

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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FRIDAY
JULY 26, 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

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P-R-O-C-E-E-D-I-N-G-S

8:32 a.m.

MS. TOIGO: Good morning, and welcome to day two of our public meeting on REMS standardization and evaluation. Good morning to the attendees in the room, and to those joining us by webcast.

I'm Terry Toigo, and I'm the Assistant Director for Drug Safety Operations in the Center for Drug Evaluation and Research. And I will be your moderator, and I also chair the FDA panel.

So before I start, can I just have a show of hands for people who are new today, who didn't join us yesterday? Okay, so we do have a few, but we'll still do the condensed version of the opening.

Okay, so just some housekeeping, we have two open public comment sessions, one in the morning today at the end of this panel, which we set up to cover standardization for those who want to comment publicly on

1 standardization and didn't sign up for one of
2 the panels. So now is last call for you to
3 sign up for that session of the open public
4 hearing. Or actually, you can do that before
5 the break, which is at 10:30 this morning.

6 Lunch today will be 12:15 to 1:15,
7 same as yesterday, sandwiches, salads,
8 beverages in the lobby, and hopefully they
9 won't run out of Diet Coke, since that seemed
10 to be the big seller yesterday.

11 Next, just to kind of remind you
12 what to expect for today, the purpose of the
13 meeting, again, just to kind of set the stage,
14 is to create a forum for interested
15 stakeholders to provide input about REMS.

16 And specifically, the Federal
17 Register notice stated that we are looking for
18 feedback on standardizing and assessing REMS,
19 and also for suggestions about potential
20 projects that will help standardize REMS, and
21 integrate them into the health care delivery
22 system.

1 And actually, this morning's
2 panel, that's pretty much, based on what we
3 got from the outlines, that's what we think
4 this panel is going to address. They're either
5 going to talk about proposed projects, or
6 they're going to share some things that
7 they've done in their institutions that we can
8 think about.

9 So the format -- yes, and
10 importantly, these meetings meet our PDUFA
11 performance goals. So the format for today's
12 meeting, FDA presenters will begin the
13 evaluation discussion. We did the overview of
14 standardization yesterday, but we'll have two
15 presentations on evaluation this morning.

16 Dr. Willy will go and give us --
17 kind of look back at some of the evaluation --
18 assessments that we've been doing, and then
19 Dr. Slatko will look forward with evaluation,
20 and present some of the thinking that we've
21 been doing related to that. And I encourage
22 you, if you haven't read the background

1 document, to please do so.

2 We spent a lot of time looking
3 back at REMS, and what we've been doing over
4 the past few years, to compile something that
5 we think will be helpful for stakeholders, and
6 it -- the other purpose is to kind of
7 stimulate your thinking, and for us to solicit
8 more feedback through the docket. So we hope
9 that background document will provide a guide
10 to help you do that.

11 So then after the FDA, or our
12 stakeholder panel, actually, they're going to
13 provide input on the questions from the
14 Federal Register notice, and comment on some
15 projects, and then we -- our FDA panel and
16 many other FDA staff in the room, will be
17 listening to the panel presentations, and will
18 be asking questions.

19 We also have been taking notes
20 over the past -- took a lot of notes
21 yesterday, and we'll do some more today, and
22 the intent, at the end of the meeting, is to

1 summarize, high-level summarize what we --
2 what we think we heard from stakeholders. Not
3 -- won't be exhaustive or comprehensive, but
4 we've been carefully listening, and we'll try
5 and do a little bit of a wrap-up at the end of
6 today's meeting.

7 And Gary Slatko chairs the
8 evaluation and the standardization working
9 groups, and so he's -- he's the designated
10 wrapper upper. So, but he's been helped by
11 people providing things that they've heard
12 throughout the -- throughout yesterday.

13 So as you can see from the agenda,
14 we have the two FDA presentations that I
15 mentioned, and then there are 16 stakeholders
16 for us to hear from today, and they're in two
17 panels. And just to remind the speakers that
18 you -- each speaker has been given a ten
19 minute slot.

20 I've looked at some of the slides,
21 and maybe not this panel, but the later panel
22 in the day, there's lots of slides, and I'm

1 going to be curious how people are going to
2 get through it in ten minutes.

3 But again, we are not putting --
4 the microphone will not turn off at ten
5 minutes, but at ten minutes you'll see the red
6 light blinking, and I'll let you go over a
7 little bit, but then at some point I'll kind
8 of give you a little look and ask you to
9 finish up if we go over ten minutes. So that's
10 how we're going to handle that, rather than
11 cut you off at the microphone.

12 And let's see -- last thing, I
13 think -- the room is a little bit warmer now.
14 People were complaining about cold yesterday.
15 We tried to adjust the temperatures. Hopefully
16 it's better for everybody today, but you know,
17 there's some things we really can't control
18 related to the meeting. So we're doing our
19 best to accommodate people's concerns, but we
20 may not get it right.

21 And so if you were here yesterday
22 -- suggested for those that were really going

1 to -- were really cold, to bring your own
2 blanket, because that's about the only thing
3 we can do for cold.

4 So with that, I think we, I want
5 the FDA panel members to introduce themselves
6 so that you know who your listeners are up
7 here, but there are a lot of listeners out
8 there, too. So, Dr. Slatko.

9 DR. SLATKO: Good morning. I'm Gary
10 Slatko. I direct the Office of Medication
11 Error Prevention and Risk Management within
12 CDER.

13 MR. KROETSCH: Hi, I'm Adam
14 Kroetsch. I'm in the Office of Program and
15 Strategic Analysis in CDER.

16 DR. WILLY: I'm Mary Willy. I'm the
17 associate director in Division of Risk
18 Management.

19 DR. AUTH: I'm Doris Auth. I'm the
20 team leader on the Assessment Team in the
21 Division of Risk Management.

22 MS. MONCUR: Good morning, I'm

1 Megan Moncur, and I'm also in the Division of
2 Risk Management.

3 DR. HUNT: Good morning, I'm Michie
4 Hunt. I'm in the Office of Executive Programs,
5 and the project manager for the REMS
6 Integration Steering Committee.

7 DR. KASHOKI: Hello, my name is
8 Mwango Kashoki. I'm the associate director for
9 safety in the Office of New Drugs.

10 Dr. MANZO: Good morning, my name
11 is Claudia Manzo. I'm the director of Division
12 of Risk Management.

13 DR. ARAOJO: Good morning, my name
14 is Chardae Araojo. I'm the deputy director of
15 the Office of Medical Policy Initiatives.

16 MS. LIPPMANN: Hi, I'm Elaine
17 Lippmann, regulatory counsel in the Office of
18 Regulatory Policy.

19 DR. WILLIAMS: Good morning, my
20 name is Marcia Williams, and I'm on the REMS
21 Compliance Team, team leader in the Office of
22 Compliance.

1 MS. TOIGO: Okay, I think that's
2 our FDA panel. So we'll get started. Gerry
3 McEvoy's going to be our first presenter, and
4 representing the National Council for
5 Prescription Drug Programs.

6 DR. McEVOY: Thank you, and good
7 morning. I'm here today representing the
8 National Council for Prescription Drug
9 Programs as lead of their SPL REMS
10 Requirements Task Group, which NCPDP formed in
11 May of 2001. I am one of approximately 1,600
12 stakeholder volunteers that regularly
13 participate in NCPDP's standard development
14 activities.

15 NCPDP is an ANSI-accredited
16 standards development organization that has
17 been working collaboratively with FDA through
18 one of its many workgroups for over four
19 years, in advising the agency of the potential
20 enhancements to structured product labeling,
21 or SPL, that focus on meaningful downstream
22 uses of these data by the healthcare

1 information technology sector.

2 It was from this collaboration
3 that arose the recommendation in November,
4 2010 to investigate the merits of using SPL as
5 the preferred path for capturing and
6 representing REMS data in a highly structured
7 and codified format suitable for automated
8 extraction and incorporation into various
9 electronic applications.

10 Recognizing the critical
11 importance of first establishing a
12 standardized electronic data structure and
13 codification mechanism for REMS data, NCPDP's
14 board designated the SPL task force as the
15 lead for its other REMS activities in August,
16 2011, including all aspects of prescription
17 processing, from the point of prescribing, to
18 ultimate receipt of the drug by the patient,
19 as well as associated authorization messaging,
20 tracking, and reporting.

21 In my day job, I am assistant vice
22 president of drug information at the American

1 Society of Health-System Pharmacists, and
2 therefore, ASHP clearly supports the
3 leveraging of SPL as a means for standardizing
4 REMS data.

5 Beginning with Adam Kroetsch's
6 excellent summary of the role of SPL in REMS
7 standardization at the beginning of this
8 meeting, to subsequent endorsements from other
9 groups yesterday, I will now attempt to
10 summarize in my comments why NCPDP and a broad
11 base of stakeholders believe that SPL is the
12 preferred path for REMS data standardization.

13 Such standardization of data,
14 codification, and structure, is absolutely
15 critical for downstream automated solutions
16 directed at seamlessly integrating REMS into
17 health-system workflow, and greatly reducing
18 the current burden, which is heavily weighted
19 by manual, and often redundant, non-
20 interoperative processes.

21 At the outset, let me clarify that
22 SPL is far more than simply an electronic file

1 of professional prescribing information, what
2 commonly is referred to as labeling, or the
3 package insert.

4 Instead, it has been positioned by
5 FDA to continue to expand into a robust
6 repository of highly-structured data about
7 drugs, and their associated products, that
8 drive a myriad of automated processes and
9 applications, including integrated
10 ePrescribing and prescription processing
11 systems, and alerting, and other safety
12 mechanisms.

13 So again, NCPDP is an ANSI-
14 accredited standards development organization,
15 and the focus on its recommendation for SPL is
16 actually linked to several of its existing
17 standards.

18 So NCPDP currently has three task
19 groups working on REMS. The task group that I
20 lead, that deals with SPL, there's a task
21 force that is looking at its integration into
22 ePrescribing, and finally, there's a task

1 group called the Safe Use Processing Task
2 Group, that's looking at its integration into
3 the prescription transaction process. So all
4 components of prescription authorization,
5 claims adjudication, and reporting standards.

6 The need. There currently is no
7 highly-structured electronic REMS submission
8 requirement. Electronic versions of REMS are
9 simply PDFs, and word processing documents.
10 And while they may follow a structured
11 outline, they are not documents that are
12 readily extractable to drive automated
13 applications.

14 There currently is no standardized
15 granular data structure, there is no
16 standardized coding mechanism, and there is no
17 codified connection with labeling. If you
18 search DailyMed to try to identify drugs that
19 are subject to REMS, you will fail. When a lot
20 of them had Med Guides requirements, you could
21 do a surrogate search and search for Med
22 Guides, and you'd at least find those, but the

1 term REMS is not even used in labeling.

2 And in addition, there's no
3 codified link. And one of the initial steps
4 that could be taken, is to simply add, as a
5 limitation use identifier, that a drug is
6 subject to a REMS. And that currently exists
7 as an opportunity within SPL.

8 There also is no method to
9 electronically and -- identify and extract
10 REMS requirements for meaningful use, and the
11 most important thing is that downstream
12 automated prescription authorization and
13 processing requires highly-structured,
14 codified REMS data to operate efficiently, in
15 a timely fashion.

16 So the proposed solution is to use
17 SPL as a highly-structured, granular mechanism
18 for REMS submission, maintenance, ready access
19 by all potential users, and meaningful use. By
20 applying data format, content, and coding
21 standards. By using SPL access via DailyMed to
22 allow meaningful data extraction, again, by

1 all potential users, including electronic
2 applications developers.

3 And to develop standards focused
4 on REMS requirements verification for
5 transactions, again, in the workflow
6 environment, for seamless prescription
7 processing, claims processing, reporting, and
8 many other functions.

9 Why use SPL? Well, there is a need
10 for incorporation into workflow, and to
11 minimize the burden for prescribers,
12 pharmacies, and sponsors, and others, that SPL
13 could easily meet. There's the need for a
14 reliable, standardized source, with required
15 elements to safely and effectively use
16 medication. Again, SPL would meet that need.

17 REMS information can be extracted
18 easily, automatically, and electronically,
19 from an SPL document, and most importantly,
20 patients and their safety, as well as access -
21 - timely access to REMS, are the most
22 important reason to standardize REMS

1 information to the SPL.

2 SPL is an existing, adaptable
3 standard already in wide use for exchanging
4 meaningful medication information
5 electronically. It's well-suited for highly-
6 granular data like REMS. SPL formatting allows
7 a mix of coding and text, and it's a highly-
8 adaptable substructure.

9 Yesterday, there were a number of
10 comments that if we standardize, we're at risk
11 of losing distinctions, important
12 distinctions, that may exist between one REMS
13 and another. And with SPL, that is not a
14 limitation. It's a very highly-adaptable
15 structure. So if something new occurs down the
16 line, it can be readily accommodated in the
17 structure of SPL as a modification.

18 There are existing mechanisms for
19 addressing issues, best practices, new
20 developments, new needs, standards, and future
21 development. There currently exists effective,
22 publicly accessible data repository, via

1 DailyMed.

2 There is a large cadre of existing
3 expertise and infrastructure to support it,
4 and sponsors have extensive experience in
5 submitting SPL data electronically to a
6 central repository with their prescribing
7 information and other information that's
8 included in SPL.

9 Where can the standard be derived?
10 NCPDP did an initial development of a schema
11 that was drawn from the draft guidance on
12 REMS, and we've been working very closely
13 through NCPDP with FDA, and FDA subsequently
14 identified data requirement gaps relative to
15 the draft guidance that would create an
16 internal database that can be used as a
17 foundation for structuring an SPL REMS data
18 standard. As I mentioned before, SPL is an
19 existing, adaptable, HL7 standard. So we don't
20 have to create something new.

21 Why standardize? Codification of
22 unique components with SPL is a way to

1 organize, standardize, and centralize the
2 content associated with a packaged product. So
3 you can do it all the way down to the NDC
4 level if you need to.

5 And there are some products where
6 the REMS is actually indication specific. It's
7 not tied to a specific generic drug, but it's
8 tied to a specific use within the label of
9 that drug. So again, SPL is well-suited to
10 make those distinctions in an automated sense.

11 It would standardize REMS format
12 and content for electronic submission to the
13 FDA. The standardized granular REMS
14 requirements would simplify integration into
15 ePrescribing applications and prescription
16 processing systems. A standardized REMS format
17 allows easy inclusion within existing
18 standards, and allows automated population.

19 I see that I'm running out of
20 time, so let me skip to the recommendations.
21 So our recommendations -- the benefits are
22 that it will be a more efficient submission,

1 and all of the processing required.

2 And NCPDP wishes to continue to
3 collaborate with FDA in moving this initiative
4 forward, and our recommendations -- this is my
5 last slide -- is to adopt SPL as a means for
6 standardizing and providing central access to
7 REMS data, to designate development and
8 implementation of SPL standardization of REMS
9 as one of the four PDUFA V priority projects,
10 and to designate NCPDP, the National Library
11 of Medicine, and others, potentially as
12 collaborators, to continue the ongoing work.
13 And I thank you.

14 MS. TOIGO: Thank you, Gerry. Our
15 next speaker is Douglas Monroe from Kaiser
16 Permanente.

17 MR. MONROE: Good morning. I'm Doug
18 Monroe. Thank you for the opportunity to speak
19 about approaches to standardizing REMS tools.
20 I'm a drug information pharmacist at Kaiser
21 Permanente, and among my areas of focus are
22 specialty pharmaceuticals and REMS. I have no

1 relevant financial interests to disclose other
2 than my employment.

3 As the largest healthcare delivery
4 system that's integrated in the United States,
5 Kaiser Permanente includes providers,
6 hospitals, 37 of them, positions, more than
7 16,000, nurses, pharmacists and other
8 clinicians, as well as regional health plans.

9 In addition to more than 440
10 pharmacies, we have one Kaiser Permanente
11 specialty pharmacy that serves all of our
12 regions. This map shows the regions served by
13 Kaiser Permanente, extending from here in what
14 we call the Mid-Atlantic region, all the way
15 to Hawaii, which you can see is near Alaska,
16 south of Texas.

17 At Kaiser Permanente, we have
18 experience with approximately 30 REMS, which
19 include ETASUs. Of those, about 16 REMS, with
20 various types of ETASU, involve multiple
21 dispensing sites, and ten such drugs are
22 dispensed by our Kaiser Permanente specialty

1 pharmacy.

2 In the light of our REMS
3 experience, when we evaluated opportunities
4 and barriers for developing standardized REMS
5 tools, we identified several recommendations.
6 I'll mention those briefly, and then focus on
7 one area in particular.

8 First, we look forward to
9 participating in an open, collaborative,
10 multi-stakeholder process to design and
11 standardize REMS tools. We support a central
12 repository for REMS documents and tools. We
13 favor more standardized approaches to
14 training, which could include stepped
15 training.

16 Knowledge pre-assessment would
17 take advantage of us specialist prescribers'
18 existing knowledge, and expedite prescriber
19 training. Pass the test, and go straight to
20 summary and certification.

21 Training should be updated with
22 information from REMS safety findings and

1 assessment results, both of which could be
2 made public, with a goal of sharing learnings
3 and improving safety.

4 REMS protocols should limit the
5 collection of protected health information, or
6 PHI, to the minimum necessary, and that should
7 be clearly stated in the REMS documents.

8 As an enhancement to REMS
9 documents, the use of a summary table at the
10 top of each detailed REMS document could
11 provide easy-to-grasp standard sets of key
12 information, such as who must be trained and
13 registered, what will be monitored, et cetera.

14 And, bolded here for emphasis, as
15 the item which I'll address most specifically
16 today, REMS should explicitly permit existing
17 distribution systems to dispense if they can
18 meet or exceed requirements. That'll be
19 especially important in considering the second
20 set of questions proposed in -- posed in this
21 section.

22 In response to the question, how

1 might health information technologies, or HIT,
2 such as electronic health records, or EHR,
3 pharmacy management systems and electronic
4 prescribing systems be used to integrate REMS
5 into existing healthcare settings, FDA should
6 look at how currently established systems and
7 practices are already developing and using
8 REMS tools in an advanced HIT environment.

9 As an example, Kaiser Permanente's
10 specialty pharmacy developed software
11 additions to our pharmacy information
12 management systems that access electronic
13 tools like EHR documents, and computerized
14 physician order entry, and we call this
15 software SPIMS.

16 Her is one screen shot
17 illustrating some of those capabilities. The
18 pharmacist screen includes the following.
19 Automatic retrieval of lab results, focused
20 display, at the bottom of the screen here. For
21 specified labs, depending on focus drug,
22 highlights and alerts for out-of-range

1 results, and notices to the pharmacist when a
2 lab is due or overdue.

3 In addition, the tool can display
4 diagnosis information, prescription history,
5 current prescription details, prescriber
6 notes, treatment plans, counseling templates,
7 shipping and logistics information, and custom
8 design screens to pull in or document other
9 important information.

10 As another example, refill dates
11 can be automatically calculated to alert
12 pharmacists to check for adherence, for
13 example by calling the patient and discussing
14 how many doses he or she has left.

15 And this can lead to advising the
16 patient on adherence measures, helping
17 patients in managing side effects, beginning
18 the refill process, and all with overarching
19 coordination with prescriber notes, treatment
20 plans, scheduled office visits, because that's
21 where dosage and medications are most likely
22 to be changed.

1 Integrated healthcare systems are
2 designed to deliver coordinated care by
3 linking providers to each other and to
4 patients, across all transitions of care,
5 often supported by HIT systems.

6 This linkage and
7 intercommunication are an integral part of
8 care experience for our members. And patient
9 linkage is vital to our members, as well. Our
10 members are now accessing Kaiser Permanente
11 online tools more than 88 million times per
12 year.

13 We heard yesterday several
14 observations about how limited distribution
15 leads to fragmentation of care when it removes
16 the dispensing and management of a REMS drug
17 from an integrated care system. The point has
18 been well made that interruption of
19 coordination across transitions of care
20 creates new problems for access and safety.

21 To be clear, distribution
22 limitations are not REMS requirements. REMS

1 themselves do not fragment care. Limiting
2 distribution to one or a few specialty
3 pharmacies, however, is usually rationalized
4 as a means of assuring the REMS requirements
5 are satisfied. But when an integrated
6 healthcare system can satisfy those
7 requirements without compromising outcomes,
8 this rationalization is not logical, to quote
9 Mr. Spock.

10 The following shows why this can
11 be important. Let's take the example of a drug
12 approved under a REMS with an ETASU that was
13 required because the drug showed
14 cardiotoxicity during qualifying clinical
15 trials. For example, QT interval prolongation,
16 arrhythmias, sudden death, and so on.

17 If basic ETASU requirements, on
18 the left here, are to assure that the
19 prescriber has completed training, or to
20 provide educational material, then virtually
21 any pharmacy with access to REMS hub can
22 perform that function. However, a specialty

1 pharmacy inside an integrated system, with
2 electronic tools, can provide an advanced
3 level of support for the prescriber or
4 patient.

5 In this example, the pharmacist
6 can check electrolyte balance, verify that
7 recommended EKGs have been done per schedule,
8 and monitor for new prescription drugs with
9 potential interactions, for example, drugs
10 that also prolong QT interval.

11 We're concerned that limiting
12 distribution means removing important safety
13 measures like this, and the result can be
14 lower safety surveillance standards in
15 contrast to the purpose of a REMS. So we
16 recommend that REMS explicitly state that
17 access to a drug or dispensing will not be
18 limited or restricted for healthcare systems
19 or pharmacies that are able to demonstrate
20 they meet or exceed REMS requirements.

21 Finally, on the question of a
22 single web portal, we recommend as part of the

1 standardization of REMS that the source of
2 tools and information about REMS should also
3 be standardized under the aegis of the FDA.

4 An excellent source of information
5 already exists of the FDA site for concise
6 REMS documents, and the most logical and
7 practical solution would be to incorporate all
8 FDA-approved materials into a single
9 centralized resource center, thus eliminating
10 the need for prescribers to find and access a
11 separate sponsor-based website for each
12 medication that has a REMS with ETASU.
13 Simplicity, clarity, and easy access.

14 We see opportunities and
15 challenges for standardization, and we hope
16 our recommendations and illustrations here
17 help to demonstrate how REMS might be improved
18 through standardization.

19 Thanks for listening. I look
20 forward to responding to any questions during
21 the Q&A period.

22 MS. TOIGO: Thank you, Doug. Our

1 next presenter is Yola Moride from the
2 University of Montreal.

3 DR. MORIDE: So good morning. I am
4 here to represent the Council for
5 International Organizations of Medical
6 Sciences, commonly known as CIOMS. So what I
7 will present to you this morning is a summary
8 of the initiative of CIOMS Working Group IX,
9 which is on the practical considerations that
10 the development and application of a tool kit
11 for medicinal product risk management.

12 So what is CIOMS? CIOMS is an
13 international NGO that was created in 1949 by
14 the WHO and UNESCO to facilitate and promote
15 international activities and harmonizations in
16 the field of biomedical sciences. The CIOMS
17 working groups frequently involve senior
18 scientists from regulatory authorities,
19 academia, and the pharmaceutical companies.

20 As part of the activities of the
21 various working groups are the publication of
22 consensus reports, such as the CIOMS Working

1 Group IX. So the scope of the Working Group IX
2 is the consensus report discussing risk
3 minimization tools for managing the risks of
4 medicinal products intended for human use,
5 best practices in the tool development, and
6 considerations governing the potential
7 application of these tools. The publication of
8 the consensus report is expected at the end of
9 this year or early next year.

10 A stakeholder perspective has
11 guided the content of the report that will
12 cover the following areas. Prescriber-directed
13 REMS tools, patient-directed REMS tools, REMS
14 tools and drug-dispensing settings, approaches
15 to standardizing the REMS tools, as well as
16 approaches to assessing the impact of the
17 various REMS.

18 The objective is really to
19 consolidate concepts of risk management tools,
20 and propose their application in order to
21 harmonize the views, and to positively impact
22 the prescriber patient interactions, and

1 globally protect the public health.

2 The goal -- the working group
3 states that the goal of a risk minimization
4 program would be the same globally but using
5 shared systems, although it acknowledges that
6 locally different tools could be used to
7 achieve the same goals.

8 So a brief summary, which can be
9 appreciated through the currently planned
10 table of content. So the consensus report will
11 include introduction, scope, and background of
12 risk minimization, the current landscape, the
13 principles for the identification and
14 applications of risk minimization tools,
15 evaluating and the methods to be used in the
16 evaluation of the effectiveness of risk
17 minimization tools, the governance and points
18 of implementation, stakeholders in risk
19 minimization, current trends and future
20 directions, as well as recommendations.

21 In addition, an appendices, there
22 will be a glossary of terminology, real life

1 examples, survey on broader stakeholders'
2 input, a decision tree for the selection of
3 REMS, risk minimization with vaccines as a
4 specific topic.

5 So as a general comment, CIOMS
6 Working Group IX acknowledges the pivotal role
7 of the healthcare system as a vital component
8 in medicine safety, and recommends that undue
9 burden on such a system should be avoided
10 whenever possible when planning and
11 implementing risk minimization and mitigation
12 strategies.

13 Now from a personal, academic
14 perspective, in my opinion, standardization --
15 two prerequisites are associated with
16 harmonization and standardization.
17 Transparency and highest methodological
18 standards. So transparency, I would urge to
19 increase the publication of results of
20 evaluation of REMS effectiveness, either in
21 the scientific literature or registries that
22 are specifically dedicated for that purpose.

1 From a methodological viewpoint, I
2 also urge to use best practices in mainly two
3 domains: pharmacoepidemiologic research, for
4 example the ISPE Guidelines for Good
5 Pharmacoepidemiology Practices, as well as
6 best practices in evaluative research.

7 And finally, a caution is that we
8 need to avoid that the assessment tools become
9 risk minimization tools themselves, otherwise
10 it biases the assessment. Thank you.

11 MS. TOIGO: Thank you. Our next
12 presenter is Marie Link from REMS Logic.

13 DR. LINK: Hello, and thank you to
14 the FDA. I value this opportunity, and
15 appreciate it very much. I am president of
16 REMS Logic, LLC, and I am a pharmacist,
17 clinician first and foremost. I started in
18 pharmacy 21 years ago, in 1992 with Revco Drug
19 Store.

20 And I have since then gained a
21 wide array of experience across various
22 healthcare settings. Prior to my experience

1 with REMS Logic, I was employed for nine years
2 by University Hospitals of Cleveland, Ohio,
3 and served as their assistant medication
4 safety officer. I was responsible for over
5 24,000 employees and 18 facilities.

6 During that time, I worked five
7 years within the Quality Institute, alongside
8 quality and risk management leaders, as well
9 as those responsible to oversee and publish
10 our national clinical compliance indicators.
11 I have a strong understanding of healthcare
12 data metrics, Joint Commission compliance,
13 CMS, ACOs, meaningful use, healthcare reform,
14 and national requirements.

15 My role reported directly to the
16 leadership, the COO, the chief medical
17 officer, the chief nursing officer, and the
18 president of Quality. To allow an unbiased
19 role and reporting opportunity for
20 improvements in medication safety, I lead
21 large scale standardization initiatives and
22 integration efforts to improve medication

1 safety throughout, and focused on projects
2 impacting 10,000 patients or more annually.

3 University Hospital's 900 bed main
4 campus with six fully owned community
5 hospitals, three joint ventures, 21 major
6 outpatient centers, a revenue of 2.2 billion
7 with 3.1 billion in assets, 93,000 discharges,
8 80,000 surgeries performed annually, and 4,000
9 physician providers, of which I had the
10 opportunity to introduce to REMS requirements.

11 So with that, today I am here to
12 share about REMS Logic, and introduce it to
13 you. It is a centralized web-based portal for
14 all REMS compliance. REMS Logic addresses
15 prescriber, pharmacy, patient directed tools,
16 as well as many well-thought-out suggestions,
17 and requests and concerns that were presented
18 yesterday.

19 REMS Logic is an integrative and
20 facilitative model that accommodates the
21 intricacies inherent with federal laws and
22 requirements. However, it looks at the big

1 picture of what the end goal serves to
2 accomplish, which is patient safety,
3 medication safety, and allows something that
4 is complex to be made manageable.

5 REMS Logic has honed in on a
6 variation -- on the variation that exists
7 among current REMS programs with the clear cut
8 focus to streamline and optimize medication
9 safety through evaluation of quality and
10 effectiveness data to yield an infinite
11 software versions, much like Twitter,
12 Facebook, and LinkedIn, constantly emerging
13 with the market that -- progress in line with
14 healthcare quality advancement.

15 So variability, I want to share
16 first a little bit of the clinical -- what the
17 clinical team has collected to showcase the
18 variability. I had to pick out some things
19 quickly, so to really give a good example, so
20 for 25 ETASU drugs we've broken out -

21 And I have Set A and Set B of our
22 data to share with you, we have 11 patient

1 enrollment forms, 19 prescriber enrollment
2 forms, 14 facility, and you can see the rest.
3 Informed consent forms, seven, informed
4 consent form names, are seven.

5 Set B of the data, counseling
6 documents, eight, appropriate use checklist,
7 six, brochures for patients, healthcare
8 providers, we have ten different brochure
9 names. There are 18 miscellaneous forms, some
10 of which are prescription forms, and then
11 there's just other types of forms. There's 15
12 different form names among them. Thirteen of
13 pharmacy requirements.

14 So from the prescriber
15 perspective, we have 25 ETASU drugs with 163
16 individual requirement details. This is a lot
17 to manage, so how do we effectively do this?

18 This is just highlighting high-
19 level progress over time with REMS changes, so
20 we know that it's quite a dynamic process, and
21 continuing to evolve throughout the years.
22 This is recent, and then we heard yesterday

1 some July statistics that are even not on this
2 slide.

3 So requirements for prescribers,
4 what do they look like? We have all these
5 different components for a prescriber to have
6 to think about on any given day when
7 administering or writing a prescription for a
8 REMS medication, whether it's inpatient or
9 outpatients.

10 We have ten different things
11 highlighted here, and then we get to the
12 healthcare organization and the pharmacy,
13 which we often, even though REMS are
14 prescriber-directed tools, there's a high
15 impact on the pharmacy and the pharmacist to
16 organize all these things, and then ultimately
17 the organization to oversee compliance.

18 So we have medication guide
19 distribution, staff education, verification of
20 compliance by -- of the prescribers,
21 enrollment of the facility, drug ordering,
22 restricted distribution, loan borrow, patient

1 discharge, documentation, and audits. So a lot
2 to think about.

3 So we want to think about
4 standardization, and that's why we're all
5 here. Standardization to improve integration.
6 So what does that mean to the healthcare
7 organization as the whole -- and all the
8 stakeholders here? We need -- and this was a
9 lot relayed yesterday, consistent naming
10 nomenclature for -- for obvious reasons. We
11 can't have seven informed consent forms with
12 seven different names, however they imply the
13 same meaning.

14 Categories. We need defined
15 categories for elements of compliance. We need
16 a standardized format and layout so that the
17 prescriber can -- when they're looking for a
18 specific requirement, if it exists or does not
19 exist, they can reference a specific location
20 to make that determination readily and
21 quickly.

22 We also need, not only prescriber,

1 but patient education options. I agree that
2 they need to be CME and ACPE accredited to
3 really comply with the current standard of
4 expectation by clinicians of quality education
5 that's unbiased.

6 And patient education options
7 should also be more versatile in that they can
8 be quick videos, but not so much reading
9 material that's possibly not understandable or
10 could be misinterpreted, but more in layman's
11 terms.

12 So REMS Logic Technology, what is
13 it? So this is a high-level focus, and I have
14 ten minutes to share, but what we've done to
15 standardize thus far is, on a strategic 30
16 foot thousand view, we have broken out into
17 five categories.

18 We have general drug information,
19 enrollment, education, training and
20 monitoring, forms and documents, and pharmacy
21 requirements. So these are the five categories
22 that we have created for every single REMS

1 drug. So you log in, and this is what you
2 find.

3 So under the five REMS categories,
4 we have what is called a DSQ tool, which is a
5 comprehensive, in essence, checklist, for the
6 drug sponsor or REMS Logic staff, clinical
7 staff, to manage on the back end, and within
8 that, there are 37 subcategories which
9 comprise all the various REMS elements that
10 exist today among the current programs.

11 If you were to answer, yes, to all
12 37 requirements, okay, there's 81 potential
13 details, requirement details, that are
14 attached to those 37 subcategories. So as I
15 showed earlier, we had 163 individual
16 requirements for 25 ETASU drugs. So if you
17 look at all REMS programs together, if all
18 checkmarks were to say, yes, for all 37
19 subcategories, then you'd have quite a large
20 amount of information to go through.

21 However, what we've done is we
22 have created this comprehensive tool to make

1 sure that we've left no question or no stone
2 unturned when we're evaluating a REMS
3 requirement for an individual medication.

4 So what happens is the sponsor,
5 drug sponsor, can log into the system, and
6 they can go in and create the profile for
7 their drug, and it prompts the drug sponsor to
8 go through and answer every question yes, or
9 no, or not applicable to each individual
10 potential requirement that exists today among
11 all the requirements that are out there. And
12 it walks them through all five categories.

13 So on a large scale, what does the
14 FDA REMS Logic -- or REMS Logic look like? How
15 does it work? The healthcare organization
16 enrolls their prescribers on the front end.
17 The prescribers select the drugs that they
18 use. The prescribers are made aware of the
19 requirements, and they're prompted down a path
20 to compliance.

21 The dashboard -- a prescriber has
22 a dashboard for the drugs that they use

1 routinely, so they can have one-click access
2 to whatever forms that they're needed. And the
3 drug companies in turn, on the back end, can
4 manage the drugs that they produce, and have
5 security rights for their medications only.

6 And all of this is facilitated --
7 so REMS Logic is truly a facilitation. Methods
8 to assess efficacy. Absolutely thought of
9 that. We have to have a lot of reports.

10 Ability to verify prescriber
11 compliance will be in the tool trick, and
12 reports, healthcare organization oversight,
13 compliance and non-compliance, drug use
14 statistics, prescriber activity -- and we'll
15 be able to correlate prescriber compliance
16 within -- with national medication error data
17 to ultimately find out if we're successful or
18 not.

19 So in summary, what is REMS Logic?
20 REMS Logic is what TurboTax is to accounting.
21 So it's a simplified tool to manage a complex
22 federal requirement. TurboTax is to accounting

1 as REMS Logic is to REMS. Benefits -- and
2 that's it. That's my contact information, and
3 I look forward to hearing from you.

4 MS. TOIGO: Thank you, Marie. Our
5 next speaker is Catherine Sigler from United
6 BioSource Corporation.

7 DR. SIGLER: Good morning. My
8 name's Catherine Sigler, and I'm senior
9 director of safety, epidemiology, and risk
10 management at UBC. UBC's been working in the
11 area of risk management since 1999, and has
12 been involved with many RiskMAPs and REMS.

13 Today I'm going to make the case
14 that the risk management community, industry,
15 academia, and regulators, have now had enough
16 experience with REMS to be able to come
17 together to create a best practices document.
18 That we are having this workshop is a
19 consequence of our current need for joint
20 discussion with the common goal of shared
21 experience, and a desired result of
22 standardization.

1 To have the most rational
2 approaches, I advocate that we now join forces
3 to document and learn from our mutual
4 experiences.

5 So what is a best practices
6 document? Simply put, it's a collection of
7 knowledge regarding a topic with a focus on
8 consensus opinion. Many of you will be very
9 aware of these two examples of compilations of
10 best practices, both of which represent large
11 group efforts.

12 The first can be found on the
13 website for the International Society for
14 Pharmacoepidemiology, and was written to
15 provide basic principles in conducting
16 observational research. In many ways, it is an
17 embellished checklist of items to be addressed
18 and documented when conducting high-quality
19 pharmacoepidemiologic and other observational
20 research.

21 The second is a very useful book
22 on the many considerations in designing,

1 conducting, and analyzing patient registries.
2 It is particularly useful for individuals or
3 companies whose primary experience lies in
4 clinical trials. The unique considerations of
5 registry designs are well-covered in this AHRQ
6 publication.

7 Today and yesterday's workshop has
8 a goal of sharing information about how to
9 standardize and assess REMS. We are learning
10 from each other and noting patterns. Perhaps
11 now's the time to move beyond meeting
12 transcripts and REMS case histories to the
13 creation of a repository of best practices
14 based on experience. That is, a best practices
15 book on REMS.

16 You might say that everything REMS
17 is quite an amorphous topic. Let's first begin
18 the discussion on the types of information we
19 might keep in a REMS best practices document.
20 It's true, not all -- not one size will fit
21 every REMS. They're quite different. How,
22 then, can we generalize enough to write down

1 best practices?

2 Here's the basic approach I'm
3 advocating. First, aim for a how-to focus with
4 patterns based on experience. We would
5 identify and then rely on lead authors with
6 experience in key topics.

7 As an example, we could ask a
8 project manager who has lived through the
9 design, regulatory documentation, and
10 operationalizing a REMS, to discuss milestones
11 that might be planned to get -- and in
12 particular, ETASU REMS, prepared in time for
13 marketing.

14 For the creation of the book, we
15 would use an approach similar to that of an
16 NDA compilation within a company. That is, a
17 collaboration with review, comment, and input
18 by an experienced multi-disciplinary team
19 guided by a time line.

20 Although I'm referring to the
21 document as a book, as REMS are still
22 evolving, it may be important to create this

1 new book to be more like a living document,
2 perhaps keeping it primarily online, with
3 planned additions and updates. The exact
4 nature of the document would be a topic for an
5 early organizational discussion.

6 Based on our experience at UBC,
7 here's an early draft table of contents. It
8 gives you an idea of the major topics that
9 might be addressed in chapters. To call one
10 out, I would say that drug distribution models
11 are of great importance, particularly in ETASU
12 REMS, whether retail or specialty pharmacy.

13 When still investigational, the
14 timing of decisions regarding how a drug will
15 be distributed might not be recognized within
16 a sponsor's company as being a REMS issue.
17 Certainly there are greater controls with
18 specialty pharmacy distribution than in a
19 retail setting, and these may facilitate or
20 hinder a product's proper positioning,
21 depending on the unique attributes of the
22 situation.

1 A chapter on this topic, including
2 the considerations to be made in REMS design
3 and drug distribution models, would provide
4 readers with important points for
5 consideration.

6 Here's a list of proposed next
7 steps. I will summarize it as, first, a
8 diverse participation from the various
9 sectors, with participation, contributions,
10 and leadership from, again, industry,
11 academia, and regulators.

12 Secondly, it will require people's
13 time, and we may need to find financial
14 support. So certainly, particularly for
15 academia, that would be important.

16 Thirdly, we would identify those
17 who are willing to roll up our sleeves,
18 convene the working group. Fourthly, begin to
19 draft the document, bring it to life with a
20 table of contents, by first agreeing on major
21 topics. And I shared with you just some
22 initial thoughts on that.

1 And fifth, get out a working draft
2 for the working group, and then wider review
3 and comments. As with most projects, getting
4 the timing right, not too fast and not too
5 slow, would be critical. I would like to see
6 that first draft completed a year from now.

7 I'm interested in discussing the
8 level of interest in this project, and will
9 continue to discuss with individuals who are
10 working to design and improve upon REMS. Thank
11 you for your attention.

12 MS. TOIGO: Thank you, Marie. Our
13 next presenter is Frank Gallo, from
14 Pharmaceutical Product Development.

15 MR. GALLO: Good morning, my name's
16 Frank Gallo. It's a pleasure to be here, and
17 I'd like to thank the FDA for this
18 opportunity.

19 Prior to joining PPD, I worked on
20 the manufacture side of the industry, and this
21 presentation is going to talk specifically
22 about multi-sponsor REMS programs, and

1 standardization there. And I -- when I was on
2 the manufacture side, I managed and worked on
3 programs that are now considered REMS. At that
4 time, they were risk management, and then
5 RiskMAP programs. And one of which was the
6 first multi-sponsor REMS program.

7 So we're going to look at,
8 specifically, the challenges around multi-
9 sponsor REMS programs, and some areas where we
10 could create standardization to support
11 challenges being faced by that consortium of
12 companies.

13 So as some disclosures, this is my
14 point of view, not that of PPD necessarily,
15 and not that of the companies that we
16 represent, and we do represent companies in
17 this area, and in clinical research in a range
18 of areas. So that's our financial disclosure.

19 So specifically what we're going
20 to look at it is first of all, the strong
21 trend towards multi-sponsor REMS programs, and
22 then the challenges that are being faced with

1 those programs, and some specific guidance
2 that could be addressed jointly with the FDA
3 to address those challenges.

4 Many of the challenges are clearly
5 ones that the manufacturers need to address,
6 and are addressing on a daily basis on their
7 own, but there are areas where collaboration
8 with the FDA would be helpful with items of
9 standardization.

10 So first let's look at the drastic
11 shift towards multi-sponsor REMS. And I assume
12 everyone here knows what a -- for those of you
13 that don't know, a multi-sponsor REMS is
14 exactly what it sounds like. More than one
15 pharmaceutical company working together on a
16 shared program.

17 So prior to 2011, of the 178
18 products that were on the market under an
19 approved REMS, over 97 percent of those were
20 under single-sponsor REMS programs, and only
21 a handful, less than three percent, were under
22 a single shared system.

1 But if you look at today, there's
2 been a dramatic shift. So over 40 percent of
3 the products with approved REMS are now under
4 a shared REMS program with other companies,
5 and only 56 percent are under single-sponsor
6 REMS.

7 And we see this -- that this trend
8 will likely continue to change, especially as
9 many of the single-sponsor REMS programs start
10 to get generic competition, it'll likely be
11 that the generics and the single REMS programs
12 will become shared programs.

13 So what are some of the challenges
14 that these companies face when they're working
15 together? And again, most of these challenges
16 -- all of these challenges, they address as a
17 working group, the first one of which is, the
18 multi-company communication and processes,
19 right? So you had these multiple companies
20 coming together with regulatory, legal,
21 medical operations, and they have to work
22 across company to plan, develop, negotiate,

1 build, operate, and assess these programs.

2 And they're doing a very good job
3 of addressing this, but that's a challenge.
4 And they're competitors, so they have to be
5 clearly avoiding any antitrust issues. And
6 then once they had them up and running, there
7 are always multiple vendors supporting these
8 REMS programs. And so managing multiple
9 vendors as a consortium of companies.

10 So these are some of the
11 challenges that the companies are facing on
12 their own, but we're going to dig in a little
13 deeper to one area where we believe that there
14 could be more standardization, and that's the
15 impact of subsequent members to a program.

16 So once a multi-sponsor program is
17 up and running, if the new product either has
18 a pending application, or the FDA has
19 determined that they need to now have a REMS,
20 and it is to become part of a shared REMS, the
21 process for alerting the members and
22 integrating that program into a shared system.

1 Some of the specific items where
2 we believe there could be standardization. One
3 is when a -- the notification. So when a new
4 product is -- when the FDA has deemed that a
5 product should join a multi-sponsor REMS
6 program, if there was a standard process for
7 notifying the applicable consortium as well as
8 the individual company, so that there was
9 transparency between the consortium, the FDA,
10 and the company on that notification.

11 And then if the product is either
12 already under an approved REMS, or it has a
13 different individual REMS that has been
14 submitted, the reconciliation process for
15 integrating it into the multi-sponsor REMS.

16 Once that has taken place, the --
17 the second area would be post-launch
18 stakeholder communication. As we've seen with
19 some of the presentations already, healthcare
20 providers and patients, specifically
21 healthcare providers in this case, are getting
22 a lot of information on a number of different

1 REMS.

2 So what would necessitate, for
3 example, a new healthcare provider letter to
4 be added to the program based on the addition
5 of a product, or an edited or revised
6 healthcare provider letter, and when should
7 those be sent? As part of annual mailings, or
8 as companies join?

9 Because as generics are approved,
10 or other brands come on, it's not uncommon for
11 these programs to have new entrance into their
12 consortium. And we need to make sure that
13 we're not burdening or confusing the
14 healthcare providers in the way we're
15 communicating all of these changes as we go.

16 And finally, the integration of
17 the programs into subsequent assessments. So
18 obviously the new product has to be added to
19 the multi-sponsor assessment plan, but
20 depending on when that product joins the
21 multi-sponsor consortium, it may not be
22 practical to include them in that assessment,

1 period.

2 So should there be a standard time
3 period? If a company joins within a certain
4 amount of months before the next assessment
5 period, then they should or should not be
6 included in that assessment. And if that is
7 the case, then are there any intermediate
8 needs required for that specific product.

9 And that concludes my
10 presentation. Thank you for your time.

11 MS. TOIGO: Thank you. Our next
12 presenter is Madalina Chirieac from Biogen
13 Idec.

14 DR. CHIRIEAC: Good morning. My
15 name is Madalina Chirieac, and I am here today
16 representing Biogen Idec. To speak to seven
17 years of experience with our REMS program, for
18 Tysabri in the U.S. And to address the
19 question posed by FDA regarding which project
20 could be carried out to standardize, not only
21 the provision of risk information, but also
22 benefit information to patients.

1 Tysabri is a monoclonal antibody
2 against alpha-4 integrins approved in
3 approximately 70 countries to treat relapsing
4 remitting multiple sclerosis and Crohn's
5 disease in the U.S. It is associated with risk
6 for progressive multifocal
7 leukoencephalopathy, PML, an infrequent brain
8 disease, brain infection, that usually leads
9 to death and severe disability. And therefore,
10 it has an extensive risk management program in
11 place.

12 TOUCH prescribing program is a
13 REMS with elements to assure safe use that has
14 been implemented in the U.S. in 2006. Here are
15 some of the key elements of the TOUCH
16 prescribing program. We have a mandatory
17 enrollment form that physicians as well as
18 patients have to fill out at the enrollment in
19 the program.

20 We have a centralized, or
21 controlled centralized distribution process,
22 which basically allows us to track every

1 single vial that we ship in the United States.
2 We only ship to registered infusion centers
3 that have been educated on the program, and
4 that can attest that they will follow the
5 requirements. And the program also offers
6 educational capability to neurologists,
7 infusion nurses, and the patients, as well.

8 Here are the key tools using the
9 program and the corresponding stakeholders.
10 The enrollment form. The medication guide that
11 is distributed to patients at the enrollment
12 in the program as well as prior to every
13 infusion. The Pre-Infusion Patient Checklist
14 that assesses for new neurological symptoms
15 since the last infusion prior to every dose
16 that has to be administered.

17 The prescribers also have two
18 tools. The reauthorization questionnaire that
19 is filled out every six months for the
20 duration of the treatment, and the
21 discontinuation questionnaire that has to be
22 filled out by the prescribers six months after

1 the last dose of the treatment.

2 All this are basically monitoring
3 for PML symptoms, and we -- and we feel that
4 we actually emphasize a lot the risk that the
5 product -- the potential risks for the
6 product.

7 So we have been conducting REMS
8 surveys, Knowledge, Attitude, and Behavior
9 surveys, typical REMS surveys, every six
10 months for prescribers for entry for the
11 infusion centers, since the program inception.
12 And we collected a lot of data, but we feel
13 that these surveys have some limitations. They
14 are only focused on the stakeholder
15 understanding of the risk of the program. They
16 lack the in-depth stakeholder review, and they
17 are -- they include only the current
18 participants in the REMS.

19 Therefore, we initiated the REMS
20 stakeholder project in August, 2010. The
21 research goals were largely inspired by the
22 FDA public workshop that took place in July,

1 2010, and the project targeted getting insight
2 on better understanding of the level of burden
3 associated with REMS, assessing the
4 effectiveness of tools, as well as assessing
5 the effectiveness of communication aspects.

6 And a lot of the rest of the
7 slides are going to be focused on emphasizing
8 the effectiveness of communication aspects in
9 REMS.

10 I also want to mention that we
11 focused our stakeholder project on the MS
12 population, which represents 98 percent of our
13 patients enrolled in the TOUCH program, the
14 rest of the two percent being the Crohn's
15 disease patients in the U.S.

16 Let me try to give you an overview
17 of the research approach and the methodology
18 of the REMS stakeholder project. Because I
19 think both -- over 700 participants, and I
20 would like to start by saying that, in all
21 phases of the project, we had participants
22 from all stakeholder categories. Physicians,

1 infusion nurses, pharmacists, and patients.

2 Phase one of the program was the
3 qualitative research phase, and it involves 63
4 participants. And the main goal of that was
5 using individual interviews and focus group
6 was to determine the key teams and areas of
7 concerns around the REMS.

8 Phase two was the quantitative
9 phase. That involved 645 participants. It was
10 an online survey that was administered through
11 the participants.

12 And Phase three was a drill down
13 phase where we tried to -- we tried to get
14 more detail on the teams that were identified
15 in the quantitative phase. And that was
16 conducted through interviews, as well.

17 This is one of the largest
18 stakeholder projects that have been conducted.
19 To our knowledge, there was only -- to date,
20 there's only one comparable one in size, the
21 NCCN, the National Comprehensive Cancer
22 Network survey that was conducted in March of

1 2010.

2 An important point to mention was
3 that, in our stakeholder projects, we included
4 TOUCH participants, prescribers, infusion
5 nurses, patients and pharmacies, as well as
6 non-TOUCH participants, which have been
7 provided to us from Quintiles, the vendor that
8 we collaborated with to operationalize this
9 project.

10 Now I would like to focus on what
11 we found out about communication, and what
12 type of information do stakeholders want to be
13 communicated to them from a program like
14 TOUCH, whose primary purpose is to provide
15 risk information.

16 What we found out was that the
17 majority want an equal balance between the
18 benefit and risk information. We asked
19 prescribers and patients, what would be the
20 ideal balance of benefit and risk information
21 for them in TOUCH, and ranging -- that was --
22 the ranging on a seven-point scale,

1 information -- from a desire for all risk
2 information, that is showed in red on the
3 slide -- I'm sorry.

4 So a desire for all risk
5 information, then in the middle column
6 represents the equal benefit and risk
7 information, that's presented in gray on this
8 slide. I know it might be hard to see from the
9 back. And to the right-hand side of the slide,
10 it says, desire for all benefit information.

11 And as you can see, the majority
12 of stakeholder wanted an equal balance between
13 the benefit and risk information. It is
14 presented here only for prescribers and
15 patients, but similar percentages were for all
16 stakeholder categories.

17 Then we wanted to drill down and
18 see how would this change on the specific --
19 on the specific element of the REMS. So we
20 asked the same questions for the enrollment
21 process, and as well as for the infusion, for
22 the infusion process. And as you can see, the

1 majority of stakeholders wanted an equal
2 balance between a benefit and risk
3 communication to be communicated to them.

4 Further, we tried to drill down
5 the question to specific -- to find out what,
6 exactly, what type of information do patients
7 want to receive from a program like TOUCH. And
8 as you can see, they want to receive some risk
9 information, they're higher percentages, but
10 also, they want to see -- receive some benefit
11 information.

12 They want to know if Tysabri is
13 slowing the overall disease progression. They
14 want to know how Tysabri can reduce the flares
15 or relapses. All this are leaning towards the
16 benefit information.

17 Based on our experience and the
18 data presented, we feel it's important to
19 stakeholders to include both benefit and risk
20 information in REMS. This idea of including
21 both benefit and risk information is similar
22 to the informed consent process that has been

1 used in clinical trials.

2 And although there were some
3 discussions about introducing benefit
4 information in medication guides, we feel that
5 we can go beyond that and include it in the
6 enrollment form and other materials of REMS.

7 In order to assess this approach,
8 we are proposing to conduct a pilot project in
9 our REMS program that would have the benefit
10 and risk information communicated as part of
11 the enrollment form, as well as other
12 medication guides, and other REMS tools.

13 The impact of addition of such
14 information could subsequently be assessed
15 using, for example, surveys or focus groups.
16 We would like to engage with FDA to get input
17 and endorsement for initiation of such a
18 project, and I would like to thank the FDA for
19 giving us the opportunity to present this data
20 today. Thank you.

21 MS. TOIGO: Thank you. Our last
22 speaker on this panel is Rebekah Hanson from

1 the University of Illinois in Chicago.

2 DR. HANSON: Good morning,
3 everyone. And I'd first like to thank the FDA
4 for inviting us to present today. I do really
5 appreciate the opportunity to talk about REMS
6 standardization.

7 Little bit about myself, so my
8 current role at the University of Illinois is
9 a clinical liaison pharmacist for specialty
10 pharmacy service. I do have a dual role,
11 however, at the University. This is where I
12 work. It's beautiful.

13 So my second role is I provide
14 clinical pharmacy services to the Pulmonary
15 Arterial Hypertension Service that's part of
16 the Institute for Personalized Respiratory
17 Medicine in the Outpatient Care Clinic.

18 So essentially what I do is I
19 provide ongoing medication management for
20 patients with pulmonary hypertension, and it
21 includes the entire gamut of medications that
22 they use. And that also includes REMS

1 management. So I work with a prescriber and
2 with a nurse to better, and ideally, more
3 effectively, manage our patients.

4 So what I want to talk about today
5 is one health system's idea of creating a tool
6 to better standardize safety management for
7 patients. So we're looking at safety
8 management in general for ambulatory care
9 settings, so this includes medications that
10 have REMS, of course, which is why we're here
11 to discuss this today, but also to manage
12 other medications that may have safety related
13 problems. Those with black box warnings and
14 such.

15 So I'm going to present the pilot
16 project that we are working through right now,
17 and then in addition I'm going to talk about
18 a couple of concepts that could potentially be
19 applied to the larger initiative in REMS
20 management.

21 One thing I do want to say is we
22 are not yet live with this pilot project.

1 Unfortunately, we're working through some
2 contractual issues, and are anticipating to be
3 live shortly.

4 So before I move on, I wanted to
5 mention, I heard a few comments yesterday from
6 a few of the speakers that -- that REMS work,
7 and that to change REMS would be a mistake.
8 Well, I would like to provide a modified
9 comment. I believe that REMS do work for some
10 of the patients some of the times.

11 But unfortunately, there is
12 inconsistency with REMS, and the current REMS
13 programs, the way that they're built tend to
14 promote fragmentation in care, and also
15 restrict -- or, I'm sorry, they actually
16 require polypharmacy to the patient, and most
17 pharmacists know what polypharmacy means. It
18 means a lot of different safety-related
19 issues.

20 So what I wanted to do is provide
21 a few cases. I'm going to speak about them
22 very briefly, because of course I don't want

1 to take up too much time on this, but I
2 thought it would provide a little background
3 that served as our awakening at the University
4 of Illinois to -- to work on the current
5 process that we're working on.

6 So regarding Case 1, this was a 27
7 year old male with sickle cell disease who was
8 seen through our clinic, and the decision was
9 made to start him on ambrisentan, so of course
10 a referral was submitted through the specialty
11 pharmacy process, and it took eight weeks to
12 get the medication initiated and accessible to
13 the patient. And during that time, this
14 particular patient had two urgent care visits
15 because of worsening in shortness of breath.

16 Patient Case 2 was a 56 year old
17 female who was started on Bosentan at our
18 clinic. She came for her four week follow-up
19 visit to do her routine blood work to assess
20 her REMS required labs, and also to assess how
21 she was doing with the medication. Well, we
22 did see some abnormalities on her lab, so a

1 decision was made to continue the medication,
2 but hold the dose at a lower dose. So normally
3 you start at 62.5 and titrate up to 125 after
4 the first four weeks depending on how they
5 tolerate it.

6 Well, we made a decision to remain
7 at 62.5, notified the patient, also notified
8 the specialty pharmacy, and then continued to
9 monitor the patient for a few weeks after
10 that. After two weeks we had her coming in for
11 labs.

12 Unfortunately, about ten weeks
13 into the process, the pharmacy that was
14 dispensing the medication, for reasons that
15 are still unknown, made the decision that,
16 during one of the REMS assessments calls, the
17 dose was going to be increased to the 125, and
18 did so, dispensed the medication to the
19 patient.

20 It was identified during one of
21 her routine follow-up visits, during
22 medication reconciliation, that she was on an

1 increased dose, and we rechecked her labs, and
2 notably, her hemoglobin dropped from 10.4 to
3 9.2 and the medication needed to be
4 discontinued.

5 Patient Case 3 was a 33 year old
6 female with child-bearing potential that was
7 being managed for her pulmonary hypertension
8 on ambrisentan and tadalafil. She presented to
9 clinic one day reporting that she had a
10 positive pregnancy test at home. And upon
11 review of her medical record, we discovered
12 that she was not being compliant with her
13 follow-up for her pregnancy test monitoring.

14 And we also identified and
15 discovered that the specialty pharmacy did
16 indeed talk to her, and did indeed discuss
17 with her the risks of teratogenicity, and
18 asked her if the pregnancy test was completed,
19 and she reported that yes, it was, and no she
20 was not pregnant.

21 So during that time, she received
22 one dispense at six weeks, and then also -- or

1 six weeks pregnant, and also the pharmacy was
2 trying to coordinate that next dispense for
3 her. The medication, of course, was
4 discontinued immediately, and we initiated her
5 on an infused medication, and unfortunately,
6 this patient did pass away related to
7 complications.

8 So what's our reaction to this? So
9 our reaction was very similar to that of many
10 healthcare systems. It's a knee jerk reaction.
11 So what we did was increase vigilance and
12 increase monitoring for our patients for
13 ensure that the medications, excuse me, were
14 not being dispensed until we had validation
15 that those lab requirements and other safety
16 monitoring was done.

17 So of course, this increased
18 burden on the health systems. So herein lies
19 what everybody is referring to as the
20 excessive burden on the health system. So it
21 required additional phone calls, paperwork,
22 documentations. We had to limit prescription

1 refills to ensure that those labs were
2 complete prior to dispensing medication. Of
3 course, we were performing this with no
4 additional resources, with no additional
5 tools, and of course, suffering with continued
6 fragmentation.

7 So what I want to talk about today
8 is what we are trying to do to address the
9 problem, to better manage our patients with
10 these high-risk medications in an outpatient
11 setting. And it was really a two-part process.

12 The first step was to formulate an
13 outpatient medication safety committee that
14 focuses on these high-risk outpatient
15 medications. This is coordinated and lead by
16 a medication safety officer.

17 Now, the whole purpose of this
18 committee was to leverage the expertise and
19 experience of our prescribers who manage these
20 medications every day, to develop safe use,
21 medication specific protocols for managing our
22 patients.

1 And then of course, being led by a
2 medication safety leader, this position is
3 responsible for not only managing the
4 committee, managing the development of these
5 safe use protocols, but then also managing
6 REMS as it relates to outpatient use of
7 medications.

8 So ensuring that the appropriate
9 and proper education and training are being
10 done, and that prescribers and patients are
11 appropriately certified and referred.

12 So there are a couple of areas
13 that we focused on with these safe use
14 protocols. The first one is education and
15 training as it relates to REMS and other risks
16 related to these medications.

17 Also, adherence management. One of
18 the most integral parts of safe use of
19 medication is making sure that patients stay
20 on the medication, and that they're adherent
21 with their refills and their monitoring as it
22 goes along, and also that they're staying

1 engaged with their medication therapy. It also
2 involves safe use monitoring, which includes
3 the required REMS components.

4 We also developed patient-centered
5 disease and medication-specific indicators to
6 be able to assess outcome related to the
7 monitoring. And the whole goal was to improve
8 communication, as well, both in and outside of
9 the health system.

10 And what we did is take these safe
11 use protocols that we developed that were
12 medication specific, and implement them into
13 a tool, a system, to help us improve
14 efficiency and effectiveness with managing
15 these patients.

16 So we took the setting from these
17 protocols, and built them out into a workflow.
18 And essentially what a workflow is is it can
19 be a decision tree, a diagram of processes. It
20 could be a questionnaire with branching logic.
21 And all of those are included within our
22 system.

1 It also might include checklists,
2 just to make sure that certain, certain things
3 have been done prior to the medication being
4 prescribed or being dispensed to assess
5 appropriateness of use. It might also include
6 generated tasks or follow-up management.

7 So it takes some of the burden off
8 of the individuals that are managing the REMS,
9 just gives them a dashboard and a tool to be
10 able to know exactly what they need to follow-
11 up on that day, instead of working on it in
12 more of a reactive basis.

13 And then we also used this as a
14 tool to improve adverse event reporting.
15 Anyone who works in outpatient or ambulatory
16 care knows that reporting adverse events is a
17 problem. And a lot of adverse events go under-
18 reported.

19 So we built in an assessment of
20 adverse events for these patients to ensure
21 that they're being captured, and then the
22 responsibility of the leader, the medication-

1 safety leader, is to ensure that the adverse
2 event reporting is occurring.

3 Of course, we're also using this
4 to manage REMS compliance for our prescribers
5 and our patients. Compliance reporting,
6 measure outcomes related to those disease-
7 specific and medication-specific indicators.
8 And then of course use this to evaluate REMS
9 program data. So being able to evaluate the
10 labs that are captured during, during our
11 safety management processes.

12 Goodness gracious. I'll be quick.
13 I do apologize. All right, so I just wanted to
14 show a couple of screen shots. So this is
15 really the bulk of what our safety management
16 system looks like. This is the case management
17 tool.

18 This is one of my favorite slides,
19 because it's a view to look at the time line
20 of safety management. So this is -- the staff
21 that's doing the REMS and safety management
22 for the patient, doing the appropriate

1 monitoring and ensuring that validation and
2 documentation of the processes -- or of these
3 labs have been completed prior to authorizing
4 a dispense of the medication.

5 And then this is a log function
6 that we're able to generate -- pretty much
7 anything that's entered into the system, we
8 can generate into an external log to be able
9 to improve communication both within and
10 outside the University.

11 So some of the key concepts. Of
12 course, this is not a new concept, you've
13 heard it a few times already within this
14 meeting, to develop an expert panel. So really
15 leverage the expertise of the individuals that
16 manage these medications.

17 And this could be through
18 invitation or application. I do highly
19 recommend that it's a multi-disciplinary
20 committee that engages physicians, nurses, and
21 pharmacists, and of course, absolutely the
22 ancillary support staff that helps manage

1 these REMS.

2 And then also engages industry,
3 pharmacy, information technology specialists,
4 statisticians, and possibly even
5 epidemiologists to be able to assess those
6 outcomes. Could be tied to clinical research -
7 - and I'll go on to the next one -- and then
8 of course a REMS repository.

9 One thing I just want to point out
10 about this is, could potentially use sample
11 workflows for health systems, be able to
12 better integrate this type of material into
13 their system.

14 And then, the use of technology. I
15 know that it's really a big endeavor to say,
16 let's use one system for everyone, but one
17 thing that I did think of is potentially this
18 committee could provide technology roadmaps
19 for people with their different electronic
20 medical records in their system to be able to
21 configure REMS management within their own
22 health system.

1 And this is my conclusion. It
2 summarizes everything I talked about today,
3 and I will wrap it up with these points. Thank
4 you very much.

5 MS. TOIGO: Thank you, Rebekah.
6 Okay, that concludes this panel, and we've got
7 -- we built in extra time on this one for FDA
8 questions, because we thought, based on the
9 slides, there were going to be some details.

10 But I'm planning forward here and
11 looking at what we've got, and I need a check
12 -- did we get any open public speaker -- we do
13 for standardization? How many -- one? Okay, so
14 let's -- let's see how the questions go, and
15 then we can play with the break and the FDA
16 presentations, and a longer break, and a
17 longer lunch.

18 But let's see how the questions go
19 here, and we'll be flexible. So who wants to
20 start? Doris.

21 DR. AUTH: Hi, my question is for
22 Marie Link. I think yesterday I heard several

1 times that the FDA needs to create some sort
2 of central portal, and I think everyone who
3 mentioned that set you up really nicely for
4 your presentation this morning.

5 And I was just wondering, maybe I
6 didn't catch this in your presentation, but
7 would this be something that could be used as
8 a platform for enrollment of patients into
9 REMS processes, into REMS programs, as well as
10 submission of forms and any electronic
11 verification of safe use conditions -- could
12 it do everything that we need it to do?

13 DR. LINK: Yes, absolutely. It is
14 set up -- it's actually built on an API, so it
15 could also accommodate the SPL standardization
16 labeling format, as well as -- it's built to
17 have a -- capable to interface with EHR
18 systems, and push out to the point of bedside
19 care the necessary things that are needed at
20 the bedside, as well as accommodate compliance
21 while not caring for patients directly.

22 DR. AUTH: I guess just a follow-

1 up, what sort of challenges do you anticipate
2 in managing that level of data with -- coming
3 from so many different sources?

4 DR. LINK: I don't anticipate a
5 huge, huge challenge. I mean, the technology
6 is robust and able to -- it's really going to
7 be more of an interactive interface between
8 all the stakeholders, really. So it's a
9 facilitation software engine that can be
10 flexible and dynamic, because we know that
11 healthcare and healthcare reform is not
12 consistent, and that it's every changing.

13 So it's very much a dynamic tool
14 that I anticipate will have, as I stated,
15 multiple versions. And we know, today, that
16 REMS are not where we necessarily want them to
17 be, but we need to enhance them and optimize
18 them to improve safety. And in order to do
19 that, we need to be able to evaluate and
20 assess things in a centralized, very organized
21 manner.

22 So through the audits and reports

1 system, we'll be able to evaluate
2 effectiveness to determine, just like in the
3 FMEA, what are our opportunities to improve,
4 and how do we make changes.

5 So change is anticipated, and
6 actually desired, I think, to really take the
7 big gamut and hone in to something that is
8 more streamlined and more effective for the
9 clinical end user.

10 MS. TOIGO: Mary?

11 DR. WILLY: This is a question for
12 Dr. Chirieac. So you had a presentation that
13 focused on some of the information you've
14 collected in your study in this -- discussing
15 risk/benefit. And I'm looking at your slide,
16 and you said there are other types of
17 information you're collecting.

18 And I'm interested if you could
19 share with us maybe in our docket the
20 information you've collected on the
21 effectiveness of communication, and whether
22 you've learned whether certain forms of

1 communication seem to be more effective, and
2 also what you might have learned about access
3 and burden.

4 DR. CHIRIEAC: Yes, the stakeholder
5 project collected several layers of
6 information, and I outlined them in the slide,
7 but we do have more information. So we would
8 be happy to submit that to the docket.

9 MS. TOIGO: Any other questions?
10 Adam, you were waiting patiently. I saw your
11 hand there, but -- so we'll let Megan go,
12 unless yours was a follow-on to Mary's?

13 MR. KROETSCH: No.

14 MS. TOIGO: No, okay. So go ahead,
15 Megan.

16 MS. MONCUR: Yes, my question is
17 for Douglas Monroe. And you made an
18 interesting distinction in your presentation,
19 and you said, REMS do not fragment care,
20 limited distribution does. And I apologize.
21 I'm paraphrasing. But I'd like to hear a
22 little bit more about that.

1 And also, this is kind of a
2 follow-on to that question, we try to write
3 our REMS where it's a list of requirements so
4 that, you know, if you meet the requirements
5 or exceed the requirements, you can
6 participate. But there still is a gap. And so
7 if you can help us understand what that gap
8 is, as well.

9 MR. MONROE: It's probably good to
10 specify that there are drugs with limited or
11 restricted distribution without REMS, as well
12 those with REMS. Some of those without REMS
13 have minor safety issues, some have larger
14 safety issues, and then there's REMS drugs.

15 With a lot of the REMS drugs that
16 have limited distribution, they might be
17 contracted to be dispensed only by a few
18 specialty pharmacies who do a very good job of
19 meeting REMS requirements. But the part that
20 was troubling to us is that it pulls it out of
21 our system.

22 It's not available to all the

1 providers in our system in the electronic
2 health record, et cetera. They don't know when
3 the prescriptions are being filled. Those
4 prescriptions are not necessarily coordinated
5 with office visits and treatment plans, and so
6 on.

7 The -- within our system, if a --
8 pregnancy testing is required, as an example,
9 the pharmacist does not call the patient and
10 ask if they've had their pregnancy test, as in
11 one of the examples we heard today. The
12 pharmacist calls the patient and says, when
13 are you going to have your pregnancy test
14 done? I see you haven't had it yet, and we're
15 due to refill your prescription next week, so
16 we need you to get in by such and such a date.

17 All of those measures that can be
18 taken because of the connectivity between
19 physician, pharmacy, and all the other
20 providers, plus benefits and every other issue
21 that's involved in dispensing, those are
22 benefits, many of which contribute to safer

1 use of that drug.

2 So REMS requirements might be met
3 by that restricted distribution, but new
4 issues are introduced for us, and some of the
5 advantage of our integrated approach to
6 healthcare are removed. Does that sort of
7 help?

8 MS. MONCUR: Yes, it does. Thank
9 you.

10 MR. MONROE: We have similar
11 problems with drugs without REMS, and we have
12 to deal with those, too. But with REMS it
13 becomes particularly problematic because we're
14 focusing on a safety issue and exacerbating
15 that, or at least removing what we can do in
16 a positive manner is -- is not where we want
17 to be.

18 And we feel that there's a
19 potential there at least to define that
20 systems should not be disadvantaged, that
21 drugs should not be pulled out of existing
22 systems that might integrate healthcare.

1 MS. MONCUR: Thank you.

2 MS. TOIGO: Adam?

3 MR. KROETSCH: Well one quick
4 follow-up to that, we don't want to -- I don't
5 want to pick on any particular REMS right now,
6 but we may benefit if you could let us know
7 exactly which REMS you have these issues with.

8 Because it has been our general
9 policy, it's in our draft guidance, that we
10 would like to make -- we'd like it if REMS
11 would make certification available to any
12 willing dispenser. So if you've identified
13 some cases where that's not happening, and
14 you're willing and able to dispense the drug,
15 but you're not able to, if you could just let
16 us know, just email us, that would be really
17 helpful.

18 The other question I had, and this
19 was also for you, was, Gerald McEvoy mentioned
20 a few of the initiatives that NCPDP is doing
21 to try and integrate some of the REMS tools
22 into their standards, including for claims

1 verification and ePrescribing, and then also
2 some integration into SPL.

3 And my question is, as a system
4 that is -- doesn't necessarily interact with
5 third party payers or other parties, do you
6 necessarily use those systems, and if not,
7 what can be done to make sure that REMS are
8 integrated into your system?

9 MR. MONROE: Although I may not be
10 able to speak to all of those systems, I know,
11 and -- and you may be well aware of the TIRF
12 REMS scenario, where it's been commented that
13 that -- that worked well, and it's a good
14 system. But in the case of our system and some
15 others, we don't use electronic claim
16 submission.

17 So the FDA acted to enable us to
18 use an alternative system. It may not be quite
19 as efficient, but at least we can participate.
20 And so the REMS program set up a phone
21 submission process. Extra step in the
22 pharmacy, but still we were able to keep TIRF

1 prescribing in the area where it should be,
2 and that was a great adjustment.

3 So it's probably a good learning
4 experience for us, and hopefully for FDA and
5 sponsors, and maybe the next step is we can
6 find ways to make that kind of adjustment more
7 nimble.

8 Because as we standardize, you
9 know, we have to also make exceptions for
10 different kinds of systems. Does that get to
11 where you were going?

12 MR. KROETSCH: I think so. He also
13 mentioned, I think ePrescribing is an option
14 for integrating some of these checks, and I'm
15 not sure whether you used those sorts of
16 systems.

17 And also, it does seem like the
18 telephone system doesn't have some of the
19 benefits, both in terms of workflow, and
20 perhaps in terms of making sure that those
21 safety checks are actually built directly into
22 the system. So I'm curious whether you have

1 thoughts, either now or perhaps in the docket,
2 on how to address those sorts of issues.

3 MR. MONROE: On ePrescribing, and
4 of course we have our own electronic health
5 record with physician prescribing, and
6 refills, and so on. And there may be ways to
7 integrate into that. And we'd love to work
8 with projects to do that.

9 You're right. The telephone system
10 is a little cumbersome, but the ideal would be
11 to develop an online alternative that worked
12 a little more efficiently. That takes a little
13 more work on the part of the sponsors.

14 And I don't know if that
15 particular one is progressing or not, but this
16 at least gave us an alternative to continue to
17 participate and meet the REMS requirements.

18 MS. TOIGO: Megan?

19 MS. MONCUR: My question is for
20 Marie Link. And in your presentation, you
21 mentioned counting 163 requirement details.
22 One of the things that we're interested in

1 doing is sort of coming up with a kind of a
2 common nomenclature, or sort of what is that
3 critical unit. And can you help us understand
4 what a requirement detail is?

5 DR. LINK: Sure. It's any of the
6 potential elements that are associated with a
7 drug as of this time. So as part of the
8 clinical research that we've been doing, we
9 take each individual REMS drug, and then we
10 evaluate every component of the program
11 requirements, and all of the things that are
12 associated with it.

13 And one of the things that we've
14 looked at is, is it required, is it highly
15 recommended, or is it extra, extemporaneous,
16 FYI information? And it's hard to
17 differentiate those things.

18 So right now, as -- you know, to
19 really bring everything under one umbrella,
20 we've evaluated the whole gamut, and then an
21 ultimate goal in optimization and
22 standardization is you bring everything in,

1 and then you look at, how do we take all of
2 this and then categorize it?

3 So for example, patient informed
4 consent forms. Okay, we have a category for
5 that. Pretty much, it's any form that contains
6 a signature line for a patient. They're all
7 different -- they're named all different, but
8 what we've done is we call them an informed
9 consent form.

10 So regardless of what the program
11 has called it, we've lumped it into a category
12 that we deem -- that we have deemed most
13 suitable for its fit, and then the other
14 things are pretty much in another category.
15 Because, when you get beyond five to six
16 required forms for any given program, it
17 becomes too cumbersome.

18 So we -- we want to create the
19 tool so that we really can showcase the
20 diversity, and then determine what should stay
21 as an inclusion, and then what could be
22 potentially excluded to minimize the

1 confusion, complexity, and variability.

2 MS. MONCUR: So just to clarify, so
3 a patient informed consent, would that be
4 counted as one requirement, or would that be -
5 - because there's the requirement to actually
6 sit with the patient and complete it, and then
7 there's the form, just so that we're --

8 DR. LINK: That would be considered
9 a single requirement.

10 MS. MONCUR: Okay.

11 DR. LINK: So they're on the DSQ
12 tool, the drug sponsor questionnaire tool,
13 when the drug sponsor would go in to edit, or
14 modify, or verify their drug in the system,
15 they can -- they're prompted to say, just you
16 know, is there an informed consent form that
17 a patient must sign, yes or no? And if yes,
18 they have to include that document.

19 So regardless of what the sponsor
20 names the form, we push it out to the
21 prescriber and the healthcare organization as,
22 you know, an informed consent form.

1 MS. MONCUR: Thank you.

2 MS. TOIGO: So it sounds like, I
3 think we heard from JoAnn Stubbings yesterday,
4 they've got a four-page questionnaire that
5 they do. And you have 163 requirements. I
6 don't know what we've heard from others, but
7 to the extent that those things can get
8 submitted to the docket, we've been doing our
9 own.

10 If we pool them all together,
11 it'll help us towards standardization. So
12 encourage anyone who has those kinds of tools
13 in their institutions, or wherever, to submit
14 those to the docket so that we can put them
15 all together, and it may form a basis for a
16 follow-up meeting. But clearly four page
17 documents and 163 requirements, or -- 163, I
18 think?

19 DR. LINK: Well to clarify, that is
20 -- there's 81 data fields for each drug that
21 would have to be answered, that exists today.
22 We think that that's too many, so it should be

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

2 1:19 p.m.

3 MS. TOIGO: Welcome back. For our
4 last session of the day, because we don't
5 have, at least yet, any open public speaker --
6 speakers for the open public session. So this
7 will be our last panel, and this panel members
8 are here to talk about issues related to the
9 evaluation or assessment of REMS. At least
10 based on the materials submitted before the
11 meeting, that's where we thought these
12 presenters fit best.

13 Each of our speakers has ten
14 minutes. The microphone won't cut off at ten
15 minutes, but there's the red lights blinking,
16 and I'll let you go a little bit over, and
17 especially if I see the slides, that you're
18 close, we'll let you finish. But if not, I'll
19 ask you to stop, because that way everybody
20 has the same amount of time.

21 And then after that we'll have an
22 opportunity for the FDA panel members to ask

1 because most interactions with patients in the
2 healthcare systems are discrete events that
3 occur over time.

4 And the importance of this is that
5 discrete event simulation is not overly
6 complex. It's a powerful tool for modeling
7 industrial or service-oriented systems where
8 scarce resources -- where you have scarce
9 resources and potential waiting, or queues,
10 and random events in service times.

11 The healthcare delivery is almost
12 entirely made up of these types of systems,
13 and discrete event simulation allows one to
14 experiment and manipulate the systems to
15 better understand how the alternative designs
16 may have an impact.

17 So some characteristics of
18 discrete event simulations, you have entities,
19 which must wait in queues, and then you have
20 resources, such as administrative people that
21 -- administrative personnel that would look
22 into insurance information and other

1 registration-like information.

2 You can see through this little
3 illustrated example here that you have then
4 waiting rooms and resources for patients to go
5 and actually be examined, resources such as
6 nurses to evaluate the patient, and then
7 physicians having an exam.

8 So why discrete event simulation
9 is important, because it builds in randomness
10 into the model. So in this very simple example
11 here, you can see, if you have a patient
12 arriving every six minutes and the service
13 time is 5.9 minutes, the average wait in the
14 queue is zero. But if you add randomness to
15 your model, you can see that there's a
16 significant increase in the average queue time
17 of 354 minutes, just by adding a simple random
18 variable, such as an exponential -- excuse me,
19 arrival or service times.

20 Activity times for our simulation
21 model were random and based on empirical
22 clinical data that we got through public

1 sources. And so for our hypothetical clinic,
2 we had a model with a simple ten bed clinic.

3 Scenario 1 was the workflow for
4 patients checking in, nurses triaging the
5 patients, physicians consulting, and then the
6 patients checking out and departing. The
7 alternative scenario was we included, for
8 every patient coming into this clinic, a urine
9 drug screen. And we wanted to compare how that
10 would have an impact between the two
11 scenarios.

12 Here's the output of the model.
13 And as you can see, without the extra tests,
14 you had approximately a 22 minute waiting
15 time. And with the additional three minute,
16 and we say a three minute urine drug screen,
17 increased the patient waiting time almost --
18 almost doubled the patient waiting time. And
19 as you can see, the addition of a simple three
20 minute test increased the total waiting time
21 in the office by 15 to 20 minutes.

22 And so we used this as a proof of

1 concept to say, what if we do this in a larger
2 scale and collect observational data in
3 various healthcare settings to determine how
4 our REMS initiatives may impact the overall
5 healthcare system?

6 And we plan on -- we're currently
7 in the process of working with Lehigh Valley
8 Healthcare Systems to conduct observational
9 data on different processes within the
10 hospital system. We also utilize simulation to
11 inform the decision-making process for risk
12 minimization activities, or initiatives across
13 all pharmaceutical industry stakeholders to
14 inform the decision-making process, and then
15 also to integrate prospective simulation
16 modeling with a cost-benefit analysis to
17 inform the development of these REMS programs.

18 I believe that is the end of my
19 presentation, but at this time I'd like to
20 turn the microphone over to my colleague, Dr.
21 Kris Srinivasan, who's going to give both a
22 clinical and a healthcare systems engineering

1 perspective right now.

2 DR. SRINIVASAN: Thanks. Thanks,
3 Marc. As Marc mentioned, my name is Kris
4 Srinivasan. I look forward to working with
5 Marc at ParagonRx and on fun activities such
6 as this.

7 Basically, as a clinician, and
8 also as a systems engineer, you can see the
9 value, and invaluable nature that this type of
10 tool, and these types of tools that we've
11 discussed today throughout -- from Dr.
12 Slatko's presentation, Meredith Smith's
13 presentation, and a few others, as to how
14 important it is to utilize these types of
15 tools in order to optimize and show the
16 effectiveness of REMS programs.

17 So I just want to briefly touch
18 upon two types of areas that this is highly
19 important, and give you the perspective from
20 as a clinician, and also as a systems
21 engineer.

22 So as a clinician, why this is

1 really important is that simulation modeling
2 can effectively show how REMS programs are,
3 number one, going to ensure patient safety
4 throughout my practice, and number two, in
5 turn, it can show me how to optimize my
6 practice by integrating this type of REMS
7 program into it.

8 It's very difficult for physicians
9 who are strictly clinically trained to have
10 the perspective of saying, well, as you see up
11 here, if I add a three minute test to my
12 practice, what's the burden that's going to
13 cause?

14 And if we can effectively show
15 that that three minute test can be optimized
16 into your practice to not have any burden on
17 your overall -- on the overall flow of your
18 practice, then we've done our job, and also
19 the REMS program that was designed has done
20 its job, as well. Because the overall goal
21 here is obviously patient safety and positive
22 health outcomes.

1 Now, secondly, as an industry,
2 what systems engineering methodologies such as
3 simulation modeling can do is help us
4 collaborate with the healthcare industry to
5 help ensure these types of positive patient
6 health outcomes. And I think that's a key, key
7 component that both our industry, as well as
8 a collaboration with the healthcare system, is
9 going to be critical in moving in the future.

10 Obviously, as Marc had just said,
11 we at Paragon are trying to collaborate with
12 a healthcare system -- we have a healthcare
13 system right now to do just that. We're able
14 to gain observational data, real time data,
15 across multiple different specialties within
16 that system.

17 And using that as a baseline
18 model, and make it a robust imagery of what is
19 to be expected as we develop future REMS
20 programs, and how best to optimize those
21 programs that it has a seamless integration
22 into different healthcare environments. So if

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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: 07-26-13

Place: Silver Spring, MD

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