individual pharmacist. And I would support us moving towards some kind of system that certifies a group or a system of pharmacies so that we don't have to go through these for individual pharmacists, thereby limiting the access a patient has.

When a patient comes into our system, we have three pharmacies within the University of Michigan. That patient may come to any of our pharmacies. And in certain instances, we are only allowed to provide a medication or to provide certain education requirements out of one of our three pharmacies, although we operate out of a pool of pharmacists and we fulfill all the requirements based on a health system stance and perspective.

Because of the REMS requirements, we can only send that patient to one pharmacy.

That patient must go there. And for our patients, many of them have access issues in terms of transportation and that may be a problem.

When we talk about access to medications and the inability to procure these, I have spoken a little bit about the logistical burden but it also has incredible impact on patients in terms of confusion and frustration.

As an example, there was a medication recently released that was for multiple myeloma. The patient was seen in our clinic, in our cancer center clinic. The provider identified the therapy as being appropriate and sent the patient home with a prescription for this medication. The medication that the patient needed was not able to be procured from the pharmacy the patient went to. The patient was given the prescription back and said you need to go through a separate process. There are only

certain pharmacies where this medication can be provided to you.

And while I understand the REMS and I appreciate the safety and that patient safety is paramount, from that patient perspective, I don't believe that they are truly being served. They are confused and they are frustrated and they don't understand. And I think we can do a better job.

Let's assume the pharmacy had access and was able to get that drug, as one of ours does. They come down, the patient gets the drug. Well what happens when that patient is admitted to the hospital? We can no longer provide that drug from an inpatient stance. It is only given in that one outpatient pharmacy.

And for many university health systems across the country, this is a very real situation. At that point, we turn to the patient to coordinate their own care. We say to the patient, we cannot get this drug for

you and you need to bring in what is called patient-owned med. You bring it in and we provide it to you out of your own supply.

You can imagine from a patient perspective and from a healthcare perspective that we can do a better job in their eyes. And I would tend to agree.

So access to these drugs has a crucial impact on our ability to provide care to these patients and to impact the decrease in delay for their care.

When we think about the actions we can take, REMS must be standardized in all instances where possible and appropriate. And I would agree with the statements regarding process versus any other approach. Anytime we can make it easier through a standardized approach, I agree.

Additionally, it is crucial that hospitals and health systems, in particular university health systems have access to limited distribution drugs where we can

provide a safe and meaningful care for those patients in a way that is very similar to what the REMS themselves are trying to approach.

In 2010 an NCCN white paper stated that as the new REMS paradigm developed that practical implications of the policies and processes must be carefully considered so that REMS are implemented in a feasible manner that allows patients to have access to innovative drugs and biologics. And colleagues today have stated the same thing. This statement has never been more relevant than today.

A gentleman earlier recommended better patient access. And the colleague just recently from NCPA talked about the importance of existing and trusted relationships with pharmacists.

We believe that in university health systems, pharmacists are highly qualified without certification. They have meaningful dynamic relationships with both patients and providers and we collaborate to

communicate a cohesive and similar message to patients around their medications. We understand and we have access to the data that is needed to care for and monitor safely for our patients these medications.

Our access to these drugs is crucial and the reasonable standardization is imperative.

Thank you for your energies so far to the FDA and to all of my colleagues in the room. And thank you for the work that you are doing now.

You will hear more from a colleague tomorrow from UIC regarding a process that they have implemented there. In addition, the University HealthSystem Consortium has a voluntary committee that is focused on solving these issues for university health systems. They have developed an approach and I would be more than happy to submit their approach to the docket for your consideration. I think it is a reasonable

approach for university health systems.

Again, thank you for your time.

MS. TOIGO: Thank you, Lindsey. And yes, I encourage you to submit that to the docket.

Our last speaker today is Katie Stabi from the Cleveland Clinic.

DR. STABI: Good afternoon My name is Katie Stabi and I am the REMS Drug Information Pharmacist from the Cleveland Clinic Health System.

I oversee the implementation and management of REMS programs in our inpatient and outpatient pharmacies and I assist with it with our outpatient clinics.

I would like to thank the FDA for allowing me to address questions posed in the REMS tools in dispensing settings.

The Cleveland Clinic Health System is primarily located within Northeast Ohio but has facilities in Florida, Nevada, and internationally. Our 44,000 plus caregivers

care for thousands of patients annually in our hospitals and clinics. For your reference, I will be addressing these following topics posed in the Federal Register.

The caregivers at the Cleveland Clinic are able to provide care to a large number of patients, due to our integrated healthcare system. Our 1,400-bed main campus interacts with our nine community hospitals, over 170 outpatient clinics, and 15 outpatient pharmacies. Since each of these areas has access to the patient's medical record, they are able to better communicate and provide care through each transition of care.

When REMS programs restrict use of medications in any of these areas, it can become more difficult to ensure complete patient care. This is why REMS drugs are better managed within a healthcare system and should not be restricted.

One of the questions posed was whether or not individual pharmacies should be

certified or if health system certification should exist. This health system certification would be of great benefit.

These benefits include managing patient care within a system in which all caregivers have access to the patient's medical record. This can increase patient safety. Contraindications to medications, drug-drug interactions, and disease state concerns can be easily identified.

This is opposed to a patient filling one prescription in an outside pharmacy that does not have access to any of the patient's medical record. A health system certification would increase access to restricted REMS drugs. I have a detailed example on the next slide that displays this.

A single certification for health system would also decrease the current burden of REMS programs. As of right now, I enroll 25 pharmacies in a REMS program when this is a requirement, just because the health system

certification does not yet exist.

One concern with the single certification system is if one pharmacy is found noncompliant, it would mean that every single pharmacy within that master certification is noncompliant.

We would want to limit the possibility of a medication to be removed from all pharmacies just because one pharmacy was potentially noncompliant.

I do have an example of a patient that could have benefited from a health system certification. I do not want to name the specific REMS program, so some of the details are vague.

We had a patient that ran out of a restricted distribution REMS drug. Since this drug does require specific laboratory monitoring, the patient saw the physician in the office to have the medication refilled. Our outpatient pharmacy is attached to this physician office and did have access to the

patient's medical record.

The pharmacist was able to verify that all the REMS requirements had been met. However, the pharmacist could not fill the prescription because the prescription is not stocked in that pharmacy. However, the medication is stocked in our inpatient pharmacy, which is in the attached building.

The REMS program was called to discuss what could be done for the patient to receive his maintenance medication. The pharmacist was advised by the REMS program that no dosage should be dispensed from our inpatient pharmacy. Instead, it was advised to admit the patient for care in order to receive their maintenance therapy or to have them go without until the pharmacy that only carried this medication could actually fill the prescription after verifying the REMS requirements and ship the drug to the patient's home.

If a single certification was in

place that enables all pharmacies in an integrated system to have access to a drug, this patient would have had immediate access to the medication that was needed. And this could potentially prevent costly hospital admissions in order for patients to receive maintenance therapy.

For your reference, I have summarized my main points on this slide but in the interest of time, I will move on.

Standardizing REMS is a difficult task, since there are so many different patient scenarios that must be addressed. Currently, most REMS programs address outpatient scenarios and leave the inpatient management open to interpretation by the hospital designee. It would be very helpful to create standardization or require REMS programs to address inpatient and outpatient processes. Similar to what everyone has been speaking to, the TIRF share system REMS.

Also, the burden of the REMS

requirements on the dispensing setting should be considered. We are very much familiar with the iPLEDGE program and REMS programs that have similar prescription window requirements.

The iPLEDGE program is used as an example for restricted access and burden for inpatient dispensing. This program explicitly states that inpatient pharmacies are able to dispense the medication but the pharmacy cannot dispense a partial prescription or break the blister pack. This process is burdensome for inpatient dispensing, since we write orders and not prescriptions for a 30-day supply and we dispense doses individually that are unit-dosed for patients.

Due to these requirements, we have a process in place for patients to provide their own home therapy. This can create a challenge if the patient does not have the drug readily available. Therefore, it would be helpful if REMS programs considered the different dispensing settings and therapy

initiation versus continuation when creating REMS tools and processes.

For example, if a REMS program is in place that requires monthly monitoring and a certified prescriber is required for outpatient use but is also required for inpatient prescribing, it would be helpful to allow an non-certified prescriber order the medication for an inpatient admission when all documentation of the REMS program's requirements have been met. This could prevent a delay of therapy while a certified prescriber is being found within the hospital system to assess the patient and order the drug.

The REMS requirements also need to be transparent. For example, a REMS program states a drug must be logged each time it is dispensed and the pharmacy must report to the REMS program daily. However, when the REMS program is called, the caller is informed that this requirement is only for the outpatient

pharmacy and not the inpatient pharmacy.

There are several challenges of potential authorized dispensers to obtain access to drugs and provide care for patients. Our outpatient pharmacies very often ask a specialty pharmacy, since they are in a specialized physician clinic. Medication that have similar REMS programs, such as Thalomid, Pomalyst and Revlimid are not all available at our pharmacies but some of them are. Therefore, requirements for access should be standardized, especially when programs are so similar.

As I discussed previously, sometimes inpatient pharmacy has access to the drug but due to the dispensing requirements, is not able to provide the medication to the patient.

Another frustration is that REMS programs have outlined pharmacy enrollment requirements. However, it does not always allow pharmacies to enroll in the program and

have access to the drug. This emphasizes the requirements need to be transparent and addressed by dispensing setting.

Our primary concern about difficulties obtaining and dispensing a restricted REMS drug is when access is permitted to select hospitals. There is currently a trial program for a REMS drug that allows pharmacies to stock the drug for new starts only. This can create an ethical dilemma for the pharmacist who is not able to dispense the drug to a patient for continuation of therapy, despite documentation of all REMS requirements because the patient may have left the drug at home. Instead, therapy is to be delayed for this patient until an emergency supply can be received by the specialty pharmacy.

In these situations, it would be best if medications were made available to hospitals to care for all patients. There also needs to be exceptions addressed in order

to best care for patients.

Tikosyn is a medication with many safety concerns and the REMS programs really does address these concerns well. However, there is also a patient safety concern if more than two doses of this medication is missed, in which case, the patient would then have to go through re-initiation of therapy, which is a three-day hospital admission.

By allowing an exception in this case when a patient may have not taken their doses at home and a certified prescriber is not readily available on-site, it would be appropriate to let a non-certified prescriber continue therapy and have a certified prescriber follow-up as soon as possible. This could potentially decrease medication delays and unneeded increased lengths of stay.

And once again, I have summarized my main points on this slide for your reference. The effectiveness of REMS can be improved and burden-reduced by interfacing

REMS programs with existing technologies. Currently, it is up to each dispensing setting to create processes to ensure REMS requirements are met before dispensing a drug. We have heard several places explain what their process is and one of the examples that we have done in the Cleveland Clinic includes creating a list of all of our certified prescribers in our system so that pharmacists do not have to verify and look up at each REMS program the requirements that the prescriber is truly certified.

It would also be helpful to have all REMS information accessible in one location, as opposed to individual sites having to store forms and verify patient and prescriber enrollment. A centralized online database that stores this information could be a possibility and only accessible by registered prescribers and pharmacies. Overall, information needs to be more centralized.

My current process to find information includes starting with the FDA website, then calling the REMS program, and finally -- starts with the FDA website, excuse me, and then the REMS program's specific website, and then I will call the REMS program for clarification. It is not uncommon to find contradicting and missing information between these three sources. This causes frustration and burden to the dispensing setting because these requirements really should be more straightforward, since REMS programs are here and designed for patient safety

And finally, it would be helpful to have more shared system REMS for programs with similar requirements. An example of this includes a centralized clozapine registry instead of each manufacturer having their own registry.

To conclude, I believe REMS programs should be standardized based upon the dispensing setting. This includes inpatient

versus outpatient and sometimes initiation versus continuation of therapy.

Patient care should be maintained within a healthcare system and a single certification may assist with this. Access to REMS medications need to be increased and technology should be better utilized.

Also, a centralized website or database would decrease burden on the health system, as well as increasing the number of shared systems REMS that have similar requirements.

And thank you for your time.

MS. TOIGO: Thank you, Katie. So we have about ten minutes or so for questions from the FDA panel. Anyone to start? No questions? Adam, I know you have a question.

(Laughter.)

MR. KROETSCH: So a few of you mentioned challenges getting access to medications for drugs with REMS. And I think I heard a few words or terms used restricted

distribution, restrictions, limited distribution. Could I get a sense of what exactly do you mean when you say that as far as what are the challenges that are preventing you from being able to obtain those drugs? What kind of barriers are you running into?

DR. KELLEY: I'll go ahead and start and then I suppose Katie will have something to add.

At least for us within our health system it can mean a variety of things. It can mean that we can't get the medication through our primary wholesaler, as JoAnn spoke to earlier, so we have to go to a separate wholesaler. That wholesaler may have its own accounts that we have to create, which may take time to set up. It may be an entirely different distribution process or distribution center that we would have to receive the drug from and so that may delay patient care. I would say that is probably a good instance.

In other instances, it may mean

that we do not have access to the drug; that they only provide it to a limited number of sites throughout the country and that we would have to either send our patient to that site or wait for that site to coordinate with us, which some sites do.

In the worst case scenario, a patient would have to then mail their prescription to the site and wait for the site to return the product to them or get it from the manufacturer directly.

MR. KROETSCH: Thanks. And do the others who mentioned those sorts of issues, is that generally what you have experienced as well?

MR. NICHOLSON: Yes, what we experience when I refer to patient access issues or restriction distribution, specifically we are referring to products, medications that are only available to certain locations, certain pharmacy sites throughout the country. One of the main components of

the REMS is that it is only available through a certain wholesaler to certain pharmacies.

MS. TOIGO: Mwango?

DR. KASHOKI: Yes, I would like some clarification. I think an assertion I heard a couple of people make that with regard to individual pharmacist certification there seemed to be an assertion made that pharmacists are highly trained, they are highly capable, et cetera. It may not be necessary to certify the individual pharmacist but maybe the pharmacy or even if we go a level higher, the system in which they are practicing.

So I would like some information about what specific aspects of the pharmacist training and/or way in which they practice are indicators of sufficiency that certification may not be needed. Because you could make that argument, I guess, of all healthcare providers.

And this is coming from a

perspective of trying to understand when would a REMS with all of its various interventions be needed. And so if we make the assertion that a REMS would be needed when benefits outweigh risks because we are making an assumption that either the way the drug will be used, where it will be used, who it will be used by will not be sufficient to manage the risk.

And so I am coming back that to what I heard was the assertion that no, you may not need to certify us as part of a REMS intervention because we already know, we are already doing. So I would like some more information about what are the indicators because that would inform our thoughts about when would a REMS be needed or a specific intervention needed.

MR. NICHOLSON: I'll jump in first. This is Kevin with NACDS. As a pharmacist myself, I personally having practiced as a pharmacist for a number of

years, pharmacists are trained. They go through extensive training. Right now pharmacists are required to go through a minimum of six years of education, many of that is clinical rotations and very detailed information on drug, drug use, drug risks, drug benefits. And I would -- there really are no other healthcare providers in the healthcare system that are trained on the level of drug, prescription drug, pharmacokinetics, contraindications, indications than your pharmacists.

And so we don't really see any additional certification -- we don't see that certification would provide any additional benefit to the healthcare system.

If there are specific elements within a REMS that require pharmacists to do something in particular, then the chain pharmacies, they will set up systems in the pharmacies, within the pharmacy operational system either operationally or within the

technology system to make sure that those steps are taken.

So while there may be within REMS a necessity to make sure that certain steps are taken, we feel that the base knowledge that that pharmacist comes out of school with -- pharmacists are also required to take continuing education. And just by virtue of the fact that they work with these medications -- work with medications on an ongoing basis and it is part of their professional duty to make sure that they are current on the latest therapies.

So again, we feel that they -- again, while there may be processes and steps, checks that make sure that there are certain procedures that they follow, we feel that pharmacists have the -- they come out of school with the information that is required in order for them to practice but also they also have the aptitude to grow with their profession and making sure that they are

certified for what particular medication or another particular medication really doesn't provide any additional benefit.

MR. CHEN: David Chen, ASHP. And I will just add to that I would agree. At the end of the day, pharmacists are medication use experts and I think that every drug that we handle has the potential to have unintended, undesirable outcome. I think that the challenge that you have heard through this whole day today is that REMS addresses significant drugs that have higher risk. Some of the challenges that we face are just all the various administrative burdens. But at the end of the day, pharmacists, what we do in evaluating the safety monitoring and appropriate dispensing practices is what we do with every medication.

And so I think the other elements to help ensure that certain steps are taken because they are known to help improve, if the evidence is there. That is the other thing we

are asking is if the evidence is there that certain additional steps will help improve better management across the continuum of drugs. I think that is definitely a plus through the REMS process. I think that would be an additional administrative burden on top of all the other pieces of administrative requirements for documentation with a profession where that is what we do with every medication we handle is make sure that it is handled, safely, effectively, and appropriate for our patients.

MS. TOIGO: Other questions? So I have one and I don't remember whether it was Katie or Lindsey that mentioned the University Health Systems Consortia. Could you elaborate a little bit on that on what that is?

DR. KELLEY: Not being a paid representative of UHC, I will do my best as a member.

The University HealthSystem Consortium is a group of academic medical

centers that belong to -- it doesn't serve just pharmacists but much larger, the academic medical centers as a whole. They provide many services.

The one that we are currently involved in as it pertains to this is a subcommittee of UHC focused on how we successfully navigate the waters that REMS has created within the health system. One of the ideas that we have brought together centers around the idea of consistent care across all of the health systems throughout the nation in a way that would provide a certification somewhat like a systems-wide REMS and allow us to meet the needs of the manufacturers in terms of postmarketing surveillance but also allow us to provide the care to our patients.

I think the unique components of the UHC members or of any academic medical center or hospital and health system is the access to the electronic medical record and our ability to leverage that, to look at

postmarketing data and to furthermore utilize that to do research was mentioned by some of my colleagues on the outcomes of those medications to ensure that the REMS are meeting the means that we have set them out to do.

The organization itself is, again, beyond my scope. But that is the role of the committee that we are on currently.

MS. TOIGO: Thank you. I didn't catch the committee name. So that is very helpful. There is a group that if we are looking for some listening sessions, it sounds like it would be a good group for us to set up a listening session to get some better detailed information.

DR. KELLEY: Absolutely. We would be more than happy to help.

MS. TOIGO: Thank you.

Claudia.

DR. MANZO: So I heard recommendations that rather than certifying

individual hospitals or settings that an entire health system would be certified. And I think to some extent we are attempting to minimize burden by eliminating some of the requirements on the inpatient setting side because in those types of settings patients are monitored very closely.

So now I guess we are hearing a little bit more that that causes possible access problems and it increases burden with regard to having all those different sites and roles.

So I guess I am just wondering how a healthcare setting could carry out the requirements of both the in and the outpatient setting. On the inpatient setting we usually have one person who is the authorized representative that would ensure that all of the sites -- all of the other staff were aware of the requirements. How would this occur in a hospital system?

DR. STABI: I guess I will start.

So my position, Katie Stabi from the Cleveland Clinic, is I am the REMS pharmacist for the whole health system. In other words, I was specifically hired to help manage the REMS programs for ten hospitals and our outpatient pharmacies.

And so every time a new REMS program comes to fruition, I have a process in place to review the REMS program and make sure that all of our pharmacies are enrolled if that is needed. That education is sent out to all of our pharmacists or the specific prescriber groups, as needed.

So with the health system certification in regards to access is that since there isn't one certification, our inpatient pharmacies kind of have one set of rules and our outpatient pharmacies have another set. And so my thoughts with the health system certification is to kind of blur those lines a little bit and we would all have access to the medication.

Because right now, sometimes our outpatient pharmacy can have it but our inpatient pharmacy is not allowed to stock that medication, and vice-versa.

MS. TOIGO: Megan and Gary, and then we are done.

(Laughter.)

MS. MONCUR: Let's see, I think my question is for Katie.

David mentioned that they had these 12 questions that summarizes kind of the requirements for pharmacists. Do you have something similar? And if you do, how do you develop that?

DR. STABI: I do have something similar. When I first started my position, I actually created a four-page checklist in regards to REMS programs and the different requirements. I have used this when I review a REMS program to see that I am not missing something. So our processes in place include making sure that we know prescribers need to

be certified.

Do I need to update our electronic medical record with alerts for our prescribers? Do I need to create a process so that we can store the patient-physician agreement forms in our electronic medical record?

So I do have that checklist. That is available and I have shared it with other facilities when they have asked. And in regards to that process, that is how I also communicate with all of our REMS representatives, as I call them, a pharmacist at each facility that I work with and each outpatient pharmacy that I have communication with to be able to share the REMS requirements.

MS. TOIGO: Is that something that you would submit to the docket?

DR. STABI: I can definitely submit that.

MS. TOIGO: Thank you.

MR. KROETSCH: And just to butt in for a moment, I think I would want to repeat what I suggested this morning, which is these are the sorts of tools that when you share them with us, it is really helpful. So if you are familiar with other people in your organizations who have tools like this that you would be willing to share on the docket, that would be really helpful.

MS. MONCUR: And Katie, the other thing that I wanted to add, any feedback that you can give us that would help somebody who is in your position more efficiently pull that information, that essential information from a REMS so that we make it easier to convey would be very welcome.

DR. STABI: Yes, I can definitely submit different example and suggestions to the docket. I think what comes with it is just experience of having to implement so many different REMS programs you kind of learn the ins and the outs and the very pointed

questions to ask in order to get the details.

MR. CHEN: If I could add to that, when we built our Resource Center and actually I commend the FDA's web resources are much improved since 2009-2010, it was the struggle of actually even finding where to go in the REMS documents themselves. So our REMS Resource is open to the public. And could almost envision that the portal to answer the question if it actually went to a centralized database once the information was complete, it would just be a seamless environment.

But we have found that those were, at least when we started, sort of the starting point questions just so you can get your head around what you need to do to take care of a patient that was being admitted to a hospital.

DR. SLATKO: So several of you mentioned MTM in your presentations. And we have talked about this internally and contemplated it as a possible innovative approach to providing counseling to patients.

My question is, can you give me a sense of how -- is this becoming a standard practice or is it the exception rather than the rule? Because we are trying to get a sense of what can count on or what can we look at as existing platforms that we can leverage to not disrupt the workflow but rather capitalize on what is already happening.

So give me a sense of if that practice is actually already happening and how extensively it is happening. Can anybody? I can do it sidebar. It's fine. I just was curious.

MR. NICHOLSON: As far as MTM is something that is growing. It is something that the pharmacy profession has taken and is making sure that basically the educators and the profession itself is looking for more opportunities to utilize.

Pharmacists are certainly capable of MTM services. The challenge is that often MTM services are not reimbursed. And so that

is -- so one of our goals is moving towards a system where payers and basically healthcare payers are willing -- you know, understand the benefits of MTM and are willing to provide payment and reimbursement for those services.

So at NACDS that is one of our major initiatives is to work legislatively and otherwise to expand the opportunities for MTM services.

And so with respect to your question on how widespread it is, it is not as widespread as we would like it to be but it is definitely a very high priority for us. And we are continuing to pursue opportunities to expand the provision of MTM services.

DR. SLATKO: Thank you.

MS. TOIGO: Okay, my watch says a little after 4:30.

But looking ahead to tomorrow, the morning session will be mostly presentations on the question in the Federal Register related to projects an then a few speakers in

there that didn't fit in the other panels that will speak there.

Then we will have time for an open public hearing. And if we don't have a lot people who have signed up, we might do some playing with the agenda tomorrow.

We have then two presentations on evaluation. Gary Slatko will talk about -- Mary Willy will talk first about experiences with REMS assessments to date and then Gary Slatko will do some looking forward on REMS assessments.

And then in the afternoon, we will have the evaluation speaker session. And then questions and the evaluation public hearing.

So that is how tomorrow will go. It looks to me like we may end early tomorrow; so if you are trying to do some planning.

So in closing, thank you everyone for a productive day and thank you to our last panel and to all the panel member who actually have to spend a lot of time preparing for

this. And we don't always know until close to the end, close to when the meeting time is, how much time you are going to actually be allotted. So we appreciate the willingness to work with the system and still come and present.

To our participants here and on the webcast, thank you for sticking it out through the day; to FDA panel members for listening.

And nobody held their BlackBerry out, I think. Everybody followed the rules. So good on that. We were attentive listeners from our FDA panel.

And then two special people to thank. For those of you who are presenters you probably through the REMS standardization mailbox, you interacted with Michie Hunt and Randi Clark. But they are much more than the REMS standardization mailbox. They did a lot to keep all the meeting preparation stuff in line and then they actually held the program

together and made sure we all did what we had to do and got done what we needed. So thank you to Michie and Randi and many other people that are not here but a lot of work goes into planning this. And the people do need to be recognize because it is beyond their regular jobs and not with any PDUFA funding that was sort of to accompany this process.

So again, transcription probably available within 60 days. The slides, the FDA slides probably early next week, I would say. It depends. We have to look at them and make sure that they are ready for posting.

But just check the meeting page and we will be sure to get those up. And then lastly, if you want to speak tomorrow, please make sure you sign up.

Actually not lastly because that won't be your last opportunity. The docket is open indefinitely, except we need to hear from you by September 16th if you want us to be considering it for the report or for any of

the projects.

So that is it. Thank you. We start at 8:30 tomorrow. And again, enjoy the lovely weather.

(Whereupon, at 4:37 p.m., the foregoing proceeding was adjourned to reconvene at 8:30 a.m. on Friday, July 26, 2013.)

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C E R T I F I C A T E

This is to certify that the foregoing transcript

In the matter of: Risk Evaluation
and Mitigation Strategies

Before: FDA

Date: 07-25-13

Place: Silver Spring, MD

was duly recorded and accurately transcribed under my direction; further, that said transcript is a true and accurate record of the proceedings.

Neal R Gross

Court Reporter