



U.S. Food and Drug Administration

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UNITED STATES OF AMERICA
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

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RISK EVALUATION AND MITIGATION STRATEGY
(REMS) PUBLIC MEETING

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Wednesday, July 28, 2010

The meeting came to order, at 8:30 a.m., in room 1503 of Building 31, FDA White Oak Campus, 10903 New Hampshire Ave, Silver Spring, Maryland. Terry Toigo, moderator, presiding.

PRESENT:

TERRY TOIGO, R.Ph, M.B.A., Director, Office
of Special Health Issues, (OSHI)
JANE A. AXELRAD, J.D., Associate Director For
Policy, CDER
SUZANNE BARONE, Ph.D., Team Leader, Office of
Compliance
GERALD DAL PAN, M.D., M.H.S., Director, Office
of Surveillance and Epidemiology (OSE)
JOHN JENKINS, M.D., Director, Office of New
Drugs (OND)
CLAUDIA KARWOSKI, PharmD,, Director, Division
of Risk Management (OSE)
MWANGO KASHOKI, M.D., M.P.H., Associate
Director for Safety, (OND)
KEITH WEBBER, Ph.D., Acting Director, Office
of Generic Drugs

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

2 8:32 a.m.

3 MS. TOIGO: (presiding) Good
4 morning, everybody, and welcome.

5 My name is Terry Toigo, and I
6 serve as the Director of FDA's Office of
7 Special Health Issues.

8 I welcome you to day two of our
9 public meeting to discuss risk evaluation and
10 mitigation strategies, or REMS. For most of
11 you, you were probably here yesterday. So,
12 we're going to do the condensed version of the
13 groundrules and the logistics, but there are
14 some of our speakers who weren't. So, we will
15 go through those groundrules.

16 We have diverse representatives,
17 representatives from diverse groups today on
18 our panels: health professionals, consumer,
19 patient advocates, pharmaceutical companies,
20 trade associations, and other groups as well.

21 We have 28 speakers today, and all
22 of our speakers have talked to Kristen Everett

1 or emailed with her. They knew the rules in
2 advance.

3 So thank you, Kristen, and all of
4 your colleagues for the work you did in
5 developing the agenda under Jane Axelrad's
6 leadership.

7 We have 13 panels for the entire
8 meeting. We got through, let's see, most of
9 them yesterday. We have two more topics
10 today. We got through four of the six topics.
11 The topics were requirement for REMS,
12 establishing the goals of a REMS, issues
13 regarding elements to assure safe use,
14 evaluating the effectiveness of a REMS, and
15 then today we are also going to talk about the
16 effect of REMS on generics, and protection of
17 patient information. Those will be the new
18 topics.

19 And again, our goals for today are
20 that it will be an open forum for individuals
21 to present their views without interruptions.
22 We want to have a fair process, and each of

1 our speakers will have five minutes. We'll
2 have a cushion for time, a little bit of time,
3 between our speakers, so that we can allow for
4 questions from the FDA panel.

5 For our speakers, I'll announce
6 your name, and I'll ask you to come to the
7 podium. You are going to be advancing your
8 slides yourself, and you need to do that so
9 that the people who are viewing it through
10 webcast can see as well.

11 To facilitate a smooth process --
12 and I think most of you would agree yesterday
13 went well with our timer -- a yellow light
14 comes on for our speaker after four minutes to
15 warn you that you have one more minute. We're
16 not using the buzzer, and we're not turning
17 the microphone off. But we know that you see
18 the yellow timer, and yesterday it worked
19 very, very well. If it doesn't, then I will
20 give you a little nudge and just kindly ask
21 you to finish up your comments.

22 Then, after you present, if you

1 could return to the table. When you are
2 answering questions from the FDA panel, you
3 need to hold the microphone down.
4 Unfortunately, you can't just press it. You
5 have to hold it the whole time you're
6 speaking. Otherwise, we won't hear you or
7 they may hear you in the room, but they won't
8 hear you on the webcast.

9 We do have time at the end of the
10 day today for people who want to speak in an
11 open public session. I think we have one
12 person registered. There's plenty of time at
13 the end of the meeting, if you want to make
14 comments. If you decide during the day today
15 that you hear something and you want to be
16 able to speak in the open session, please
17 register at the registration desk and we'll
18 make sure at the end of the day today that
19 everybody who wants to speak is given an
20 opportunity to speak.

21 So, at this point, I'll stop and
22 I'll ask our FDA panel to introduce

1 themselves, please, so that those who are new
2 will know who you are.

3 MS. AXELRAD: This is Jane
4 Axelrad. I'm the Associate Director for
5 Policy in the Center for Drug Evaluation and
6 Research.

7 DR. JENKINS: Good morning. I'm
8 John Jenkins. I'm the Director of the Office
9 of New Drugs in CDER.

10 DR. KASHOKI: Good morning. My
11 name is Mwango Kashoki. I am the Associate
12 Director of Safety in the Office of New Drugs.

13 DR. DAL PAN: Good morning. I'm
14 Gerald Dal Pan, Director of the Office of
15 Surveillance and Epidemiology in CDER.

16 DR. KARWOSKI: Good morning. I'm
17 Claudia Karwoski. I'm the Director of the
18 Division of Risk Management in OSE.

19 DR. WEBBER: Keith Webber. I'm
20 Deputy Director of the Office of
21 Pharmaceutical Science in CDER and currently
22 Acting Director of the Office of Generic

1 Drugs.

2 DR. BARONE: Suzanne Barone from
3 CDER's Office of Compliance.

4 MS. TOIGO: Okay. And just a few
5 last logistics. There are coffee and
6 beverages available at the break and at lunch,
7 not ideal, but at least there is something
8 here, and we did get through everybody for
9 lunch yesterday. So, we hope it works okay
10 today.

11 The slide presentations for all of
12 our presenters will be posted to the docket
13 following the meeting, and transcripts will be
14 available in about 30 days. Details about how
15 to access that information are available at
16 the bottom of the agenda.

17 And I did get some questions
18 yesterday about the webcast and the
19 availability, and I'm trying to get an answer
20 for that. I don't have a confirmed answer yet
21 this morning.

22 While we're on the topic of

1 webcast, we are being webcast. It's not an
2 interactive webcast. For our participants who
3 are listening today on webcast and weren't
4 yesterday, please make sure that your speakers
5 are on and that you turn them up, or you won't
6 get any sound.

7 We will have a break. Let's see,
8 today it's at 9:45. We are trying to stay on
9 time here, so we're pretty predictable. And
10 lunch is 11:45.

11 Then one last detail. Feedback
12 about the meeting is very important, both
13 positive and negative. It really does help us
14 make our future meetings better, based on the
15 comments that you share with us. I'm happy to
16 take them in person. My email is
17 theresa.toigo, T-H-E-R-E-S-A, dot, T-O-I-G-O,
18 at fda.hhs.gov. We welcome comments. We
19 really do learn from the negative comments as
20 well.

21 Then, since this is really for
22 many of us the first public meeting we have

1 had in this room, we appreciate your patience.
2 We're still working through some of our
3 logistical details.

4 So, thank you for listening to the
5 condensed version of that list today. We'll
6 start with panel No. 1. Our topic is issues
7 regarding elements to assure safe use. And
8 you'll notice that's continued from yesterday.
9 We had many speakers on this topic yesterday,
10 and this morning's panel will continue that
11 discussion.

12 Jeff Francer from PhRMA will start
13 us off.

14 MR. FRANCER: Thank you very much,
15 and good morning, everybody.

16 I'm Jeff Francer, Assistant
17 General Counsel at the Pharmaceutical Research
18 and Manufacturers of America, or PhRMA. PhRMA
19 is a voluntary, nonprofit association that
20 represents the country's leading
21 pharmaceutical research and biotechnology
22 companies.

1 As I stated during yesterday's
2 panel, for PhRMA and its member companies,
3 protecting patient safety and enhancing FDA's
4 implementation of REMS are of the utmost
5 importance.

6 Yesterday I discussed PhRMA's
7 ideas to enhance transparency around REMS
8 requirements and the reasonableness use of
9 medication guides. This morning I will
10 address a third principle, mitigating burdens
11 on patients and healthcare providers.

12 When a REMS is appropriate, FDA
13 should be prudent in order to minimize risks
14 without unnecessarily encumbering drug
15 availability or unnecessarily restricting
16 patient access to medicines or complicating
17 healthcare delivery.

18 FDA requirements for REMS with
19 elements to assure safe use give rise to
20 concerns about additional burdens on patients,
21 healthcare providers, and pharmacists. As we
22 heard yesterday, under the most restrictive

1 REMS, FDA can require mandatory counseling and
2 medical testing for patients, prescriber
3 education and certification, and restricted
4 distribution of medicines. These requirements
5 are intended to promote safe and informed
6 prescribing.

7 The National Comprehensive Cancer
8 Network REMS Work Group has observed that,
9 quote, "To meet some REMS requirements,
10 providers must spend additional time on
11 administrative tasks like registration,
12 training, certification, and documentation,
13 which may take away valuable time from patient
14 care activities, including thoroughly
15 presenting the benefit/risk ratio of a
16 proposed therapy." Unquote.

17 Under the FDA Amendments Act, FDA
18 is required to take into account the burdens
19 on patients and healthcare providers when
20 determining whether to require a REMS and
21 determine the required elements. It is
22 unclear how FDA has been evaluating and taking

1 these burdens into account.

2 PhRMA offers the following
3 recommendations to FDA regarding methods for
4 addressing burdens on patients and healthcare
5 providers:

6 First, consistent with FDAAA, the
7 agency should aim to use the most efficient
8 and least burdensome elements necessary to
9 achieve risk minimization. FDA should explain
10 its process for considering burdens on
11 healthcare professionals and patients. FDA
12 should account for these burdens in the action
13 letter when requiring a REMS for a specific
14 medicine or class, as well as describing the
15 benefits of the medicine and the risk
16 addressed by the REMS.

17 FDA should conduct systematic and
18 ongoing outreach to specific patient and
19 provider groups to help FDA gain a better
20 understanding regarding the potential burdens
21 REMS can cause on patients and healthcare
22 professionals in specific clinical settings.

1 We believe that this type of consultation can
2 provide appropriate stakeholder input on REMS
3 generally.

4 Finally, REMS process
5 requirements, such as approved documentation,
6 pre-approved effectiveness goals, and
7 associated third-party assessments, can create
8 substantial burdens on the healthcare system,
9 as we heard yesterday. These process
10 requirements should be reserved for medicines
11 that require restricted or conditional access
12 in order to maintain a positive benefit/risk
13 balance; in other words, REMS with elements to
14 assure safe use.

15 Reserving full-scale REMS
16 implementation for ETASU programs only would
17 enable all stakeholders to focus more
18 resources on the most critical risk
19 minimization activities.

20 By increasing transparency around
21 how FDA evaluates REMS burdens on patients and
22 healthcare providers, and by limiting process

1 requirements to the handful of REMS that
2 require restricted access, FDA can effectively
3 help mitigate the burdens of REMS on the
4 healthcare system.

5 In conclusion, PhRMA appreciates
6 the efforts of FDA in organizing today's
7 meeting. We hope to continue to serve as a
8 constructive partner, together with other
9 stakeholders, as the agency continues to
10 implement its REMS authority.

11 Thank you.

12 MS. TOIGO: Thank you, Jeff.

13 And our second speaker is from
14 Biogen Idec, Dr. Carmen Bozic.

15 DR. BOZIC: Good morning. My name
16 is Carmen Bozic, and I'm the Senior Vice
17 President and Global Head of Drug Safety and
18 Risk Management at Biogen Idec.

19 I would like to thank the FDA for
20 convening this important meeting and giving me
21 the opportunity to speak to you today.

22 Biogen Idec is a global

1 biotechnology company that specializes in the
2 discovery, development, and commercialization
3 of innovative therapies. We are a company
4 that is committed to putting the patients
5 first and developing important treatments for
6 patients with high unmet medical needs, such
7 as patients with multiple sclerosis, lymphoma,
8 and rheumatoid arthritis.

9 We have a great deal of experience
10 with the REMS programs through the development
11 and implementation of the TOUCH prescribing
12 program for Tysabri. Tysabri is a monoclonal
13 antibody directed against alpha-4 integrins
14 that's approved in more than 50 countries for
15 the treatment of relapsing MS. It provides
16 significant benefit in what is a very
17 devastating disease.

18 Due to the rare risk of PML, which
19 is a serious viral infection of the brain, we
20 have implemented global risk management
21 programs. In the U.S., we have implemented
22 the TOUCH prescribing program, which is a

1 highly complex REMS with multiple elements to
2 assure safe use.

3 Based on the data we have
4 collected over the past four years in the
5 TOUCH prescribing program, I would like to
6 describe our observations, learnings, and
7 challenges and recommendations regarding these
8 types of REMS programs.

9 So, first, in terms of the
10 benefits of REMS, these types of REMS allow us
11 to very effectively communicate risk
12 information to prescribers and patients, and
13 to do so in a very direct manner. These REMS
14 also allow us to collect very high-quality
15 data to better characterize the risk. For
16 example, we have a much better understanding
17 of the frequency of PML and risk factors for
18 PML over the course of the past four years.

19 And these programs may also
20 improve healthcare outcomes. So, for example,
21 70 percent of patients who develop PML with
22 Tysabri treatment survive, and that's a much

1 higher survival rate than what was originally
2 described with PML in other populations.

3 Nevertheless, these programs come
4 with significant challenges, and I am going to
5 go through these in the next few slides.

6 One important challenge has been
7 our ability to communicate benefit and risk
8 information on a balanced way. Several
9 speakers spoke about this yesterday, and I
10 would like to echo many of those comments.

11 These programs inherently
12 communicate risk information frequently and
13 extensively, but it is important for the
14 patient and doctor to know both the risks and
15 the benefits of a therapy in order to make an
16 informed decision. So, if you can't
17 communicate the benefit in the context of a
18 REMS program, there is an imbalance of
19 information. One consequence of this might be
20 the patients may avoid appropriate treatment
21 for their therapy.

22 So, yesterday we heard a lot of

1 discussion around the need to add benefit
2 information to medication guides. We would
3 take this one step further and advocate to
4 include benefit information in other REMS
5 elements as well. So, for example, if there's
6 an enrollment form for your program where the
7 prescribers and patients have to attest to
8 understanding the risks of the drug, they
9 should attest to understanding the benefits as
10 well.

11 This is no different than the way
12 informed consents are administered in the
13 context of clinical trials. Informed consents
14 standardly provide both benefit and risk
15 information that a patient needs to attest to.
16 So we would like to see the same for REMS
17 programs.

18 We also believe that it's very
19 important to communicate to prescribers in a
20 very timely fashion any emerging safety
21 information that you gather from this program.
22 In these types of programs, prescribers give

1 us a great deal of information, and they
2 expect in return that we communicate to them
3 any new learnings around safety that we have
4 around the drug.

5 We believe that these
6 communications for a company to prescribers
7 regarding safety information are not a priori
8 promotional. However, a pathway for companies
9 to proactively communicate emerging safety
10 information doesn't currently exist, and it
11 should be established through a dialog with
12 the FDA review divisions.

13 Now I will speak about burden.
14 There was a great deal of discussion yesterday
15 and this morning around the impact of these
16 programs on the healthcare system. We have
17 survey data from prescribers who participate
18 in our program that indicates that the
19 majority of prescribers need between one and
20 three individuals in their practice, including
21 themselves, to administer the TOUCH
22 prescribing program. That is, indeed, a

1 considerable burden on these practices.

2 And in order to address this, we
3 encourage the FDA to allow companies to more
4 rapidly implement changes in their programs as
5 they gather information about their programs.
6 So, for example, if you discover that an
7 element imposes a high burden, but doesn't
8 really have any benefit in terms of improving
9 patient safety, that element should be
10 removed, and it should be removed
11 expeditiously.

12 And finally, REMS should be
13 applied in a much more flexible manner to take
14 into account the variety of healthcare
15 practices that we have here in the U.S.

16 We also think, therefore, it's
17 very important that we have a very streamlined
18 process for modifying existing REMS. We get
19 a great deal of information as we implement
20 the REMS. We need to apply it in continuously
21 improving the program. So, we need very clear
22 mechanisms and timelines for engaging with the

1 FDA on this.

2 We propose that the FDA have
3 specific categories for REMS modifications.
4 We should be able to implement administrative
5 changes much more rapidly, and substantive
6 changes should have specific timelines for
7 review and approval.

8 So I think, in summary, then,
9 these are our REMS experiences and
10 recommendations, and I thank you very much for
11 the opportunity to speak to you today.

12 MS. TOIGO: Thank you, Dr. Bozic.

13 Our next speaker is Dr. Frances
14 Duff-Warren from Actelion Clinical Research
15 Incorporated.

16 DR. DUFFY-WARREN: Good morning,
17 and I would also like to thank you for the
18 opportunity for me to come and speak here.

19 My name is Frances Duffy-Warren.
20 I work for Actelion Pharmaceuticals. We are
21 also a global pharmaceutical company. Our
22 headquarters are in Switzerland, and we have

1 four marketed products, all of them orphan
2 diseases. A lot of our experience as well is
3 related to the orphan diseases and the
4 elements to assure safe use in our REMS
5 program.

6 We, of course, have, as we heard
7 yesterday, one of our products to clear has a
8 REMS. It was originally approved in 2001 for
9 pulmonary arterial hypertension. It was
10 approved with a very extensive riskMAP, and we
11 were one of those products which was deemed to
12 have a REMS in effect in 2008, and our REMS
13 was then approved in 2009, August.

14 So, some of the comments that I
15 have here and take into account are really in
16 the light of the experience that we have in
17 transitioning from our riskMAP and, also,
18 then, moving into implementing that REMS for
19 Tracleer.

20 Some of the thought processes that
21 we are going through and looking into in terms
22 of products within our current development

1 pipeline, where we are already thinking ahead
2 about how could we address any issues as they
3 come up.

4 So, as you have already heard a
5 little bit and it came up yesterday, sponsors,
6 when we propose REMS with element to assure
7 safe use, although those proposals are in the
8 light of development of tools, databases,
9 processes, and sometimes that's on a
10 theoretical basis, we haven't tried them out
11 and there may well be gaps within them. What
12 is the appropriate level of detail to actually
13 include in those proposals?

14 Part of our final approvment of
15 the REMS is with the approval of the drug, and
16 there really is a bit of a timing mismatch
17 between the proposals, our practical
18 experience, and the final version that we will
19 end up getting actually approved.

20 Under the extensive REMS, and if
21 they have a REMS with extensive elements to
22 assure safe use, in the light of our

1 experience, I'm really a little bit skeptical
2 as to whether there would ever be a drug that
3 would have a prioritative review and still
4 manage to get a REMS approved within a
5 prioritative review timetable.

6 So, some of the issues that we
7 have come up and have also been highlighted by
8 the previous speaker is, once you have your
9 REMS in place and you have the processes,
10 you're trying to implement it, and having the
11 processes approved, then the ability to change
12 those processes is actually very difficult.
13 A lot of them require pre-approval
14 modifications and prior approval before
15 implementation. That means you can't
16 continuously improve your REMS as you go on.

17 One of the issues -- and I don't
18 think it has really come up very much so far
19 -- is there is a complicated interface between
20 the REMS as it is published on the website and
21 the supporting documentation. It is the
22 supporting documentation where you get a lot

1 of the details behind the processes, and then
2 the connections between the individual
3 processes are going in place to support the
4 elements to assure safe use.

5 And part of the issue that we
6 would then raise is, if we come up with an
7 issue in the implementation, and we find it's
8 very difficult to implement that, how can we
9 guarantee the continued access to the drug
10 through the implementation, and if there is a
11 change that we think should be implemented?

12 So, in terms of some of the
13 suggestions that we would actually make, and
14 in terms of the guideline, it is really
15 whether there can be additional clarification
16 and identification of how you can
17 change/modify any elements to assure safe use
18 during the implementation phase. That may
19 include some of the issues that were raised
20 yesterday as well, whether it's possible to
21 have some kind of pilot phase prior to
22 implementation or finalization of the REMS;

1 whether it's perhaps possible to have a phased
2 introduction which might be, for example, that
3 you would go into a distribution chain that
4 might be using specialty pharmacies before
5 moving into an inpatient hospital situation.
6 Some of that would depend on the type of drug
7 that you're actually working with and what is
8 its normal usage.

9 Also, and again in line with what
10 the previous speaker was then saying, is
11 perhaps define some of those changes which are
12 administrative rather than substantive
13 changes, and whether they could be reported or
14 changed during an annual report or through
15 some kind of prior notification procedure not
16 requiring pre-approval.

17 So, then, for us in terms of what
18 would be very useful for us as sponsors and
19 manufacturers is really to have some clear
20 guidance on what responsibilities are, and if
21 there is an opportunity to include
22 stakeholders in the overall implementation of

1 elements to assure safe use, so that all of
2 these distribution systems do work seamlessly.
3 Then there would also have to be a clear
4 definition of what those roles and
5 responsibilities would actually be.

6 We heard a little bit yesterday as
7 well about potentially having different types
8 of REMS, ones which have perhaps communication
9 and education aspects, rather than the full
10 element structure of safe use. Perhaps one of
11 the options to take into consideration would
12 be to have client timelines related to each of
13 those types of REMS within the review process.
14 Because, of course, one of the issues that
15 then comes up, that you may not know the full
16 safety profile until you get to the end of
17 your phase 3 trials. It's only at that point,
18 then, that you would actually have an idea of
19 whether you need a REMS to assure safe use or
20 what level of REMS you will actually require
21 in that circumstance.

22 And the timeframe available to all

1 those processes and procedures is in line with
2 or workable within the normal timeframe for
3 the review and approval process that you have
4 in place today.

5 So, finally, I would just say it
6 would be useful, as a sponsor, if we have
7 actually implemented the REMS and gone through
8 the transition period, some additional
9 guidance on the level of detail expected
10 within the supporting documentation, so that
11 we don't tie ourselves up in knots a little
12 bit for the procedures to be put in place.

13 So thank you again for the
14 opportunity to speak.

15 MS. TOIGO: Thank you, Dr. Duffy-
16 Warren.

17 Our next speaker is Dr. Richard
18 Wagner from Kaiser Permanente.

19 DR. WAGNER: Good morning. My
20 name is Richard Wagner. I'm a pharmacist with
21 Kaiser Permanente.

22 Many of the issues that we would

1 like to address have already been addressed.

2 So, I'll try to simplify my presentation a
3 little bit.

4 Again, one of the things that we
5 have found lacking with REMS, especially the
6 ones that have been in place for some time, is
7 an assessment of the evidence and the
8 potential for actual improving clinical care.
9 We will present some evidence later today
10 about our own assessment of the iPLEDGE
11 program within our system, and also some
12 information that we would like to share later
13 today about patient confidentiality and
14 protected rights.

15 If we're going to be collecting
16 information about patients, we also do need to
17 be very mindful of the impact that we could
18 have on patient confidentiality. That's an
19 important factor for patients. They do want
20 to maintain that confidentiality.

21 The other aspect is, of course, we
22 do believe that at the times that REMS are

1 developed, especially with ETASUs, we need to
2 be at the table. We actually believe the
3 statute requires this. So, healthcare
4 providers, health systems, and others,
5 especially in regards to the burden which has
6 been discussed a lot yesterday and is certain
7 to be picked up again this morning, we need to
8 be at the table when the REMS with the ETASUs
9 are being considered.

10 The impact on the healthcare
11 delivery system, I do think yesterday it was
12 brought up, and one aspect that we can
13 actually contribute back to the FDA, as I
14 think Dr. Jenkins brought up yesterday, is we
15 have not actually -- in this room, folks have
16 gotten up and talked about the burden, but we
17 have actually not provided the FDA with any
18 evidence of what burden looks like.

19 So, something for the FDA and the
20 health system providers to work on would be,
21 how do we actually quantitate when we say
22 burden? I think everybody in the room has

1 heard it from the providers, and it certainly
2 is a burden. Some discussion about how to
3 assess burden from a workload/workflow
4 perspective would be important.

5 The other thing that we would like
6 to bring to the attention is in some ways it
7 would be better to set standards rather than
8 tell us how to manage our patients. So
9 standard-setting rather than processes or
10 trying to manage our internal processes would
11 be better for all of us, especially in an
12 organized healthcare system.

13 So, for an example, if we had some
14 flexibility around meeting the standards, it
15 would also allow us to do some experimentation
16 that maybe would allow us to actually exceed
17 those standards and also report back into the
18 literature, back to the agency about new,
19 innovative ways to hit or exceed the standard,
20 very common approaches that are done within
21 health systems for quality improvement.

22 So, instead of defining the

1 processes that we have across this variety of
2 healthcare delivery systems from the single
3 doctor office to a very large, organized
4 healthcare system, set the standards and let
5 us develop some expertise, some new ways of
6 doing things, and share that in a very
7 rigorous fashion. Hold us accountable to very
8 high standards. Give us flexibility on the
9 processes.

10 In terms of monitoring and
11 assessing the effectiveness of REMS, we need
12 that input early. We actually believe, again,
13 the statute requires that that input be sought
14 from healthcare providers and health systems.

15 We also think we should recognize
16 there's a potential conflict of interest if
17 the sponsors only do the evaluation about the
18 effectiveness. It is an inherent conflict of
19 interest, and other third parties with
20 expertise should be brought in to help make
21 this assessment. That's an important factor
22 because we do need that data to be credible,

1 both back to the provider community and to our
2 patients.

3 Again, it's been brought up many
4 times, assessing the burden on the healthcare
5 system, that's going to take direct input. I
6 do think the challenge back to the health
7 system, and speakers today and yesterday, is
8 helping the agency really quantitate what
9 burden looks like, both on the cost of care,
10 the time involved with care, the process of
11 care that's impacted by this. So, that is
12 challenge for all of us to work with the
13 agency on.

14 And we would also like to really
15 be focused on rate-based metrics. This is
16 very difficult in the organized healthcare
17 system, or the lack of organized healthcare
18 systems that we have, but rate-based metrics
19 are actually most important for us in terms of
20 tracking effectiveness and also tracking
21 unintended consequences. We can't ignore the
22 impact of a program like iPLEDGE on Accutane

1 or isotretinoin prescribing without
2 considering that up to 40 percent of our
3 female patients dropped off in terms of the
4 rate of patients getting Accutane or
5 isotretinoin prescriptions.

6 And lastly, I would like to
7 encourage the agency to consult with experts.
8 I have just listed a few of the experts here:
9 the National Quality Foundation, the Joint
10 Commission has great expertise, has worked
11 with other federal agencies in terms of health
12 improvement, and also IHA. So, the other
13 large agency for HHS has Dr. Don Berwick, who
14 is an expert in quality assessment/quality
15 improvement, and would be something to
16 consider in terms of reaching across the
17 channels and asking for Don Berwick on how we
18 can improve this overall system for improving
19 how we manage REMS.

20 Thank you for the chance to
21 present.

22 MS. TOIGO: Thank you, Dr. Wagner.

1 And our last presenter on panel 1
2 is Glenn Naphy from Springboard Associates.

3 MR. NAPHY: Okay, thank you. Good
4 morning. My name is Glenn Naphy.

5 Springboard is a global provider
6 of qualitative and quantitative market
7 research. So, one of the things I wanted to
8 kind of highlight today is that one of the
9 things we get involved in is being an integral
10 part, an independent provider of quality
11 market research.

12 So, one of the things that seems
13 to be a common theme, and I was thinking about
14 it a little bit yesterday, is the key element
15 from our perspective is we're missing the "B"
16 in benefits from the REMS. I don't know if
17 it's RBEMS, or whatever we want to call it,
18 but, essentially, one of the things that we
19 have been able to have some good insight on is
20 that REMS have been beneficial at times and
21 also restrictive at times. So, what we are
22 going to do is we're going to present some of

1 the information as it pertains to actually
2 executing some of the REMS programs.

3 So in the era of reality shows,
4 this is kind of our reality. So, what we were
5 able to do, some of the good news is that a
6 lot of our clients have been investigating
7 REMS and the impact of REMS post-approval of
8 a product. So that has afforded us the
9 opportunity to actually meet with providers,
10 whether it's the actual implementers or
11 physicians, pharmacists, patients, and allow
12 us to kind of capture their viewpoints.

13 The great news is that a lot of
14 our clients that we're working with now are
15 actually moving into the pre stage for REMS
16 development. We have been working with
17 approximately 10 products that have some
18 degree of REMS, whether it's just a medication
19 guide or extensive restrictive use, but we're
20 also working with products that are in early
21 stage clinical development to help shape their
22 clinical development programs and also provide

1 an insight as to what the landscape may change
2 over a period of time from the REMS
3 perspective.

4 However, we are learning the
5 process as we go. I think with respect to
6 this program over the last couple of days, we
7 are trying to capture some of the key
8 learnings and make this program a better
9 success. And with that, we're trying to
10 reflect on what are some best practices and
11 trying to set up standards throughout, even in
12 our market research approaches.

13 So the good news is, as we get
14 into the future, and we haven't seen it yet,
15 but the REMS will be better. That is
16 definitely in the forecast. We have seen,
17 just in the short time that we have been doing
18 market research on REMS, we've seen drastic
19 improvements, better understanding, also
20 bringing in a collaborative approach, and
21 we're actually working on some methodologies
22 to make that more prevalent in our market

1 research efforts.

2 So a couple of the observations
3 that are key to what we have kind of
4 summarized here with all of our clients is,
5 No. 1, ACPs are definitely struggling. So our
6 healthcare providers are definitely trying to
7 struggle with the burden of REMS to assure
8 appropriate use versus providing the highest
9 quality of care.

10 In addition, restricted use of
11 REMS, originally designed for high-risk
12 products, has been appropriately limiting
13 access to our lower-risk patients. So that is
14 good news.

15 As the number of steps limit to
16 increased REMS, the more restrictive REMS are.
17 So, if we give a physician 16 steps to execute
18 a REMS, you can guarantee almost that they're
19 going to try other medications for longer
20 periods of time.

21 The next thing is that sometimes
22 we have to look at just simple fixes. And

1 even a simple fix of education and answering
2 the question of why has actually improved the
3 receptivity of a REMS, and it's actually
4 helped us in help steering some of our
5 clients.

6 Then let's get creative. One of
7 the things we want to think about is like we
8 have a lot of smart people on a lot of these
9 teams. So we can get creative, bring in some
10 creative ideas and suggestions.

11 Two observations I want to kind of
12 point out for us. No. 1 is that the
13 burdensome REMS optimize therapy by decreasing
14 the probability of inappropriate use. The
15 danger is we want to make sure that we don't
16 discourage physicians too often by encouraging
17 them to use initial therapy as a longer period
18 of time, and maybe even delaying optimal
19 therapy or never even prescribing optimal
20 therapy.

21 The next observation is that REMS
22 occasionally increases access. And here's one

1 of the things I was talking about earlier, is
2 the benefit. If we can give physicians a
3 safety net to make them feel better and
4 reassured that the products are going to be
5 used in an appropriate manner, that benefits
6 healthcare and it benefits the physician
7 practice. That gives them assurance that they
8 have all of the appropriate tools in place to
9 monitor and assess their patients.

10 A couple of things I wanted to
11 kind of summarize at the end is like, how can
12 REMS be created to decrease inappropriate use,
13 but not limit patient access? So what we
14 found is that most successful REMS have three
15 essential elements, and they answer the three
16 following questions: what is the specific
17 risk? Is it street use? How big is the risk?
18 Is it happening everywhere? Do we think that
19 the drug would be misused frequently? Then,
20 how significant is the risk? Is it death? Is
21 it just an inconvenience of rash or something
22 like that? We need to assess that.

1 And what is the most efficient
2 means of reducing the specific risk? And we
3 really need to kind of headline how to do
4 this. This is where our creativity comes into
5 play.

6 And least successful REMS are
7 usually the high restrictive REMS for lower-
8 risk products or low probability of misuse.
9 So, we have tightened the reins on physician
10 prescribing too tightly and then can't use it
11 appropriately.

12 There kind of the findings that we
13 have structured for review of today: we are
14 excited about the use of REMS and being able
15 to expand on the use and make sure the
16 products are used appropriately, and giving
17 the opportunity for new products to come to
18 the market.

19 Thank you.

20 MS. TOIGO: I've got too many
21 buttons here to press.

22 Thank you, Glenn.

1 And on that, Dr. Bertch may be
2 here later today. So that's the end of panel
3 1.

4 Now it's an opportunity for our
5 FDA panel to ask questions. Leading us off is
6 Gerald Dal Pan.

7 DR. DAL PAN: Okay. I have a
8 question for Dr. Bozic, and if some of the
9 others have answers as well, I would
10 appreciate that.

11 Do you feel that you and your
12 company understand the burdens of the REMS in
13 place for your product, and could you have, in
14 retrospect, predicted that reasonably
15 accurately before the program was put in place
16 by surveying prescribers, et cetera, et
17 cetera?

18 DR. BOZIC: So, when we were
19 developing the program together with FDA, we
20 actually solicited extensive stakeholder
21 feedback. We actually consulted with more
22 than 400 neurologists, nurses, and pharmacists

1 in a variety of different ways through focus
2 groups, through advisory boards, through
3 quantitative research. So, we had a very good
4 understanding, I think, of the type of program
5 that could be implemented before it was
6 implemented.

7 Having said that, you can't
8 anticipate everything. So, as you implement,
9 you always uncover new things. That's why I
10 spoke about the importance that, as soon as
11 you find out that a certain aspect of the
12 program is burdensome but doesn't add to
13 patient safety, it should be quickly
14 eliminated in discussions with FDA. That's
15 why I think it's very important to have a
16 process where we can rapidly engage the FDA
17 and get approval to implements the changes
18 that we need to really improve the program.

19 Conversely, if there's a new
20 important information that you've gathered on
21 the risk side that means you have to add
22 additional elements to the program, that, too,

1 needs to be rapidly implemented. So, it has
2 to go both ways.

3 But I can't underscore the
4 importance of being able to rapidly modify an
5 existing program because you can't completely
6 anticipate everything that you're going to
7 find once you implement.

8 DR. DAL PAN: So, I guess the
9 implicit answer to the first part of my
10 question is that you do feel you understand
11 the burdens of the program?

12 DR. BOZIC: I do think so. I
13 think, because of the frequent TOUCH contacts
14 that we have with prescribers, patients,
15 nurses, the pharmacies that do the
16 distribution, we have a lot of feedback on
17 them, on what are sort of the specific aspects
18 of the burden, and we have implemented that in
19 our REMS discussions with FDA and brought that
20 up. So I think we do have a very good
21 understanding of what aspects of the program
22 are the most burdensome.

1 MS. TOIGO: Did anyone else on the
2 panel want to add anything to that?

3 DR. WAGNER: I can just add one
4 thing. Again, Richard Wagner from Kaiser
5 Permanente.

6 I think, actually, the flexibility
7 and the ability to change relatively quickly
8 does make sense. I think that's an obligation
9 that the sponsor may have with the FDA.

10 I would, also, just again remind,
11 though, the agency and the sponsors that we
12 should actually include the health systems in
13 that evaluation. So that should be a direct
14 contact between the FDA and the health system
15 or the healthcare provider.

16 So, again, we can work with the
17 sponsor, work with the agency. But I don't
18 think it should just be sponsor to agency
19 alone, and that's one of the things that we
20 brought up in our citizen petition, that we do
21 have a right to be at the table and should be
22 at the table, for all the right reasons, to

1 make sure that any assessment back on
2 healthcare systems, healthcare providers, is
3 done with all of our inputs.

4 So, again, I want to work with the
5 sponsors, work with the agency, but want to be
6 heard directly, too.

7 MS. TOIGO: Dr. Duffy-Warren, did
8 you want to talk about any specific experience
9 that you have?

10 DR. DUFFY-WARREN: I was going to
11 say, for our REMS, it was a slightly different
12 situation because we had many, many of the
13 elements already in place through the riskMAP
14 and had several years of experience in running
15 the risk minimization activities. For us, it
16 was very much an upgrading.

17 But in doing that upgrading of a
18 lot of the systems and the documentation, then
19 there also was a lot of stakeholder feedback
20 from the processes that we already had in
21 place. And it was trying to build that in,
22 but the biggest issue is trying to anticipate

1 every eventuality. Even very late in the day,
2 we were thinking, oh, we didn't think what
3 happens if a patient goes on vacation. What
4 are we going to do for that situation? Or
5 what happens under different circumstances?

6 So, that level of anticipation for
7 every eventuality is very difficult to take
8 into account. That's probably where we do
9 need a lot of the flexibility to be able to
10 address some of those issues on an ongoing
11 basis.

12 DR. BOZIC: I just want to give
13 one other example of a process improvement
14 that we wanted to put in place for the TOUCH
15 program. When we launched, we launched with
16 a paper-based system. We knew very early on
17 that prescribers and infusion sites very much
18 desired an online version.

19 So, we submitted that to FDA, but
20 it took about nine months to get that
21 approved. So that I think can be streamlined
22 and done much more quickly, when it was very

1 clear early on that it was sort of an obvious
2 process improvement to minimize paperwork and
3 reduce burden, and it's been very well-
4 received since we implemented.

5 MS. TOIGO: Thank you.

6 Next, Dr. Jenkins?

7 DR. JENKINS: This is for Dr.
8 Bozic.

9 You mentioned in your
10 presentation, and I think we heard from others
11 on the panel, about including benefit
12 information, so that patients can make an
13 informed decision. Have you given thought
14 about how would you present the benefit
15 information? Would it be, basically, a
16 summary of the clinical trials experience
17 that's on the label? How would you make that
18 patient-friendly and get around what I am sure
19 are going to be our concerns that it is going
20 to be promotional? So, have you given thought
21 to what that would look like?

22 DR. BOZIC: Well, I would say

1 that, you know, for example, many of these
2 REMS with elements to assure safe use have an
3 enrollment where there is an attestation of
4 risk basically. It is a very lengthy list
5 only of the risks.

6 Even something as simple as
7 saying, you know, this drug or Tysabri reduces
8 the risk of relapses and slows the disability
9 progression associated with your disease, even
10 that level of very simple conveyance of
11 benefit information would be an improvement
12 compared to what we currently have because,
13 you know, it is a long litany of risks.

14 There was a speaker yesterday who
15 spoke about some of the other similar
16 programs, how frightening it can be to a
17 patient to just see the risks. Therefore,
18 they are uniquely relying on their doctor to
19 convey in words the benefit, but what they are
20 reading is only the risk.

21 So I think there is a way to do it
22 in a very simple way, to add in amongst the

1 lengthy list of risks a couple of bullets.

2 I'm not saying it should be 75 percent of the
3 enrollment form, but a few additional points
4 that explain what are the benefits that they
5 might anticipate receiving with this drug.

6 And we do this in informed
7 consents all the time, right, in clinical
8 trials, and it tends to be very simply
9 explained.

10 DR. JENKINS: To follow up on
11 that, some of the drugs that are under these
12 REMS are used off-label. So, how would you
13 address the fact that you might be
14 providing -- your program doesn't allow off-
15 label use, but some of the programs do. So,
16 hypothetically, how would you address the fact
17 that you would be including in the information
18 the benefits for the on-label use and the
19 patient would be getting it for an off-label
20 use? How would you kind of bridge that
21 concern?

22 DR. BOZIC: That's a very

1 difficult issue to address because, obviously,
2 the product label from, which you would be
3 really deriving your statements that go into
4 these forms, doesn't really have any benefit
5 information on the off-label use because it's
6 really not proven to the level of the agency's
7 standards on that. So, I don't have a good
8 explanation on how to include that. It would
9 be, actually, quite difficult, I think, to
10 include benefit information on that.

11 Other people want to comment on
12 that.

13 MS. TOIGO: Yes?

14 MR. FRANCER: Hi. I just wanted
15 to also address that question, as we had also
16 advocated for inclusion of benefit
17 information.

18 I think all we were asking for is
19 inclusion of a patient-friendly version of the
20 FDA-approved indication. It would be up to
21 the healthcare professional to provide any
22 other information.

1 MS. TOIGO: Thank you.

2 Glenn?

3 MR. NAPHY: One of the things that
4 we have seen somewhat anecdotally, but a lot
5 of the PPI information, your doctor has
6 prescribed product X for XYZ, whether it's
7 increasing hemoglobin that came up yesterday,
8 it's at least a basis for what the medication
9 does do, and it is in patient-friendly
10 language. So I think there are some things
11 that are already approved that can be
12 repurposed to introduce the medication.

13 I know that the companies have
14 negotiated that language with the FDA. So
15 that would be an easy improvement. It doesn't
16 address completely all the off-label, but at
17 least it explains what the product does and
18 what it is indicated for, and maybe leave some
19 space for other indications.

20 MS. TOIGO: Anyone else?

21 (No response.)

22 Okay, Jane?

1 MS. AXELRAD: Yes, I would like to
2 explore this idea of standardization of REMS
3 in a little more detail. A number of people
4 have suggested we do it. Dr. Wagner, you
5 suggested that we go to a higher level and
6 that we prescribe standards, define standards,
7 and then let the individual healthcare setting
8 define how they are going to meet those
9 standards.

10 I was wondering if you could talk
11 a little bit about if you have any specific
12 ideas about how that might work. Taking, for
13 example, a drug in which the risk is
14 teratogenicity and you want to prevent
15 pregnancy, most of the programs that have that
16 kind of a risk have physician education about
17 the risk, patient education about the risk,
18 and pregnancy testing.

19 So, could you talk a little bit
20 about how one might standardize REMS or
21 develop standards for a REMS and how you would
22 make sure that individual healthcare

1 practitioners or healthcare systems were
2 meeting those standards?

3 DR. WAGNER: So we have a lot of
4 experience with this at Kaiser Permanente
5 because most of the efforts around quality
6 improvement come from bodies that set
7 standards primarily. So, whether it's our
8 Department of Public Health in California or
9 the Joint Commission, or other agencies that
10 help set standards for quality improvement and
11 quality assessment in organized healthcare
12 settings or hospitals, most of those are
13 standards that are put in place, rather than
14 processes.

15 There may be certain cases where
16 processes are prescribed. So, a very common
17 approach in quality improvement activities
18 that's got a lot of attention in recent years
19 is around never events, for example. So, for
20 example, a surgeon should never operate on the
21 wrong site during surgery, and processes are
22 put in place to prevent never events.

1 Those never events have been
2 really well-described in the quality
3 improvement literature, and we should follow
4 specific processes in that situation to never
5 have a never event, so to speak.

6 But for other quality improvement
7 activities, really standards are put in place,
8 and then the organized healthcare setting, the
9 hospital, others have to then demonstrate how
10 they meet the standard. So, there's
11 flexibility in the organized healthcare
12 environment to adjust those processes to meet
13 the standard.

14 So, specifically, back on how do
15 we avoid teratogenic exposure to patients on
16 certain medications, we really, therefore,
17 should set up internal systems to govern that.
18 Then, we did that with the SMART program
19 previously before iPLEDGE. We had a patient
20 registry. We had our dermatologist buyoff in
21 terms of assessing females of childbearing
22 potential. But one of the things that we

1 didn't do at that point in time was have our
2 males enrolled in the patient registry for
3 this process because we didn't feel that that
4 burden of doing this was actually offset with
5 a commensurate improvement.

6 So, for example, that process of
7 care did define that every prescription before
8 it was dispensed out of a Kaiser pharmacy
9 required a negative pregnancy test by that
10 particular patient right before that
11 dispensing activity. In that process of care,
12 if the patient did show up in the pharmacy and
13 did not have a negative pregnancy test, we
14 were able to redirect that patient. Within
15 two hours, she could get a pregnancy test and
16 we could dispense that prescription.

17 That was done very efficiently.
18 We took advantage of all of our systems
19 technology, and the burden back to the
20 dermatologist was really minimized.

21 Add the iPLEDGE program in, and
22 the very defined processes that you have to go

1 through and the very defined timelines that
2 are in place, you can't be flexible with the
3 patient. If they show up right outside that
4 time window, and there's been some adjustments
5 to iPLEDGE, so I'm talking about some past
6 experiences, we actually could not take care
7 of our patients in certain times.

8 So, the flexibility was set on a
9 standard; no patient was dispensed a
10 prescription without a negative pregnancy
11 test. The flexibility to meet that and to be
12 very cognizant of how to take care of that
13 patient in that setting, working very closely
14 with our dermatologists, that flexibility was
15 built into the system that we previously had.

16 As we have now implemented
17 iPLEDGE, we have lost a lot of that system
18 flexibility, but have seen no commensurate
19 improvement in pregnancy testing rates and/or
20 our ability to prevent teratogenic exposure to
21 isotretinoin.

22 MS. AXELRAD: Yes, I would just

1 like to follow up on that. I mean I can't
2 speak to Kaiser's experience, but I believe
3 the reason that they went from the SMART
4 program to iPLEDGE was that we felt that there
5 was an unacceptable level of fetal exposures
6 to the drug.

7 So, in that case, if one set the
8 standards a certain way or defined a program
9 that was somewhat flexible, and we found that
10 it wasn't meeting its goals, then there would
11 be a need to tighten the program.

12 So what would you suggest in that
13 kind of a situation?

14 DR. WAGNER: Well, the 2007
15 assessment of iPLEDGE, which was on the first
16 year of iPLEDGE information, so that's on the
17 FDA website, it appears to me, by reading that
18 document, that the number of fetal exposures
19 during the SMART program per year was in that
20 120 range. And post iPLEDGE, that number of
21 fetal exposures was in the 120-patients-per-
22 year range.

1 And if you take into account that
2 there was a significant reduction in female
3 patients getting Accutane during that year
4 after iPLEDGE, and part of that was due to
5 implementation of the program, but in our own
6 program, a 40 percent reduction. Then, if the
7 number of patients that became pregnant during
8 that first year remained constant and a 40
9 percent reduction in the number of Accutane or
10 isotretinoin prescriptions happened, then,
11 actually, the rate might have gone up or the
12 reporting got better. We don't know.

13 But the point being it's not clear
14 to us that iPLEDGE has improved things, and
15 our belief is that it significantly has added
16 to the burden.

17 And an example of unnecessary
18 burden, we believe, of iPLEDGE is, why are we
19 registering males and have no insight at all
20 that that has any value to the system? But it
21 doubles the workload in terms of using the
22 system. That was not something that we had to

1 deal with before iPLEDGE came.

2 DR. JENKINS: I have a question,
3 Terry, if I could follow up on that.

4 I would like to ask, Dr. Wagner,
5 if you can try for a second, take off your
6 Kaiser hat and put on a hat of someone working
7 at FDA. Because what you describe makes a lot
8 of sense in a closed system like Kaiser, but
9 how would we implement standards for the
10 thousands or millions of doctors who are in
11 private practice who aren't part of a closed
12 healthcare system? So, how would you
13 implement that for teratogenicity concerns for
14 a product?

15 So, if you don't put in place the
16 exact processes that everyone has to follow
17 and just put out the standards, how do you
18 have a level of assurance you will meet your
19 goals, when we don't have a single system of
20 healthcare? We have a very disparate system
21 of healthcare.

22 DR. WAGNER: And that is a very

1 good question, and I don't want to advocate
2 that everybody has to behave just like Kaiser.
3 I do think that if we do come up with a system
4 where the processes of care need to be defined
5 in an organized or less-organized healthcare
6 system, it would be all right for the less-
7 organized folks to adopt those processes of
8 care because that may be the best solution for
9 them to actually document or improve care.

10 But as you move into the more
11 organized systems of Kaiser Permanente, the
12 Veterans' Administration even, the Cleveland
13 Clinic, and others that have been here, I
14 think then there should be some flexibility
15 around the process. Legitimately, we should
16 be able to document that we hit or exceed that
17 standard. It should be done in a very
18 rigorous fashion that would be shared with the
19 agency, would be submitted for peer review in
20 terms of publication, so that it was actually
21 done in a very rigorous way.

22 Also, I would do it to encourage

1 the agency to experiment. Take an integrated,
2 organized healthcare system and say we do want
3 to hit the standard, but can you actually do
4 something that would take us 20, 30, 40
5 percent better than the standard that has been
6 set? What would you put in place to actually
7 exceed that standard or make it sustainable
8 over time?

9 And that challenge back to us
10 would actually be something that we would
11 welcome because we would like to set new
12 standards around preventing teratogenic
13 exposure. If everybody has to follow the same
14 process of care, we never have that potential
15 for that public/private partnership that the
16 Commissioners talked about for the safe use
17 initiative. How do we incent private
18 organizations to actually go beyond the
19 standard, set new standards, and help in terms
20 of public policy development around drug
21 safety?

22 I don't want to advocate that

1 everybody has to do it the Kaiser way, quite
2 frankly, but let Kaiser and others hit that
3 standard, exceed it, and then come back with
4 new information about the value that we bring.

5 MS. TOIGO: Mwango?

6 DR. KASHOKI: Could I just follow
7 up on that?

8 I would like to get the reaction
9 from the pharmaceutical companies to that
10 proposal, because under the REMS system, the
11 FDA holds sponsors accountable for achieving
12 the goals, et cetera, on implementation of the
13 REMS. So, if a disparate number and type of
14 providers are failing to meet a particular
15 standard, and so on, and we are holding you
16 accountable, what is your reaction to that?
17 And how would you implement that under your
18 own programs?

19 DR. DUFFY-WARREN: Frances Duffy-
20 Warren here.

21 I'm going to try to assess some of
22 that. I think I tried to hit some of that at

1 least in one of my slides in terms of we're
2 not against having stakeholder input, but we
3 do seriously consider that you hold us
4 responsible and accountable for that. That
5 has a huge influence on the distribution
6 system that we then choose and how much
7 control can we exact from that.

8 So, almost by default, we end up
9 doing a certain amount of phasing. Now, for
10 us, as Actelion, our drugs are often -- we
11 don't have a huge distribution system out
12 there. Our experience isn't into widespread
13 use drugs at all.

14 Within the orphan situation, it
15 might actually be a little bit, may be a
16 little bit easier for us, then, to maintain
17 control within a closed system. But we are
18 struggling even to think how to develop that
19 whole system at all and be able to maintain
20 any kind of control. So, for us, it is a big
21 issue, and I don't think we've got any
22 solutions right now, unless we come up with

1 some way of sharing the accountability and the
2 responsibility. I know that's not yet on the
3 table.

4 DR. BOZIC: Yes, I think the devil
5 is in the details on this one. We kind of
6 have to see exactly what we mean by standards,
7 processes, tactical implementation because we
8 may not be all speaking the same language.

9 One advantage of using a standards
10 approach rather than a detailed review of
11 systems is that I guess there may be some more
12 flexibility in modifying the system and
13 adapting it to the individual healthcare
14 practice.

15 But, again, I think it needs to be
16 thought through very carefully in terms of how
17 it would be implemented and then how do you
18 monitor kind of the impact of such a program.

19 MS. TOIGO: Jeff, did you want to
20 provide a PhRMA perspective?

21 MR. FRANCER: Well, I guess two
22 principles, and one of them I think you hit on

1 specifically. It can be very, very difficult,
2 obviously, for companies to be held
3 accountable for the behavior of the entire
4 healthcare system. I think that has to be
5 taken into account.

6 As we have said before, we believe
7 that there has to be a significant amount of
8 outreach to healthcare professionals before
9 and during implementation of various REMS
10 programs.

11 MS. TOIGO: Thank you.

12 And Dr. Wagner?

13 DR. WAGNER: So, one quick
14 followup. I do think the devil is in the
15 details.

16 But, also, if the agency would
17 communicate to the sponsors that there was a
18 possibility for flexibility, for a standard-
19 setting approach -- one of the problems we
20 have with the sponsors and one of the reasons
21 we want to be able to directly advocate to the
22 agency is that the sponsors often come back to

1 us and say, well, the agency has told us we
2 could only have one program or the agency has
3 indicated we can only do it this way. End of
4 conversation.

5 We just don't think that's the
6 right decision. So I'm not picking on anybody
7 on this panel, but we have had experience
8 where sponsors will tell us what the agency
9 has told them. That may be true or it may not
10 be true because it may not reflect what you've
11 actually said, but that's what we're hearing
12 from sponsors.

13 So, what we would like to say or
14 encourage the agency to do is encourage the
15 sponsors to have maybe an element of a REMS
16 with ETASU, where there is the potential for
17 flexibility to do it on a standards basis
18 rather than a process basis.

19 We should enter into a written
20 agreement, agree to behave appropriately,
21 agree with all the protections for patient
22 confidentiality, et cetera, to provide data

1 that demonstrates that our standards-based
2 approach can at least meet the quality
3 standard or exceed it. And if we can exceed
4 it and we can identify the reasons why we got
5 better, we should be willing to share that
6 more widely and encourage the agency to review
7 that because we could make improvements maybe
8 in the rest of the system.

9 So, I think the agency
10 communicating back to the sponsors that there
11 is the potential for flexibility in a system
12 that is willing to make a written agreement to
13 get there would actually open up that channel
14 for further discussion.

15 DR. BOZIC: I think one area where
16 standards could work well is in the area of
17 education. I think we can sort of agree on
18 sort of the broad principles about what we
19 want to educate, let's say, for a particular
20 program. Then, in terms of the
21 implementation, the how, the tactics, you
22 know, that could be left up to the individual

1 company on how to do it, again, because you
2 might want to educate a prescriber who is in
3 private practice a little bit differently than
4 prescribers that are part of a large
5 healthcare network. So, I think standards
6 might work very well in the area of education.

7 MS. TOIGO: I think Suzanne was
8 next and then Claudia.

9 DR. BARONE: I'll wait.

10 MS. TOIGO: Okay. All right, then
11 you're on, Claudia.

12 DR. KARWOSKI: I guess a question
13 for Kaiser or industry. If there was the
14 ability to have this flexible process, what
15 sort of information could you provide to the
16 sponsor to give them some assurance that the
17 program was being followed? Or would there be
18 the ability for the sponsor or any third party
19 to come in and sort of audit whether the
20 processes are working and whether these
21 required tests are being done, and so forth?

22 DR. WAGNER: So, I'll start.

1 Again, Richard Wagner from Kaiser Permanente.

2 I do think we could come up with
3 some written agreements. I think our
4 preferred method would be to do something
5 through an organized research effort through
6 an IRB-approved process, for example.

7 One of the advantages of going
8 through an IRB-approved process is it does
9 ensure that patient confidentiality is
10 protected appropriately. So that would be
11 another process for us to engage in, as more
12 of a formal research process. So that would
13 entail a retrospective type of process,
14 involve the appropriate controls, appropriate
15 scientific design of the project, and do it in
16 a very rigorous fashion that collected
17 information over time. So that if it was
18 initially reviewed and felt that it would be
19 valuable, it would actually then be subject to
20 post representations, peer review,
21 publication, and that type of approach would
22 make the most sense.

1 Actually, we are not very
2 interested in having folks come in and audit
3 us, quite frankly, but we would, then, have to
4 set up an alternative system that would
5 actually demonstrate in a very open,
6 transparent way that we have actually met or
7 exceeded that standard that was designed ahead
8 of time.

9 So, we would want to do it in a
10 very organized way and I think through an IRB-
11 approved study protocol it would make the most
12 sense.

13 MS. TOIGO: Anyone else on the
14 panel want to comment?

15 (No response.)

16 No? Okay.

17 Keith?

18 DR. WEBBER: One of the points
19 that was made by the panel is concern over
20 burden to healthcare providers with
21 implementing REMS. As we all know, the market
22 of a new drug upon approval over the years

1 after approval is pretty dynamic. Lots of
2 things change in terms of the market, and new
3 drugs becoming available that compete with
4 that, as well as alternative therapies.

5 So, when you overlay on top of
6 that a REMS and education of healthcare
7 providers and implementation of the learning
8 process, how would you advise us in terms of
9 evaluating what metrics to use with regard to
10 a burden in that dynamic type of environment
11 where the burden is changing? As healthcare
12 providers get more familiar with the REMS, the
13 burden you would think would decrease. So,
14 it's a very complex system. I would like to
15 see what recommendations you might have.

16 DR. BOZIC: This is Carmen Bozic.

17 I think one approach would be
18 through a survey methodology, such as what we
19 used in surveying prescribers about, first,
20 whether they've experienced burden, what areas
21 of the program are the most burdensome, how
22 many people do they need in a practice to

1 administer the program, and whether they
2 needed to hire additional people or did they
3 repurpose sort of the existing people they had
4 in the practice. And then whether that had
5 any impact, for example, in terms of the
6 amount of time they could spend with their
7 patients.

8 So, I think you can survey very
9 specifically I think on some of those
10 dimensions directly from prescribers and other
11 healthcare professionals that are involved in
12 the administration of the program.

13 MS. TOIGO: Glenn?

14 MR. NAPHY: Glenn Naphy from
15 Springboard.

16 There's a couple of things. First
17 of all, as a product gets longer and longer in
18 its life cycle, yes, the burden of executing
19 the REMS for five years on a physician that's
20 been prescribing it for five years is probably
21 already systemized or optimized at that point.

22 The other concern is that if you

1 relax that, new physicians then come into the
2 marketplace and new products. So the constant
3 reminder is not a bad thing. So I don't think
4 it's all the survey methodology is completely
5 where we really want to go because we have to
6 also measure these unintended impacts.

7 They often come up in what we have
8 seen in some of our qualitative market
9 research, when we're actually probing around
10 and trying to understand what is the impact of
11 a particular program on staff that was
12 mentioned earlier and yesterday as well. But
13 there may be other things where now they have
14 to have a patient counseling session. Then we
15 may need to say to Medicare, hey, do we need
16 to compensate for these other coaching areas?

17 So I think it is a dynamic
18 process. Unfortunately or fortunately, once
19 a REMS is established, it kind of needs to go
20 with the life of the product. That's just
21 been what we have seen thus far, but we are
22 continuing to learn the process like everybody

1 else. So, that's just some highlights.

2 MS. TOIGO: Gerald.

3 DR. DAL PAN: This is for Mr.
4 Naphy. You mention that education can reduce
5 inappropriate prescribing. I was wondering if
6 you could tell us a little bit more about
7 that.

8 You know, we have shown -- our
9 staff here has published stuff from the
10 nineties that showed that "Dear Healthcare
11 Professional" letters aren't particularly
12 effective. Labeling recommendations aren't
13 followed. And we heard last week at the
14 opioid REMS at least some skepticism about
15 education.

16 So, I was wondering if you could
17 expound on your comment a bit.

18 MR. NAPHY: Yes, I agree it's not
19 the one-size-fits-all. Education is not going
20 to solve all of our REMS issues.

21 What we have seen, though, in some
22 of this education is we think about the

1 physician environment today. As the
2 physicians spend less and less time with their
3 patients, just because of other demands, they
4 have hospital rounds and other demands on
5 their practice, such as insurance, et cetera.
6 So, one of the things is just taking a step
7 back and really explaining back to the
8 patient, hey, you're on this medication. It
9 does have these side effects. Just as a
10 reminder, that's what we mean by some of these
11 education.

12 The other thing is that we have
13 seen a push by some of the sponsors, because
14 they have REMS, putting more attention into
15 those patient education tools or the patient
16 information, more PPIs are being discussed.
17 And also, we have these healthcare extenders,
18 we call them, where it may be a PA or a
19 nurse's assistant also spending time with
20 patients. If we can help them educate the
21 patients on the products, it will alleviate
22 some of the REMS. It doesn't replace, I

1 guess, the need for a med guide in a lot of
2 cases, but it does allow an opportunity for a
3 dialog that may not exist today.

4 MS. TOIGO: Suzanne?

5 DR. BARONE: This is for Jeff.

6 You mentioned, and I don't want to
7 misinterpret what you said, that assessments
8 or full implementations should be reserved for
9 ETASU REMS. Can I extrapolate that to mean
10 that you only think REMS should be those
11 things with elements to assure safe use or do
12 you feel that a full assessment should only be
13 done if it has elements to assure safe use?
14 Then, what would be the role of the
15 communication plan and feedback and whether
16 something worked or not?

17 MR. FRANCER: Yes, thanks for the
18 question. I'm happy to clarify.

19 FDA has actually, I think, an
20 enormous amount of discretion in how the
21 agency is authorized to implement REMS. There
22 are certain minimal requirements that are in

1 the statute, and then the FDA has discretion
2 for the rest, and also discretion in how it
3 requires, for example, an assessment and what
4 an assessment means.

5 We advocate for really a graduated
6 approach. The drugs with the most serious
7 risk should have the most serious REMS. And
8 what I mean by serious is all the bells and
9 whistles that we talk about.

10 For a communication plan, it's
11 possible to assess how it works based on
12 changes in the pharmacovigilance, and in a
13 much more, I think, informal method than
14 requiring patient comprehension surveys, et
15 cetera.

16 MS. TOIGO: Mwango was next, and
17 then John. Then I think, then, unless, Jane,
18 did you have one more? Okay, well, then let's
19 try this: Mwango first.

20 DR. KASHOKI: I have, first, a
21 request for Mr. Naphy. You talked about your
22 experiences and findings with regard to

1 characteristics of what are the most
2 successful REMS or the least successful REMS.
3 If you haven't already, could you provide
4 those data to us? Either submit it to the
5 docket, or if you summary reports that expand
6 upon the findings that you presented?

7 MR. NAPHY: We will definitely
8 look into that. The reason why is because
9 companies do hire us to do market research and
10 things of that nature. But we will definitely
11 take that request back and see if we can
12 summarize in an appropriate manner that does
13 not share directly with any company.

14 DR. KASHOKI: Thank you.

15 And then the question is for Dr.
16 Duffy-Warren. You had spoken about the
17 challenges of getting, potentially even
18 getting an approval of a priority drug or a
19 drug under a priority review timeframe that
20 has a REMS.

21 Now given all of the feedback that
22 we have had or suggestions we've had over

1 these discussions about increasing stakeholder
2 involvement, getting evaluations of the
3 burden, and so on and so forth, do you have
4 any recommendations as to timeframes that are
5 currently existing with regard to review of
6 applications? Do you have suggestions about
7 whether these should be expanded or
8 suggestions for how we can potentially revise
9 our review processes to try to take into
10 account all of these suggestions?

11 DR. DUFFY-WARREN: Yes, Frances
12 Duffy-Warren here.

13 I was pondering a lot of this last
14 night as well because I know it is really a
15 challenging time of practicalities of being
16 able to do some of this, and the overall
17 timeframe that is available to us and also for
18 you to stay within the PDUFA.

19 In terms of when you could do it,
20 I sometimes think sometimes a signal does come
21 up early in development, and we have the
22 development safety update report. So, if you

1 get teratogenicity coming up during
2 development from the preclinical, that could
3 for some products, depending on the
4 indication, the population, and the drug
5 itself, that could already put a very early
6 amount into the system for those ones to say
7 maybe we should be talking at that point and
8 starting there. If it is severe enough,
9 already identified as a signal that is likely
10 to end up with a REMS with elements to assure
11 safe use, already trigger at that point,
12 trying to put some of the processes in place.

13 Of course, for us, the risk is
14 always, will we ever finish our clinical
15 trials and actually have something worth
16 submitting? But I think at least that would
17 give us one opportunity for some of the drugs
18 out there.

19 The other one that I was trying to
20 think about a little bit was perhaps looking
21 through treatment INDs to put some pilots in
22 during a treatment IND phase to test out some

1 of the process and procedures and see if they
2 could work under that auspice. Because,
3 again, those kinds of things usually start
4 before you put your IND in, but at least might
5 give you some opportunity to try out some of
6 what we have been making.

7 I think the third one that I was
8 actually trying to think about was perhaps
9 what applies more to the orphan drug
10 situation, but it would potentially come post-
11 approval, but that might be for modifications,
12 is try them out within disease registries or
13 a lot of the drugs have registries post-
14 approval, and try out some of the changes
15 there before coming to finalization and
16 implementation of those changes.

17 So those are three of the things
18 that I could think of in practical terms.

19 DR. BOZIC: This is Carmen Bozic.

20 I would like to echo that, that I
21 think the earlier we can speak to FDA about a
22 REMS, the better. For a new chemical entity,

1 you know, often the end of phase 2 is the
2 appropriate timeframe to start talking about
3 the REMS, and then perhaps already piloting
4 some of the REMS elements in your phase 3
5 trials. So, you're kind of doing some pre-
6 testing at that point.

7 Then, the other place is at the
8 end of the pre-BLA or pre-NDA meeting to
9 discuss the REMS in more detail. And finally,
10 earlier, during the review process by the FDA,
11 that we can engage and have the conversation
12 as early as possible during the review about
13 sort of what the REMS is going to look like,
14 what the elements are going to be.

15 We do have to be sort of practical
16 as well, right? As I mentioned previously,
17 even with a great deal with stakeholder input,
18 you may still not know everything until you
19 implement, and therefore, it's still very
20 important to have a process to rapidly update
21 the REMS after it's approved and implemented.

22 MS. TOIGO: John, did you want

1 to --

2 DR. JENKINS: It's a very complex
3 question as far as the answer. The question
4 is easy; the answer is going to be tough. So,
5 maybe I'll put it out there, and if anyone has
6 a quick answer, but maybe it's something
7 people can respond to in the docket.

8 As part of Mr. Francer's
9 presentation, he mentioned that FDA should use
10 the most efficient and the least burdensome
11 tools to minimize risk. That sounded great as
12 it kind of came through, but then I was trying
13 to think of, what does that actually mean?

14 So, I was wondering if people have
15 actual examples they could provide, say using
16 a risk of like teratogenicity. What are the
17 most efficient and the least burdensome tools
18 that would minimize that risk? They almost
19 seem opposite in their direction. Most
20 efficient to me means that you would be most
21 effective at actually minimizing the risk,
22 minimizing exposure of women of childbearing

1 potential, but then I hear least burdensome.

2 So, anyone have any ideas of how
3 you could minimize exposure to teratogenicity
4 through the most efficient but the least
5 burdensome approach?

6 MR. NAPHY: This is Glenn Naphy
7 from Springboard.

8 We have had the same observation.
9 There's no blanket statement that REMS should
10 be less burdensome because in some cases they
11 should be more burdensome. It's almost like
12 the burden should match the risk.

13 And if the incidence of misuse is
14 very high and the consequences of misuse high
15 as well, whether it is death or some
16 debilitating event, then the burden should be
17 appropriately matched. I think that is what
18 we are finding out, and this is definitely
19 early for us from a market research
20 perspective. But that is what we are seeing.

21 I will take the request back. If
22 there is other insight that we can provide

1 more concrete examples from our data, we will
2 be glad to submit them to the docket.

3 MS. TOIGO: Jeff, did you want to
4 comment?

5 MR. FRANCER: Well, I'm not going
6 to comment on the teratogenicity question, but
7 what I would like to say is that, in sum, what
8 we are talking about is balance. There has to
9 be, obviously, the most appropriate balance
10 between, obviously, protecting the safety of
11 patients, which is of the utmost concern, but,
12 also, doing so in a way that doesn't cause
13 unnecessary burdens and inefficiencies in the
14 healthcare system.

15 MS. TOIGO: Okay, Jane, this will
16 be the last question, and then we'll move to
17 the next panel because we will continue the
18 same theme.

19 MS. AXELRAD: Okay. Well, I'm
20 going to peg off of what John said. The devil
21 is in the details. We're the ones that have
22 to work with the sponsors to determine what is

1 an appropriate program.

2 So, just saying generally we want
3 to be least burdensome, I mean the statute
4 says that, least burdensome, you know,
5 preserve access. The question is, how do you
6 do that?

7 The reason I wanted to ask this
8 question of this panel is that we heard a lot
9 from other panels about the pharmacy systems
10 and electronic systems that can be used in the
11 pharmacy, but we haven't heard very much
12 specifics about how we can reduce the burden
13 on prescribers, which everybody acknowledges
14 that, if you have one system, it's one thing,
15 but if a prescribing is prescribing a bunch of
16 different drugs that under REMS and they have
17 multiple education responsibilities,
18 certification forms, and patient counseling
19 requirements, that it doesn't take much. You
20 don't really need to do an assessment to see
21 that that might be burdensome.

22 But what I haven't heard is much

1 in terms of solutions to that. And taking it
2 up a level, where should we be looking to try
3 to figure out ways of reducing the burden or
4 standardizing the programs that are just going
5 to be built in, if you have to have those
6 elements associated with at least some drugs
7 that have serious risks?

8 MS. TOIGO: Dr. Wagner?

9 DR. WAGNER: And I think system
10 technology is what's going to actually help
11 drive improvements in the system. So, I think
12 you've got to go back to vendors like Epic and
13 Cerner and others who actually are
14 implementing electronic health records across
15 the country. And if Epic's website is
16 correct, and they have 75 million Americans
17 within the Epic healthcare system, what can we
18 build into that Epic system, other systems
19 equivalently that can actually facilitate
20 patient care?

21 So, an example of something that
22 we do, not with isotretinoin, but in other

1 programs we have within our electronic health
2 record the ability to do what we call a
3 proactive office encounter. So, we could
4 anticipate a patient in a REMS program because
5 we can identify them upfront. If there's
6 aspects of care that need to be done under the
7 direct supervision of a physician, or even
8 with another healthcare provider that can
9 actually perform that function legally under
10 statute, then we can actually set that up to
11 be done routinely. So, we can actually make
12 it easier for the doctor to be successful
13 because the patients are queued up, so to
14 speak, in terms of the proactive office
15 encounter approach.

16 And we do that with other
17 improvements that we are trying to make for
18 quality. So, if we have a diabetic patient or
19 a high blood pressure patient or a patient
20 with cardiovascular disease, we can actually
21 identify what they need for the optimum care.
22 If there are gaps in the care, the proactive

1 office encounter system sets up for that
2 patient, that nurse, that medical assistant,
3 that pharmacist, others, to follow up
4 appropriately, so that that patient never
5 falls outside of the standard of care, so to
6 speak.

7 We also have a system to track if
8 you have failed to do what the doctor has
9 asked you to do. So you are two weeks late to
10 a laboratory test. Then the absence of you as
11 a patient taking some steps that are
12 appropriate can also be tracked and feed back
13 into the health system. Then the folks who
14 are at the right level to provide that care,
15 that followup, that intervention with the
16 patient, can actually be tasked to do that.
17 And they stay on that task until they get it
18 completed.

19 So, I would go back to the systems
20 technology approach, either on the pharmacy
21 system side or maybe even more powerfully, as
22 we move into an era over the next 5 or 10 or

1 20 years, implementing electronic health
2 systems, how do we embed this into the
3 electronic health system? How do we embed it
4 into eprescribing? And how do we embed it
5 into pharmacy systems, so that at the time of
6 dispensing, if that turns out to be the right
7 intervention, that we pick up that patient and
8 assure that the standard of care is met?

9 And it's going to take that type
10 of discussion, I think, with vendors that
11 provide those types of systems. That would
12 be, again, another opportunity for a
13 private/public partnership in terms of, again,
14 not something to fix REMS next year, but
15 something that is going to set us up to have
16 successful REMS programs over the next several
17 years.

18 I think that approach with the
19 electronic health systems is going to make
20 sense as the healthcare delivery system
21 evolves in that fashion.

22 DR. BOZIC: This is Carmen Bozic.

1 There also could be a common
2 platform or technology for delivering
3 education across a range of drugs. I see it
4 that you would have to have sort of one
5 overseer of that. Perhaps it is a medical
6 association or something like that. But we
7 already have that with guidelines across the
8 treatment of various diseases. All of these
9 educational tools that we're developing for
10 very specific drugs could be incorporated into
11 sort of a common sort of educational platform
12 and technology, and be an internet-based one,
13 for example.

14 MS. TOIGO: Okay. Thank you very
15 much, panel 1, for a stimulating discussion.

16 And for others in the audience who
17 may have responses to some of the questions
18 that were posed by the FDA panelists, the
19 docket is open. And if you would like to
20 share your perspective, please do so and
21 include it in the docket.

22 And if panel 2 could come and take

1 their seats?

2 And a reminder about the open
3 public session: if this last panel stimulated
4 anybody who wants to maybe go sign up to make
5 some public comment, please do so as well.
6 You have 45 minutes now.

7 Okay. Welcome, panel 2. We're
8 going to continue to talk about the topic
9 issues regarding elements to assure safe use.
10 Starting us off is Nicole Kelly from the
11 American Chronic Pain Association.

12 MS. KELLY: This is live? I don't
13 have to push the button? Okay, thanks. Okay.
14 Thank you very much.

15 Because we are an organization
16 that deals primarily with people with pain
17 problems, our concerns directly are concerned
18 with opioid REMS. So, that's the topic I'm
19 going to be discussing today.

20 For 30 years, the American Chronic
21 Pain Association has focused our efforts on
22 educating people with pain in pain management

1 strategies and with the idea that they can
2 help to improve the quality of their lives.

3 Over these three decades, we have
4 learned a great deal about how people with
5 pain learn and respond to information. I
6 would like to share some of that with you
7 today.

8 Clearly, consumer education will
9 need to be part of the REMS for opioids. As
10 your requirements for this information take
11 shape, we urge you to keep in mind the special
12 needs of the consumer group and the
13 circumstances in which opioid education is
14 likely to take place.

15 People with pain may be quite
16 intelligent, but they are also likely to be
17 distracted, confused, and fearful. Some will
18 have language or literacy issues. Some will
19 have poor vision or hearing.

20 Standard printed materials are
21 unlikely to meet the needs of this diverse
22 population. In addition, the press of time in

1 most health practices will make one-on-one
2 education a challenge, and we have heard a lot
3 today about the burden on the practice.

4 We suggest that for each class of
5 drug that requires a REMS that there should be
6 a standardized multimedia package developed.
7 This package could include such elements as a
8 very simple printed piece, augmented by
9 graphics, that illustrates the key elements,
10 for example, of opioid safety; a video which
11 explains what an opioid is, reasonable
12 expectations for treatment because this is a
13 big issue with opioids; how to and how not to
14 use the medication; how to store them safely,
15 and how to dispose of them properly.

16 The ACPA has recently produced a
17 video that does all those things, and we would
18 be happy to share it with anybody who is
19 interested in seeing an example of what I'm
20 talking about.

21 We also suggest a checklist for
22 dosing, storing, and disposing of opioids,

1 along the lines of our care card, which is
2 another graphical tool that we have that helps
3 people remember how to take their medications
4 properly.

5 And we would suggest that this
6 page also have on it space for providing for
7 the provider information, phone numbers, and
8 so forth, and emergency numbers in case of
9 overdose or problems with the drugs.

10 Finally, we would suggest the
11 development of a standardized website which
12 could house all of these elements that would
13 be accessible in multiple languages for
14 viewing and downloading by the prescribers'
15 offices, by the person, the consumer, and also
16 by the general public.

17 Such a package of materials can
18 help to ensure that all patients receive the
19 education they need while at the same time
20 respecting the financial and time constraints
21 of the practitioners.

22 We also believe that opioid

1 agreements can play a role in ensuring
2 responsible use and informed consent on the
3 part of the consumer, but we urge the
4 development of standardized language for these
5 agreements. This common document should be
6 created by professional communicators and not
7 just by attorneys.

8 This can enhance the agreement's
9 usefulness as an educational tool and help to
10 ensure that these agreements are reasonable
11 for the person with pain, and also used for
12 the protection of the consumer and not just
13 for the practitioner. Also, a sample of this
14 agreement also could live on this common
15 website.

16 But ensuring that people who use
17 opioids understand how to use them properly is
18 really only half the battle. We also need to
19 educate the general public, and opioid misuse
20 is clearly a major public health hazard, and
21 it's important that we educate the public
22 about the risks of opioids when used by those

1 for whom they have not been prescribed.

2 We would urge you to require
3 development of a series of PSAs, billboards,
4 ads, and other public media, focusing on the
5 dangers of taking medications not prescribed
6 for you, using opioids recreationally, and
7 other high-risk behaviors. Such a campaign
8 might be funded by pooled contributions from
9 the industry.

10 It's in everyone's interest that
11 opioids remain available to all who can
12 benefit from their use, and the ACPA and other
13 nonprofit organizations with an interest in
14 helping people with pain can be invaluable
15 resources in this education effort.

16 We urge you to call on us to work
17 in partnership with the FDA and with the
18 industry to ensure that the benefits of
19 opioids are balanced against their risks and
20 that education is delivered in the most
21 efficient way possible.

22 Thank you.

1 MS. TOIGO: Thank you, Ms. Kelly.

2 And our next presenter is Marc
3 Boutin from the National Health Counsel.

4 MR. BOUTIN: Good morning,
5 everyone.

6 I am going to start off first by
7 thanking the FDA for allowing us to present
8 and speak with you all today. I also want to
9 thank the FDA for the tremendous amount of
10 work it does on behalf of people with chronic
11 diseases and disabilities, with extremely
12 limited resources. That's an issue that the
13 patient community would like to address.

14 I want to speak to you today about
15 REMS and the patient perspective around REMS,
16 but I want to put it into context, the context
17 of somebody with a chronic condition and the
18 context of the patient advocacy community as
19 a movement. We are relatively young and
20 relatively immature in our advocacy efforts.

21 First, let me start by explaining
22 that we view people with chronic diseases and

1 disabilities as patients and somewhat distinct
2 from consumers. We recognize that patients
3 and consumers are part of the same stakeholder
4 group, but we represent opposite ends of the
5 spectrum. As a result, we have very different
6 perspectives on how FDA ought to deal with
7 benefit/risk and how it applies to REMS.

8 And I want to illustrate the
9 example by explaining that many people can be
10 a consumer and a patient at the same time.
11 Some people are patients and not consumers,
12 and vice versa.

13 The easiest way to understand the
14 distinction is I'll say by way of show of
15 hands, how many people here suffer from hay
16 fever or allergies, if you would raise your
17 hand?

18 So quite a few people. Now I
19 would suggest that many of you are probably
20 taking some kind of medication for your
21 allergy, and your tolerance for a really bad
22 side effect is probably very, very low.

1 But I ask you to imagine that you
2 get a call from your doctor, based on some
3 test results because you were having stomach
4 pain last week. It turns out you have
5 pancreatic cancer. Your prognosis is about a
6 year, maybe a year and a half, if you're
7 lucky. There are no good treatments for
8 pancreatic cancer. And I would suggest to you
9 that your tolerance for a risky medication to
10 treat your pancreatic cancer, to extend your
11 life, to improve the quality of your life,
12 dramatically rose, but recognize your
13 tolerance for a really bad side effect for
14 your allergy medication still is pretty low.
15 You can be a patient and a consumer and have
16 very different perspectives on how we treat
17 medications.

18 Now let me put this in the context
19 of the patient advocacy movement. We really
20 cut our teeth only a couple of decades ago.
21 In fact, the patient advocacy movement was
22 largely responsible for calling attention to

1 the fact that we needed to speed up the drug
2 approval process. You had folks chaining
3 themselves to the fence saying we need new
4 medications to treat HIV and AIDS. At that
5 point in time, a diagnosis was a death
6 sentence, and a really horrible death
7 sentence.

8 And we saw dramatic changes.
9 Right now, it's a chronic disease that is
10 managed by many people in the United States.
11 We saw PDUFA come about, and we saw tremendous
12 advances over the PDUFA II and III, in
13 particular. We saw advances for people with
14 cancer and heart disease.

15 The patient community became
16 somewhat lackadaisical. We actually moved on
17 to NIH and worked to secure doubling the
18 funding of NIH. We were very excited about
19 that, but we expected a doubling of the
20 treatments. And what we realized was we had
21 lost our focus on the FDA. We need to bring
22 our focus back to the FDA. Basic research is

1 important. We have to make sure the second
2 half of the development process is addressed.
3 The FDA is more than a regulatory body. It's
4 a public health and science body. We need to
5 appropriately fund it and make sure it can do
6 its job.

7 With respect to REMS, our concern
8 on this issue really came from our activities
9 in PDUFA IV, where we worked to make sure that
10 not every product would have to have a REMS,
11 and it was our view that a REMS would be used
12 to get a more risky medication for somebody
13 who had pancreatic cancer to them quicker. It
14 was intended by us as a tool to speed up the
15 process.

16 It's our perception that, for a
17 variety of reasons, largely because we put it
18 into a system where we have not yet built our
19 surveillance systems, we don't have our
20 electronic records, we don't have the delivery
21 systems exactly where we want, that many of
22 the REMS procedures have created barriers.

1 Our recommendation is that you
2 need to bring the patient and consumer
3 community involved in the process determining
4 when a product is going to get a REMS and what
5 kind of REMS would be appropriate, given its
6 benefits and risks. Addressing a product for
7 somebody with pancreatic cancer or ALS or a
8 rare disorder without any effective treatment
9 has a very different benefit/risk profile. We
10 are willing to take a risk on a risky
11 medication because the consequence of our
12 disease is far worse, but if we are addressing
13 the development or growth of eyelashes, our
14 risk tolerance is far less. Let's match the
15 process to the product and let's be
16 responsible and give FDA the ability to go to
17 both extremes.

18 Right now, we have forced FDA into
19 the center because we criticized it from both
20 ends. We need to help it and work with the
21 FDA to actually expand this out, so that we
22 can have those drugs that we need to treat

1 conditions without treatments as well as
2 address safety issues that are of concerns to
3 consumers.

4 Thank you.

5 MS. TOIGO: Thank you, Marc.

6 Our next speaker is Dr. Sidney
7 Schnoll from Pinney Associates.

8 DR. SCHNOLL: Good morning. I'm
9 Sidney Schnoll, Vice President for
10 Pharmaceutical Risk Management at Pinney
11 Associates.

12 And Pinney Associates is a
13 healthcare consulting firm that develops,
14 implements, and evaluates a number of REMS
15 programs.

16 I would like to go over some key
17 principles that I think are very important in
18 this entire REMS process. We have heard a lot
19 of talk about standardization, but there
20 should be predictability and feasibility in
21 the process, along with transparency, as has
22 been discussed over the last two days.

1 When it comes to shared REMS, I
2 think the FDA has to take some responsibility
3 in not only encouraging that all the marketers
4 work together, but has to be very much
5 involved in the entire process.

6 This morning's panel is dealing
7 with elements to assure safe use, ETASU. In
8 looking over the elements to assure safe use,
9 one of the things about which we have been
10 very concerned is that most of these elements
11 have never been studied to demonstrate that
12 they can have the effect that they're supposed
13 to have without reducing benefit. This has
14 been, again, very intensely discussed in the
15 past two days.

16 So, we need to develop something
17 that is predictable and feasible for moving
18 forward. I would like to give you some
19 examples of some issues about which we have
20 concerns.

21 There are three products currently
22 on the market. All have the same API. All

1 have the same indication and very similar
2 delivery systems.

3 One of these products has a very
4 intensive REMS, and the others have REMS that
5 are very light. As you can imagine, there is
6 preferential prescribing of these products,
7 and this has persisted for some time.

8 In terms of both prescribers and
9 patients, it is hard for them to understand,
10 is this a product, is the API one that has a
11 lot of risk or doesn't it have a lot of risk?
12 We have to come up with something that is
13 consistent, so we are giving a consistent
14 message to everybody.

15 Also, in terms of evaluation of
16 REMS, we need consistent tools and programs so
17 that there can be comparisons of data.
18 Presently, we use very different systems. So,
19 we can't look at whether or not certain
20 elements really work or don't work when we try
21 to look across different drugs.

22 One of the things that was very

1 disturbing to us was when the guidance was
2 published there really was no consistency
3 between what was in the guidance and certainly
4 what was given as the model REMS at the end of
5 the guidance, and there hasn't been
6 consistency as new REMS have been developed.
7 So, we need to see more consistency in what is
8 coming out in terms of the REMS and what the
9 FDA is approving.

10 We have heard a lot about
11 standardization, but this has to begin very
12 early in the process. It needs to begin
13 during preclinical and throughout clinical
14 development programs, so that sponsors really
15 understands will they need a REMS and how
16 significant the REMS elements need to be.

17 In terms of feasibility, we have
18 to look at the fact that one size does not fit
19 all in a REMS. Certainly, a single medication
20 guide for all extended release opioid products
21 will not be sufficient to convey appropriate
22 messages to patients. Neither does all the

1 antiepileptics have suicidality as a problem.

2 And I know we are going to get
3 into discussion of generics in a little while,
4 so I won't go into that now.

5 We need to have transparency in
6 terms of what we are doing. As we can see
7 here, there are some issues that have occurred
8 when products have become generic in
9 discussions between ANDA- and NDA-holders and
10 these need to be addressed.

11 As has been pointed out, the FDA
12 has to seek input from all stakeholders in the
13 development of a REMS to understand the full
14 impact that the REMS is going to have.

15 In summary, we have to look at the
16 fact that the FDA has proposed REMS tools and
17 elements that should be demonstrated to be
18 effective prior to asking industry to use
19 them. We have discussed the fact that these
20 can be a burden on the healthcare system. We
21 need a predictable and feasible process for
22 developing REMS with ETASU, and FDA should

1 seek input from all stakeholders to avoid
2 overly-elaborate REMS programs that inhibit
3 access, excessively burden the healthcare
4 system, or inhibit competition.

5 Thank you very much.

6 MS. TOIGO: Thank you, Dr.
7 Schnoll.

8 Our next speaker is Paul Brown
9 from the National Research Center for Women
10 and Families.

11 MR. BROWN: Good morning. Thank
12 you for the opportunity to comment on behalf
13 of the National Research Center for Women and
14 Families on the issues regarding elements to
15 assure safe use.

16 Our Center is a consumer-oriented
17 think tank. We do not accept contributions
18 from companies that make medical products.

19 Our position is that any
20 modifications to REMS, such as streamlining or
21 standardizing the process, must not weaken one
22 of the primary purposes of REMS, which is to

1 ensure that the benefits of medications
2 outweigh the risk of the product.

3 My main point is that REMS does
4 provide access to medications. Yesterday at
5 the meeting I heard several times people
6 bringing up the issue of patient access to
7 medication. It was listed in The Federal
8 Register also. Let's remember that elements
9 to assure a safe use, the main purpose, which
10 was stated in the guidance, and that is the
11 elements to assure a safe use are intended to
12 provide safe access for patients to drugs with
13 known serious risk that would otherwise be
14 unavailable.

15 Let me emphasize the last part:
16 drugs with serious risk that would be
17 otherwise unavailable. Without ETASUs, these
18 drugs would be unavailable.

19 ETASUs, every time I hear that
20 phrase I want to say, "Gesundheit." It's an
21 interesting phrase.

22 Pharmacy organizations have stated

1 that REMS requirements can disrupt the usual
2 workflow. Yes, they are purposely designed to
3 do that. We're talking about medicines with
4 serious risk to patients. No one wants to
5 dispense these medications as quickly as
6 possible, as if they were hamburgers from a
7 fast food restaurant.

8 What's the percentage of REMS that
9 require elements to assure a safe use? Less
10 than 10 percent of new REMS contains ETASUs.
11 And it's also noted that 70 percent of newly-
12 approved REMS only require a medication guide
13 and a timetable, the least burdensome
14 requirements.

15 I want to touch on a few other
16 points, and then I'll wrap up. There has been
17 criticism about dispensing some drugs only in
18 certain settings, such as hospitals. I think
19 that is done out of common-sense precaution,
20 in case the physician needs access to
21 medications or equipment due to an adverse
22 reaction or allergy.

1 However, it does seem reasonable
2 for hospitals without certified prescribers or
3 pharmacists to have access to REMS medications
4 in emergency situations. I believe that was
5 described yesterday by someone from the
6 Cleveland Clinic or perhaps the University of
7 Chicago. That does seem reasonable to me.

8 Dispensing of drugs to patients
9 with evidence of safe use conditions. Some
10 stakeholders are concerned about the effect of
11 these restrictions on patients' access to a
12 medication. Again, I say, without the
13 elements to assure a safe use, these
14 medications would not be available at all.

15 REMS and the healthcare system.
16 Should REMS with elements to assure safe use
17 be compatible with the established
18 distribution systems, so as to minimize the
19 burden to the healthcare system? Maybe not.

20 Minimizing the burden has the
21 potential to undermine REMS. The focus of
22 REMS should be on ensuring that the benefits

1 of medication outweigh the risk of the
2 product, and if that imposes a burden, such as
3 educating and tracking patients, then that is
4 part of the cost of allowing drugs with known
5 or potentially serious risk onto the market.
6 I think that was stated also in the earlier
7 panel that was just before us.

8 Standardization. Can the elements
9 of REMS be standardized and streamlined for
10 sponsors, prescribers, and pharmacists? Of
11 course. And I think the FDA started off with
12 their templates, and I think those are good
13 examples. They're quite specific, and I think
14 the FDA could probably do some more examples
15 of that.

16 Overall concern regarding these
17 issues of the concerns and problems that have
18 been brought up. I think the FDA must
19 scrutinize carefully to determine if they are
20 systemic problems with REMS or if they are
21 simply startup and implementation problems.
22 That's also been mentioned.

1 In summary, streamlining or
2 standardizing the REMS process is fine as long
3 as it does not weaken the primary purpose of
4 REMS. The percentage of medications requiring
5 elements to assure safe use is small. So
6 let's keep the burdens for prescribers and
7 pharmacists in perspective.

8 And finally, REMS is providing
9 access to medication that would otherwise be
10 unavailable.

11 Thank you for the opportunity to
12 comment.

13 MS. TOIGO: Thank you, Paul.

14 And our next speaker is Bill
15 Vaughan from Consumers Union.

16 MR. VAUGHAN: Thank you very much.
17 On behalf of Consumers Union, the publishers
18 of Consumer Reports, we appreciate this
19 opportunity.

20 We like REMS, agree with the
21 comments of the National Women's Health
22 Network yesterday and with what Mr. Brown just

1 said.

2 There has been a lot of talk about
3 costs. Like Kaiser Permanente's point about
4 the need for more studies and hard data as to
5 what the burden really is and what the costs
6 really are, and not just anecdotes or whining,
7 but let's get some hard information on this.

8 We hope that you all, on the basis
9 of science, can give us more data on the
10 benefits of a good REMS, the baby that's born
11 without lifetime defects or the young person's
12 suicide that's been avoided.

13 A lot of talk about the medication
14 guides. There are really very few REMS. To
15 count medication guides as one seems kind of
16 strange. I mean, for gosh sakes, it really
17 shouldn't be considered a terrible burden to
18 be able to describe to patients fairly simply
19 the pros, cons, and how to use a drug.

20 The real issue with medication
21 guides is their complexity, way too complex
22 for many patients, and apparently for some

1 providers or prescribers. We need to do an
2 awful lot more to make them usable and
3 effective. We have been urging a rapid
4 movement toward the kind of drug fact box that
5 Drs. Woloshin and Schwartz have recommended,
6 and that the new health law talk about.

7 Clearly, there are many of the
8 industry's issues that can and should be
9 probably pretty easily addressed, whenever
10 possible, uniform approaches in forms.
11 Yesterday's discussion of templates made great
12 sense to me, and yesterday afternoon's
13 discussion of standardization and the
14 discussion on, I will say, pregnancy tests
15 made sense. But, then, so did the last
16 panel's discussion. That was a very good one
17 where you have a group like Kaiser, if they
18 can meet the standards, some flexibility, but
19 for most groups it probably isn't that easy.

20 Part of the problem is, of course,
21 we are a couple of years too soon on HIT and
22 electronic health records. I hope you call

1 can reach out to ONCIT and maybe work with
2 them to make sure that these programs will
3 make it easy to use REMS. The kind of delay
4 that the Cleveland Clinic people described
5 yesterday was pretty sad and ought to be
6 somewhat solvable by good HIT. But as the
7 doctor said, easier said than done.

8 And we particularly agreed, also,
9 with Kaiser Permanente's comments on
10 confidentiality. That was a terrible,
11 outrageous example of signing a consent form
12 which just is an open sesame to getting all
13 these other kinds of ads from a company.

14 In the future, in terms of safety,
15 to determine the safety and efficacy of a drug
16 subject to a REMS, we hope you all could
17 target these drugs under a sentinel program.
18 And while that is a couple of years away, we
19 hope you could plan now to prepare for
20 researchers and software teams to monitor the
21 long-term outcomes of REMS-related drugs.
22 Data from that could determine whether a REMS

1 really is needed, whether the drug's dangers
2 outweigh the benefits, or whether safer
3 alternatives are available.

4 We also hope you might consider
5 using some new electronics to ping, if you
6 will, periodically consumers to report on side
7 effects and aftereffects. There's some data
8 that consumers can often report on problems
9 better than providers and could be another
10 source of consulting.

11 In conclusion, REMS can be very
12 important for permitting drugs to market, and
13 the resources needed to administer REMS should
14 not interfere with the rapid approval of
15 lifesaving drugs. If necessary, we should
16 consider changes in PDUFA V revenues in order
17 to ensure both timely drug approvals and the
18 audited enforcement of REMS.

19 Thank you very much.

20 MS. TOIGO: Thank you, Mr.
21 Vaughan.

22 And our last speaker on this panel

1 is Ms. Jean Steckler from iReminder.

2 MS. STECKLER: Good morning. I am
3 Jean Steckler. I'm Senior Vice President of
4 iReminder, a healthcare technology company
5 that focused on increasing medical compliance.

6 iReminder's products include
7 Compliance for Life, a medication adherence
8 program; Persistent Refills, a medication
9 refill program; Global eTrials for
10 multilingual communications with patients in
11 clinical trials worldwide, and MedTrigger, for
12 risk management programs.

13 I appreciate this opportunity to
14 address risk management issues with the FDA
15 and collectively share our experiences with
16 our colleagues from pharmaceutical companies,
17 managed care, pharmacies, and their associated
18 trade organizations.

19 In previous sessions, we have
20 heard recurring things: the need for
21 efficient REMS administration for prescribers
22 and pharmacies and the need for templated

1 programs and consistencies.

2 In the spirit of CDER's Director,
3 Dr. Woodcock's challenge that we continue to
4 remodel REMS as we simultaneously construct
5 the REMS model, we address the efficacy of the
6 paper-based model of patient communications
7 regarding risk.

8 In the next few minutes, I will
9 address how automation can improve patient
10 communication, prescriber and pharmacy access
11 status, and patient compliance to laboratory
12 testing requirements.

13 Regarding patient communications,
14 we know from research as far back as 1885 that
15 was done by Herman Ebbinghaus that people
16 remember only 20 percent of what they have
17 been told one day later. Why is this
18 important? Patient medication treatment
19 decisions are not made in isolation. They are
20 based on the patient's aggregate of all their
21 risk profiles.

22 We also know that patients have

1 different optimal learning styles. Some are
2 visual learners; some are auditory learners,
3 and others learn best through interactions,
4 such as restating back their understanding of
5 their risk profile.

6 Despite our collective best
7 efforts to design medication guides to be
8 readable and culturally-appropriate, the
9 guides are typically quickly discarded by
10 patients. It is the opinion of the
11 pharmacists that we have interviewed that
12 paper-based REMS programs are deficient for
13 several reasons.

14 First, lack of persistence. When
15 the patient discards the medication guide, it
16 is no longer available to them for
17 consideration when they are exposed to
18 additional risk profiles. Also, the poor
19 recallability that we just described.

20 We propose a methodology to make
21 it simpler for sponsors to provide consistent
22 patient communications across the myriad

1 prescribers, pharmacy chains, independent
2 pharmacies, and their associated pharmacy
3 management systems.

4 We recommend communicating safety
5 information to patients repeatedly. These
6 communication programs should provide both
7 push and pull aspects. Push programs
8 automatically remind patients at the critical
9 points in their care timeline. Pull programs
10 provide patient-friendly online access to risk
11 documentation through FDA directories and
12 emailed medication guides to the patients
13 directly.

14 We believe that automation can
15 both increase effectiveness and reduce the
16 burden on prescribers. These automated
17 programs will improve patient and healthcare
18 provider and pharmacy compliance. Automation
19 such as electronic medical records also allows
20 for greater transparency of patient status for
21 both the healthcare provider and the pharmacy.

22 For example, the pharmacy could

1 have access to whether or not the patient has
2 had a pregnancy test, for example, if that's
3 required before refills, as well as the
4 healthcare provider.

5 Automation can also provide
6 electronic communications to patients, not
7 paper-based. The advantage of electronic
8 communications is that the patient can then
9 store, search, and retrieve the information at
10 different times along their care.

11 To appreciate the value of this
12 online access, I would ask all of us to recall
13 when we kept shelves of photo albums in our
14 homes. More frequently, we keep our photos
15 online, so that we can store them, we can
16 search for them, and we can retrieve them at
17 will.

18 The patient's medical status is
19 not static. Additional medications are added.
20 They're changed over time. The patient
21 condition changes over time. The patients
22 need to be able to recall the information from

1 their medications both at the time of the
2 fill, but also as other treatments are
3 introduced. Electronic reminders as well as
4 online access enable patients to more easily
5 refer to this information.

6 We recommend sponsors and the FDA
7 consider IVR, email, SMS reminders to patients
8 for upcoming laboratory testing and refill
9 dates, alerts to the providers and pharmacies
10 when patients report that they are not going
11 to comply with laboratory testing or refill
12 pickups, and electronic printing and
13 distribution of the medication guides, as we
14 have discussed.

15 The benefits to us seem pretty
16 apparent. Introducing this method of
17 communication, patient communications, helps
18 keep the patients more compliant with the risk
19 management protocols. It can reduce the
20 healthcare provider's workload because they
21 are not making repeated calls back and forth
22 to make sure that the patients have done what

1 they needed to do in a timely fashion. It
2 lightens the pharmacy's workload because the
3 pharmacy is not saying, "Sorry, I can't fill
4 that. We don't have documentation yet that
5 you have had your testing completed." And it
6 coordinates care across the patient, the
7 provider, and the pharmacy.

8 MS. TOIGO: Ms. Steckler, we're
9 going to need you to wrap up soon.

10 MS. STECKLER: Okay. Well, I can
11 end there, and I appreciate your time, and
12 thank you.

13 MS. TOIGO: All right. That's our
14 last presenter for this session. And now we
15 have 15 minutes for our panel questions.

16 And who wants to get us started?
17 John?

18 DR. JENKINS: This is for Dr.
19 Schnoll.

20 In your presentation, you have a
21 statement that says, "Proposed REMS tools and
22 elements should be demonstrated to be

1 effective prior to asking industry to use
2 them." How would that actually work? So, how
3 are we going to validate that these tools are
4 effective before we use them, when we are in
5 a situation where we have a safety concern
6 that we need to address? So, isn't that kind
7 of a Catch-22, that you can't do anything
8 until you know for sure that it works?

9 DR. SCHNOLL: Well, it's a
10 Catch-22 for everybody, and I think that it is
11 an important question.

12 There are some ways that things
13 can be pilot-tested. In the previous panel,
14 it was suggested that some of these could be
15 tested during the phase 3 development program
16 of a drug, and it could be, as I mentioned,
17 that there would be pilot-testing of a
18 specific element that would occur.

19 I think we need really to look at
20 this very carefully because, as I mentioned,
21 these are now being required on some
22 companies. We don't know if these elements

1 will be effective in terms of what they are
2 supposed to do.

3 Maybe another approach would be at
4 this point to develop sort of a natural
5 experiment where we very carefully look at
6 some of the REMS that have been implemented,
7 but initiate that review by NIH or AHRQ to
8 really determine whether or not, through some
9 very careful investigations by them, we can
10 demonstrate the efficacy of these programs,
11 just as we have to demonstrate the efficacy of
12 a drug before it comes to market.

13 DR. JENKINS: Doesn't the statute,
14 though, include that because we're required to
15 have assessments? So, the statute anticipates
16 that you may need to put something in place.
17 You assess it at specified timeframes, and
18 then you can make modifications, if needed.

19 I'm just thinking back to last
20 week's opioid REMS panel where I heard
21 interesting comments from some of the panel
22 members who said we have a crisis and a

1 growing problem of prescription opioid abuse
2 in this country, but don't do anything until
3 you know for sure what you're going to do will
4 work.

5 How do you reconcile that?

6 DR. SCHNOLL: Well, as I said,
7 there is no easy answer to that. But, once
8 again, I think we need to develop some model
9 programs, maybe some pilots that can be
10 adequately tested to look at what is going on.

11 One of the things we want to make
12 sure of, and is sort of coming out over the
13 last two days, that we are implementing things
14 that may not be always in the best interest of
15 the patient, and we want to avoid that. So,
16 by developing some models, some pilot
17 programs, we may be able to assess some of
18 these things on a smaller scale that can give
19 us an idea of what might or might not be
20 effective.

21 It is a Catch-22, and we
22 understand that, but I think we have to think

1 innovatively about how to approach it.

2 MS. TOIGO: Jane?

3 MS. AXELRAD: I have a question
4 for Mr. Brown.

5 You and a number of other speakers
6 have said that it's really important that we
7 reserve the restrictive REMS with elements to
8 assure safe use for drugs that have the most
9 serious risks, where a REMS is necessary to
10 ensure the benefits of the drug outweigh the
11 risk.

12 I was wondering, is there a sense
13 out there that we're not doing that, that the
14 REMS with elements to assure safe use are not
15 being reserved for that? I mean I think our
16 sense is that, by and large, the drugs that
17 have restrictive programs have got those
18 serious risks. But I wanted to hear your
19 view.

20 MR. BOUTIN: Yes. Thank you.

21 There we go.

22 It's not that you're not looking

1 at issues of risk. The challenge is to look
2 at the risk and benefit in context, and I
3 think that's where we have some concerns. So,
4 it's a combination of the risk factors versus
5 the benefit compared to the risk and benefit
6 of the condition being addressed.

7 So, you could go back to the
8 opposing ends of the spectrum of a patient
9 consumer. A consumer is looking at products
10 that are based on a condition that has very
11 little risk. So I think that is where we have
12 some concerns, and I think we would like to be
13 part of the process to help determine when
14 these REMS would be applied and how they would
15 be applied, and then looking at the
16 consequences of the REMS themselves in terms
17 of what they do to access.

18 MS. AXELRAD: Just a followup, and
19 I don't want to put you on the spot, but do
20 you have an example of a specific drug where
21 you think that we have struck the balance in
22 the wrong way, where there's a drug that

1 doesn't have a serious risk, but we have
2 required a restrictive program or an
3 inappropriately-restrictive program?

4 MR. BOUTIN: We have looked at
5 some anecdotally reported from our patient
6 organization members that they have indicated
7 that they feel the balance was off. Now what
8 we don't have is good information and data on
9 it. So it's still anecdotal.

10 But our patient organizations are
11 coming back to us saying there are a number of
12 examples of drugs that they feel that the
13 balance is off, while at the same time we work
14 with some of the consumer organizations;
15 they're saying that it's off as well in the
16 other direction.

17 So I think that is where the FDA
18 has been caught in a Catch-22, and I think the
19 solution to that is to invite both the patient
20 and consumer perspective into that
21 deliberation, because then we can come back to
22 our organizations and validate that for our

1 groups. I think it relieves some of that
2 pressure.

3 MS. TOIGO: Just to follow up on
4 Jane's, if there are some specific examples
5 that some of the patient groups would want to
6 share, they can certainly do that in the
7 docket.

8 MR. BOUTIN: Thank you.

9 MS. TOIGO: Claudia?

10 DR. KARWOSKI: I wanted to ask the
11 patient and consumer groups whether you have
12 any suggestions for how we can get information
13 about access problems for drugs that have REMS
14 or even where patients have read some of the
15 risk averse information and have decided not
16 to take the drug. Do you have any suggestions
17 for how we might be able to obtain that sort
18 of information?

19 MR. BOUTIN: During the last PDUFA
20 reauthorization, the National Health Council
21 actually conducted some primary research in
22 that space as well as secondary research in

1 that space, which I would be happy to share.

2 The challenge we found was those
3 sorts of decisions were highly contextual,
4 based on the life circumstances of the
5 individual, the conditions they were
6 suffering, their culture, their socioeconomic
7 status, as well as how the information was
8 communicated to them and from whom.

9 So, the challenges were infinite.
10 We thought it would be a lot easier to address
11 this.

12 I think the issues of collecting
13 that data, we are getting better at collecting
14 that data. What we have seen very little of
15 is how we address that in real-life
16 circumstances. So, I think it is a huge
17 challenge.

18 MS. TOIGO: Bill or Paul, did you
19 want to add a comment?

20 MR. VAUGHAN: Just back to some of
21 the recent literature about, with today's
22 emails and smartphones and stuff, one could

1 devise -- I'm sure they wouldn't be perfect
2 polling and sampling, but devise some follow-
3 up questionnaires to people who have been
4 taking a particular drug as to both adverse
5 events and their impression of the drug.

6 And again, in the dream world of a
7 sentinel system that really works in three or
8 four years, people who switch a prescription,
9 to ping them as to why and "Gee, how did it
10 work for you?" There's a lot more of that
11 that's going to be possible. Today? No.

12 MR. BROWN: I would just like to
13 add, on the access issue, we must focus, was
14 it actually the REMS problem? I know
15 yesterday someone stated there was a problem
16 with co-payments. That's not necessarily
17 related to REMS at all. So, when we are
18 collecting this data, even if it's a drug and
19 they have that problem with the access, what
20 was the reason for it?

21 MS. KELLY: With regard to
22 opioids, we are currently developing and about

1 to field a study on exactly that topic. What
2 are attitudes toward the medications? What
3 are the things that have developed or have
4 influenced your decision to take or not take
5 a medication? It will be random dial survey.
6 So, statistically, it ought to be fairly
7 accurate. We will be happy to share that with
8 the FDA, once we have some results.

9 MS. TOIGO: Thank you.

10 Mwango?

11 DR. KASHOKI: This is a question
12 to the representative from iReminder. Do you
13 made some suggestions about how we could
14 increase automation, I guess to remind people
15 about how to access information. Either
16 that's available in a medication guide or
17 provided directed materials.

18 I am wondering how that would
19 happen without the sponsor having to collect
20 or amass a database or even perhaps a registry
21 of patients and providers. This would be
22 largely for products, given the majority of

1 products have only a medication and a
2 timetable, this would be for products for
3 which FDA would have determined that a
4 registry for enrollment was not necessary.

5 MS. STECKLER: We already have
6 programs in place. Typically, they are
7 embraced more in Europe right now than they
8 are here.

9 The process of what happens is
10 that the patient fills out a paper enrollment
11 form or, if the healthcare provider wants to
12 go online and enter their information, the
13 patient supplies their contact information,
14 their preferential contact information. So,
15 they say, "I prefer to get my information by
16 email. I prefer to get first. And if you
17 can't reach me by email, you can then reach me
18 at this phone number. And if you can't reach
19 me at that phone number, you can reach me by
20 texting me."

21 So, the system will cycle through
22 and find them wherever they say they are going

1 to be. So it addresses the needs of people
2 who live an active life and may not be in one
3 place, maybe on vacation from time to time.

4 Once they are enrolled, an
5 automatic enrollment piece of information goes
6 out. That information can include the risk
7 profile and any other information that the
8 sponsor thinks is appropriate for them to have
9 at the initial onset of the program.

10 And at that point, there is a
11 schedule of when the patient needs to do which
12 things, when they need to get blood tests or
13 when they need to get whatever the test
14 requirements are. That system is
15 automatically programmed into the program.

16 They receive the notifications.
17 It's a two-way communication. So, they
18 respond back. Did they make the appointment,
19 yes or no? Did they, then, at some point, did
20 they go to the appointment to have the lab
21 work done, yes or no?

22 If they can't be reached after the

1 series of attempts to reach them, then an
2 alert can be sent either to a backup
3 healthcare provider or to a family member to
4 follow up with them.

5 Then these reports are available
6 to the provider, so that at some point they
7 can scan through all of their patient lists
8 and see who's complying and who's not.

9 DR. KASHOKI: So, in other words,
10 in order for your proposal to work, the
11 companies would have to require either
12 enrollment of providers or patients in order
13 for that system to work, under their REMS
14 program?

15 MS. STECKLER: Yes, the way it has
16 worked to date is that the sponsors have
17 supported this program. It is in their
18 interest to keep the patients compliant with
19 what their requirements are. So, it has
20 worked well for them, the patients, and the
21 doctors.

22 MS. KELLY: Can I make a comment

1 about that?

2 MS. TOIGO: Go ahead.

3 MS. KELLY: I agree that
4 electronics and a lot of those systems are
5 excellent, and I'm really excited about the
6 day when that will be available to everyone.
7 But I think as you develop communications
8 around any of these classes of drugs, you have
9 to remember that there's a lot of people who
10 just don't use that technology. So, we need
11 to make sure that we can implement within the
12 provider's office enough education, enough
13 followup, whether that means somebody is
14 sitting in a room and watching a video, and
15 then responding to follow-up questions from a
16 nurse or someone, or whether it means really
17 excellent print materials. Because for some
18 people, that's going to remain the standard
19 for the foreseeable future. So, I absolutely
20 endorse using the technology to the limit, but
21 we have to remember that not everyone is there
22 with us.

1 MS. TOIGO: Thank you.

2 Okay, my FDA colleagues, since we
3 are going to leave the topic of ETASUs after
4 the break, does anyone have a last question?

5 Okay, Keith.

6 DR. WEBBER: Just one followup, as
7 long as we have time, to Jean Steckler.

8 Does the information -- I mean it
9 sounds like your service provides information
10 to patients, reminders, et cetera. What sort
11 of information flows back to you, and do you
12 send or have the ability to send that back to
13 manufacturers?

14 MS. STECKLER: There are several
15 tiers of reporting that goes on. The most
16 comprehensive reporting is reported back to
17 the doctor. We generate compliance scores for
18 each different activity that the patient is
19 supposed to be doing. That compliance score
20 and patient information is communicated to the
21 primary care doctor or the doctor who is doing
22 the prescribing.

1 The next level is the de-
2 identified reports. So the sponsor never sees
3 any personalized information, but they can
4 monitor how well the program appears to be
5 working from their perspective, based on
6 aggregated data and de-identified reports.

7 MS. TOIGO: Okay. Thank you,
8 panel, and thank you for working with me on
9 the time constraints. I hope you will agree
10 that the dialog enriches our process, and if
11 we don't maintain the timeframes, we don't get
12 the good dialog. So, thank you for doing
13 that.

14 And we will be back in 15 minutes
15 with panel 3 today, topic No. 4, evaluating
16 the effectiveness of a REMS.

17 (Whereupon, the foregoing matter
18 went off the record at 10:45 a.m. and resumed
19 at 11:04 a.m.)

20 MS. TOIGO: Okay. We're going to
21 get started, if those who are outside want to
22 join us, for panel No. 3, topic 4, evaluating

1 the effectiveness of a REMS.

2 Before I do that, one housekeeping
3 that I said I would get the answer because
4 somebody asked yesterday. Yesterday's
5 recording is now available and posted on the
6 web, and it is at
7 collaboration.fda.gov/p86609578/. We posted
8 that on the REMS meeting web page. So I don't
9 know who asked, but there's your answer.

10 We'll get started with this panel
11 with Dr. Thomas Hostetter from the American
12 Society of Nephrology.

13 DR. HOSTETTER: Thanks again to
14 the FDA for allowing the American Society of
15 Nephrology to comment.

16 I'll reintroduce myself briefly.
17 I'm Tom Hostetter. I'm a practicing
18 nephrologist and on the faculty of the Albert
19 Einstein College of Medicine in New York, and
20 representing the American Society of
21 Nephrology, which is the largest of the
22 professional organizations for physicians and

1 teachers and researchers taking care of and
2 studying kidney disease.

3 We don't purport to have the
4 expertise to know how to do the evaluations.
5 We simply have a couple of warnings that we
6 are concerned about.

7 And I have to say at the outset I
8 don't envy the people who try to devise a
9 scientifically-valid assessment of this
10 process, but we all agree that the best
11 approach that can be made is clearly needed.

12 Our first concern really derives
13 from what I emphasized yesterday, that the
14 patients who receive these erythropoiesis-
15 stimulating agents, ESAs, are at least with
16 respect to the kidney patients in many ways a
17 vulnerable group, tethered to a dialysis
18 machine three times a week with a lot of
19 comorbidities and a lot of socioeconomic
20 disadvantages, usually even before they start
21 dialysis.

22 So, we think that whatever

1 evaluations are devised of the REMS, and
2 particularly the medication guide on which I
3 have focused, should be sensitively and
4 respectfully designed. I'm sure that attempts
5 will be made to that, but I call attention,
6 again at the risk of redundancy, that the
7 medication guide, which we are now required to
8 give to patients, begins by saying, what's the
9 most important thing you can know about this
10 drug? The answer is the most important thing
11 is that you could die or have a serious other
12 consequence of taking the drug. It's clearly
13 a frightening message.

14 I would hope that any kind of
15 evaluation, a phone call that came on a
16 Saturday afternoon after patients had spent
17 three other days of the week in their dialysis
18 unit would not include, as at least an opening
19 statement, has your dialysis facility told you
20 that you are taking a drug that could cause
21 you to die?

22 I think we have to be very

1 cautious in how we devise these. The patients
2 deserve the information, but they deserve it
3 in some kind of sensitive and respectful way.

4 Secondly, and I think this is
5 something that harmonizes with what others
6 have said in other respects of the REMS
7 process, and perhaps other panelists today
8 will say it, that the patients and physicians
9 and other providers should be involved in the
10 development and evaluation of REMS. I think
11 there are specificities to probably each of
12 these categories. Again, I speak very
13 specifically of the patient with end-stage
14 kidney disease who is on dialysis and
15 receiving these for anemia.

16 They are very different
17 situations, and the providers and patients, at
18 least in our case, have had access to these
19 drugs for essentially 20 years, and so have a
20 great deal of experience with them. So, I
21 think it would be critical in helping to
22 devise any kind of evaluation that's provided.

1 I'll stop there and thank the FDA
2 again for allowing us to comment.

3 MS. TOIGO: Thank you, Dr.
4 Hostetter.

5 And our next speaker is Ronna
6 Hauser from the National Community Pharmacists
7 Association.

8 DR. HAUSER: Good morning. Thank
9 you for once again allowing me the opportunity
10 to share the community pharmacies' perspective
11 recommending REMS at this time, specifically
12 related to evaluating the effectiveness of
13 REMS.

14 I'm Ronna Hauser, the Vice
15 President of Policy and Regulatory Affairs at
16 the National Community Pharmacists
17 Association. We represent America's community
18 pharmacists, including the owners of more than
19 23,000 community pharmacies.

20 Once again, we do appreciate the
21 opportunity that FDA has allowed us, making
22 this process transparent, and we feel that

1 there is a great impact on community
2 pharmacists and pharmacies related to REMS.

3 So, once again, we're happy to be here.

4 Specifically evaluating the
5 effectiveness of REMS, we believe that REMS
6 should be monitored and assessed frequently
7 enough to evaluate effectiveness as well as to
8 evaluate overall burden on the healthcare
9 system.

10 For example, the number of minutes
11 a healthcare provider dedicates to each
12 component of a given REMS should be captured
13 and evaluated. In certain instances, this
14 information may be collected by online
15 methods, especially related to provider
16 training or enrolling of patients in a
17 specific REMS program. In other instances,
18 methods should be developed or expanded that
19 will allow for capture of time spent by the
20 provider with their patient discussing
21 elements associated with REMS.

22 Metrics for determining the

1 effectiveness of REMS should be specified at
2 the time REMS are approved. NCPA recommends
3 that efforts to create REMS are equally
4 matched by efforts to evaluate the
5 effectiveness and outcomes of a given REMS and
6 its individual components.

7 FDA must ensure that the
8 components of any REMS are proven to be
9 effective in mitigating the specific defined
10 risks and are workable for patients,
11 prescribers, pharmacists, manufacturers,
12 wholesalers, and system vendors.

13 In addition, FDA should make
14 outcomes information available to required
15 participants of any given REMS program, as
16 this applies transparency to the process, so
17 that participants are aware of their
18 contributions to achieving agreed-upon goals.

19 In order to measure the effect of
20 REMS on health outcomes, we recommend that
21 data be classified into general categories.
22 Depending on the specific product, these

1 categories could be further defined as
2 patient, prescriber, pharmacist knowledge;
3 behaviors such as an inappropriate prescribing
4 and non-medical use and abuse, and outcomes
5 such as serious adverse effects and patient
6 access to care.

7 Though we all admit the challenges
8 of trying to measure these outcomes, NCPA
9 believes that, through a concerted effort to
10 define a set of metrics, REMS will meet the
11 goals of reducing serious adverse outcomes
12 while maintaining access to medications.

13 Lastly, surveys can provide an
14 initial of patient and healthcare provider
15 understanding of the risks and safe use of a
16 drug. Optimally, data drawn from systems such
17 as electronic health records could serve as
18 validation of surveys. As industry moves
19 toward a fully electronic inoperable
20 healthcare system, this will be come a more
21 robust option for measuring the effectiveness
22 of REMS and should be started to be looked at

1 and developed today.

2 In conclusion, we urge you to
3 leverage the value that pharmacists offer
4 related to the properties of medications,
5 again, the importance of their role and
6 involvement of independent community
7 pharmacists in the creation of REMS programs.
8 We appreciate the FDA for recognizing that.

9 And I thank you for your time.

10 MS. TOIGO: Thank you, Dr. Hauser.

11 The next presenter is Marcie Bough
12 from the American Pharmacists Association.

13 DR. BOUGH: Good morning. Again,
14 my name is Marcie Bough. I'm the Director of
15 Federal Regulatory Affairs for the American
16 Pharmacists Association, APhA.

17 APhA is the first established and
18 largest professional pharmacists'
19 organization, and we represent over 62,000
20 members who provide care in all practice
21 settings.

22 I want to start my comments today

1 by first addressing one of the questions that
2 Jane Axelrad asked us yesterday in panel 6
3 regarding pharmacies' work and effort to look
4 at potential best practices or ways to move
5 forward with standardized elements and what we
6 might be doing within pharmacy.

7 And a followup to that question,
8 since I didn't get it answered yesterday, is
9 that I have been referencing APhA's REMS white
10 paper that we published in our Journal in
11 2009. We built that off of a small
12 stakeholders' meeting where we looked at some
13 what we have been discussing in the white
14 paper.

15 We plan to hold a meeting one of
16 the first two weeks in October as a followup
17 to that and look at many of the issues that we
18 have been discussing today and look at some
19 potential guiding principles and
20 recommendations as we move forward. So, I
21 wanted to let FDA know we will continue to
22 keep you updated as we finalize those meeting

1 plans and keep you updated.

2 With reference to APhA's white
3 paper that I have been referring to, I also
4 wanted to let everyone know that it is
5 available on pharmacist.com for anyone
6 interested in looking at it.

7 With that, I will turn to our
8 specific panel discussion on evaluation of
9 effectiveness of REMS programs. APhA supports
10 efforts to better define and provide guidance
11 on evaluation and assessments of REMS programs
12 and the outcomes of those programs. We need
13 to ensure that efforts used to create REMS
14 need to be equally matched with efforts used
15 to evaluate the effectiveness of the REMS
16 program itself and then the individual
17 components in those REMS programs.

18 Specifically, any REMS program
19 should ensure that patient access to necessary
20 medications is not prevented or delayed and
21 that achievable and measurable outcomes are
22 designed and identified at the time of

1 approval of a REMS product.

2 In addition, those components
3 within a REMS program need to have proven
4 effectiveness for the identified risk that
5 they are to mitigate. In addition, components
6 need to be workable for all stakeholders,
7 including patients, prescribers, pharmacists,
8 manufacturers, wholesalers, and the system
9 vendors.

10 We also need to ensure
11 stakeholders accountability for implementing
12 specific REMS components are defined at the
13 point of approval with the REMS program as
14 well.

15 Importantly, reasons for failures
16 and/or successes should be documented and
17 assessed for different components within REMS
18 programs. For example, outcome metrics need
19 to be captured for reasons why a patient had
20 failure or success with a particular component
21 of a REMS program, rather than just
22 documenting the occurrence. We need to be

1 able to learn from the information we gather
2 through implementation.

3 In addition, unintended
4 consequences, for example, decreases or
5 changes in patient access, provider
6 participation in a REMS program, shifts in
7 risks to non-REMS drugs, or shifts in
8 prescribing practices and disruptions to
9 delivering patient care also need to be
10 monitored.

11 As mentioned earlier this morning,
12 we need to work together to find appropriate
13 ways to document and assess and report the
14 burdens, both cost and administrative, on the
15 healthcare system to improve the REMS programs
16 and utilize metric systems to achieve those
17 goals.

18 Additional evaluation requirements
19 related to the quality of REMS programs
20 include capturing and reporting the frequency
21 of components not being met and what those
22 components were. Again, delays in patient

1 access due to the components not being met or
2 lack of compliance with the REMS program, and
3 the number of prescriptions being dispensed
4 with the REMS. Allowing continuous quality
5 improvement will allow us to reevaluate,
6 assess, adjust, or discontinue components or
7 different parts of a REMS program throughout
8 the life cycle of a REMS.

9 Finally, we need to aim for a
10 balance between appropriate benefit/risk
11 management, provider participation, and
12 patient access while appropriately managing
13 risk and the cost and benefit to the
14 healthcare system. We also need to remember
15 that these programs are risk management
16 programs, not risk avoidance programs, and we
17 need to have a balance between efficiencies
18 and effectiveness of the programs.

19 Through thorough risk/benefit
20 analysis, we need to ensure that patients
21 continue to have access to these much-needed
22 medications.

1 With that, I will end my comments
2 and again want to express our appreciation for
3 FDA's ongoing effort to gather input on these
4 important topics, so that we can ensure
5 successful REMS programs are implemented in
6 the future.

7 Thank you.

8 MS. TOIGO: Thank you, Dr. Bough,
9 and thank you for sharing what the followup
10 will be to Ms. Axelrad's question from
11 yesterday.

12 Our next presenter is Mr. David
13 Chen from the American Society of Health-
14 Systems Pharmacists.

15 MR. CHEN: Good morning, and thank
16 you again.

17 For those that may be new, my name
18 is David Chen, and I'm the Director of
19 Pharmacy Practice Sections at the American
20 Society of Health-System Pharmacists.

21 ASHP is a 35,000-member national
22 professional association representing

1 pharmacists who practice in hospitals and
2 health systems, including ambulatory care
3 clinics, hospital outpatient pharmacies, home
4 care, and long-term care.

5 And I want to say I'm really
6 excited, yet realizing it is very daunting the
7 last two days that there's been, in my
8 opinion, a very clear set of themed issues
9 that I think stakeholders, the FDA, and
10 sponsors can really look forward to addressing
11 to improve the REMS process, especially now as
12 you have these new REMS that are impacting the
13 marketplace like ESAs that are going to be
14 broad-reaching and really impacting a number
15 of care providers along the continuum of care.

16 In order to monitor and assess the
17 effectiveness and overall burden on the health
18 system of REMS with elements to assure safe
19 use, we believe the FDA will need to design a
20 process that conducts research similar to
21 existing research on various means of patient
22 and provider intervention with the different

1 REMS elements. This research would include
2 the validation of choices approved that make
3 up the elements of the REMS, such as evidence-
4 based means to affect prescriber and patient
5 behavior.

6 ASHP would encourage, and as we
7 have heard in other comments, the FDA to first
8 work with stakeholders to standardize the
9 different elements of REMS and address the
10 concerns that we have heard over the last few
11 days in order to make the monitoring more
12 effective, efficient, and generalizable to
13 future REMS.

14 For example, it was noted in past
15 ASHP comments to the FDA we believe educating
16 patients is clearly important, but there is a
17 lack of research relating to the role, scope,
18 and effects of patient understanding on med
19 guides and resulting patient behavior. The
20 usefulness and effectiveness of med guides as
21 they are currently written and distributed as
22 tools for counseling patients about serious

1 risks remains to be established through
2 adequate, well-designed research.

3 We have heard from many
4 stakeholders on the various aspects of burden
5 being felt by the healthcare system due to
6 REMS. ASHP would offer the suggestion that
7 very soon the FDA work with stakeholders to
8 collect data on this burden, so that future
9 changes we hope to achieve through
10 standardizations and improvements to various
11 aspects of REMS can be accurately measured.
12 The survey data that we have heard discussed
13 from the NCCN on REMS is a great example of
14 the opportunity to collect information from
15 the frontline provider.

16 ASHP also has experience in
17 collecting data from members on the impact of
18 other non-REMS-related federal requirements
19 introduced to the healthcare delivery system.
20 We would be happy to assist the FDA in
21 collecting data from our members relating to
22 the impact of REMS.

1 We believe that there is a great
2 opportunity to collect information on the
3 burden and patient access to the ESAs over the
4 next six to nine months. This is one of the
5 top challenges facing our members, as the
6 pharmacy is often leading the efforts in their
7 health systems, especially since the perceived
8 risk and actually spelled-out risk of non-
9 compliance with a single patient apprised
10 acknowledgment is the loss of the ability to
11 purchase ESAs for their facilities.

12 The goals of specific REMS should
13 be included in the analysis when deciding on
14 metrics, but metrics should also be considered
15 for measuring unintended consequences similar
16 to those that we have heard during this
17 meeting. There will need to be metrics
18 developed to determine the impact on
19 medication use as it relates to the burden of
20 the ETASUs, and there should also be routine
21 metrics in place to measure patients'
22 participation and understanding of the

1 risk/benefit decision that they are being made
2 part of, and through the medication guide and
3 some of mandatory processes, and measure that
4 effect and measure its effect on the use and
5 access of REMS medications.

6 And there I'll stop and allow the
7 panel to ask us questions.

8 MS. TOIGO: Thank you, Mr. Chen.

9 Well, clearly, this panel wants to
10 get to lunch because we all went way under
11 time. And as somebody pointed out, FDA will
12 fill up the time with questions, but we'll
13 see.

14 (Laughter.)

15 So, who wants to be first?

16 Claudia?

17 DR. KARWOSKI: So, if we were to
18 require an increased role of the pharmacist in
19 the retail setting, for instance, if we
20 required, as part of an element to ensure safe
21 use, that counseling occur of patients prior
22 to dispensing a drug, can you describe how

1 documentation of that counseling might be
2 captured, given that many pharmacies require
3 patient signature regardless of whether they
4 actually receive counseling?

5 DR. HAUSER: Yes, Ronna Hauser
6 from NCPA.

7 There are a variety of systems
8 currently in place today that our members
9 utilize unrelated to medication therapy
10 management and documentation and payment for
11 those services. And throughout the process of
12 working with industry partners and
13 stakeholders to discuss the long-acting opioid
14 REMS, we are made available and know of
15 multiple offerings out there that will allow
16 that data to be tracked, reported on, et
17 cetera, so that you could ensure that the
18 counseling had occurred at the point of
19 dispensing of the product.

20 DR. BOUGH: Marcie Bough from
21 APhA.

22 To add onto that, there are

1 systems in place, as Ronna mentioned, that can
2 be seamlessly integrated into processes of
3 claim submission and tying information onto
4 those existing infrastructures, so that there
5 could be documentation of patients receiving
6 counseling. That type of information would be
7 sent, for example, to a REMS administrator, so
8 that there could be a checkoff box of that
9 type of information and the other REMS
10 requirements for that particular program, and
11 there could be information and data reported
12 from the REMS administrator on the compliance
13 with those particular provisions and
14 attestation that the counseling has been
15 completed at the point of dispensing.

16 So, the counseling could certainly
17 be documented, just as we are doing with
18 medication therapy management in programs, as
19 I mentioned yesterday, with Medicare Part D
20 and other provisions where we can send
21 documentation, or not the documentation, but
22 the notification of compliance with those

1 requirements.

2 DR. HOSTETTER: In the particular
3 case of the ESAs in dialysis patients, it is
4 probably one of the easiest. The physicians
5 see the patients typically four times a month,
6 once a week, and leave some kind of note. And
7 in most cases, those are electronic records
8 now, and I believe at least one of the large
9 dialysis organizations has urged the
10 physicians to document that they have
11 delivered the medication guide and discussed
12 it with the patient. So, since it's sort of
13 a quasi-inpatient situation, it may be easier
14 to satisfy that kind of testing.

15 DR. BOUGH: If I could add on, I
16 wanted to reference that, as the healthcare
17 system itself moves to more electronic-based
18 electronic health record activities with
19 incentive programs and things being driven
20 through Medicare, there's definitely
21 opportunities for pharmacists to be able to
22 document themselves into a patient's

1 electronic health record for completion of
2 requirements such as counseling and medication
3 therapy management, so that we could have an
4 interoperable system and the exchange of
5 information in the future that's electronic-
6 based that could ultimately be reporting data
7 into a REMS administrator.

8 MS. TOIGO: Thank you.

9 Jane?

10 MS. AXELRAD: Yes, we've heard a
11 lot about the need to capture data on the
12 burden. One of the suggestions we just heard
13 was to capture the number of minutes a
14 healthcare provider spends on a REMS. But I
15 can imagine that if we were to say, and in
16 fact we suggest in our approval letters for
17 REMS assessments that we collect data like
18 that, that, again, that would just be adding
19 to the burden of the program. Because not
20 only do they have to do what they have to do,
21 but then they have to keep track of all the
22 time that is spent on it.

1 I know the issue we have when we
2 have tried to get more data in terms of our
3 time reporting system from our people, that
4 that just is one more thing they end up having
5 to do.

6 So, could somebody on how we get
7 around that?

8 DR. HAUSER: Ronna Hauser from
9 NCPA.

10 Sorry. I just think I'm the one
11 that probably made the comment that there are
12 current situations today where a provider has
13 to log onto a system to complete a component
14 of a REMS, and that was something that we felt
15 could just be documented by a time or
16 technology could document how much time had
17 been spent.

18 Now, obviously, you get into the
19 difficult task when you talk about how much
20 time you are spending discussing with a
21 patient. I know there's methods out there, I
22 know there's research that's been done, but,

1 admittedly, that's something that we could
2 look to for the future, but I don't think that
3 is something that could easily be done right
4 now.

5 MR. CHEN: David Chen with ASHP.

6 I think what we are saying is
7 that, as we look at developing standard
8 processes, we need to be looking and taking
9 sort of a snapshot, and stepping back, of how
10 these things are affecting the marketplace
11 today, and doing some good, fundamental
12 research about what does it look like today to
13 register a patient.

14 I will give you an example of what
15 we are dealing with with the ESAs. Right now,
16 a physician needs to get an online CE. They
17 need to sign the acknowledgment form of the
18 patient. Then they need to take all that
19 information, either by fax or with the
20 patient, and send it to the hospital, and
21 everything needs to be duplicated a second
22 time.

1 And if that patient shows up to
2 the hospital with orders and we don't have an
3 acknowledgment on file, then, all of a sudden,
4 we have taken someone offline to pursue that
5 document. So, what's that type of burden?

6 I think some of those lessons
7 learned can help us identify what the
8 potential impact is on any one of these
9 particular elements that we are using as a
10 tool to either educate our patients or enroll
11 patients. And the question, does it need to
12 necessarily be done with every REMS and do you
13 start to have a template, for lack of a better
14 word, recognizing that those particular steps
15 do have a fairly known impact on the
16 healthcare delivery system?

17 MS. AXELRAD: Yes, I guess I was
18 saying, since it's sort of easy to see that if
19 you have to duplicate things and you have to
20 fax things around, and it's not being done
21 electronically, that it is going to be
22 burdensome. So, I guess the question is, how

1 much effort should we expend assessing that
2 particular burden, instead of spending our
3 time developing electronic systems that could
4 be used to replace that kind of a manual
5 system and standardizing across various
6 programs, so that people don't have to go
7 through that?

8 MR. CHEN: I would agree that the
9 effort needs to be on how do we make it
10 electronic. I think having baselines, now we
11 have made some improvements in the process.

12 I would say, taking the example of
13 counseling a patient, I am sure there's plenty
14 of statistics as to how many minutes that
15 would cost. And I know in one conversation,
16 the retort that I had was we know
17 statistically, for example, with opioids how
18 many are being dispensed from any particular
19 pharmacy on any particular day. So, if we
20 know that it will take six minutes to stop and
21 then counsel a patient, what does that
22 actually mean on the industry, if you're doing

1 that 20 times a day? How many pharmacists
2 will it need to be hired into the system to
3 actually execute that activity?

4 So I think that is where we are
5 looking at doing some research from that
6 level, so we know what we are actually doing
7 mathematically as an impact onto the
8 healthcare system.

9 DR. BOUGH: Marcie from APhA.

10 I think there's probably a little
11 bit of both of looking at the assessment of
12 the burden on the healthcare system, but with
13 more of a focus on figuring out how we can
14 utilize systems that we know will limit that
15 as we implement them. So, if we build on
16 existing infrastructures and processes within
17 medical practice and pharmacy practice that we
18 know can have a seamless interoperability with
19 what we are doing for patient care already,
20 that will limit the amount of time we have to
21 try to assess the burden on that. So, if we
22 can build on those existing infrastructures

1 and processes, so we are not asking healthcare
2 providers to step away and do something
3 different, we will ultimately get to a better
4 process, so that there's more commonality
5 between the different REMS programs. If there
6 was more standardization of the components, so
7 that if we knew we were doing a REMS program
8 that had maybe three different elements, we
9 know what level of expectation we're supposed
10 to do to implement that program, because the
11 more alike that we can make the processes,
12 understanding that the risks will be
13 different, that will improve efficiencies with
14 implementation of the program.

15 MS. TOIGO: Thank you.

16 Mwango?

17 DR. KASHOKI: I'll admit here that
18 I am a little bit unclear. I guess I haven't,
19 to my mind, heard much in the way of specifics
20 as yet, and perhaps those will come forth in
21 the next panel.

22 But to continue on the theme of

1 burden and access, and trying to figure out,
2 in addition to just measuring it, like
3 thinking about questions about how would we
4 measure, people have mentioned time and
5 perhaps amount of effort. But is there a
6 sense already of how much would be considered
7 too burdensome?

8 By nature of the REMS, there will
9 be additional things that people have to do.
10 So, is there a sense already from people that
11 "X" amount is too much?

12 And, then, have people started to
13 think about how to balance that in terms of
14 access? Some people may not get therapy or
15 may have delays in therapy. And have people
16 started to think about how much of that they
17 would tolerate, and how would that balance be
18 achieved?

19 MR. CHEN: I guess I will start to
20 try and answer that. I think today some of it
21 is anticipation of what the burden will be.
22 We look at, and I will continue to use the

1 ESAs as an example, but it's the anticipation
2 that if there's more REMS, as they get
3 developed, since there's so much variation
4 that exists in the few today, if we don't
5 start working towards standards of the way we
6 apply them with the patient level, that we
7 will have a multitude of ways of how we're
8 trying to provide care to patients.

9 To give an example with the ESAs
10 you give the acknowledgment form. Within the
11 acknowledgment form, it requires that you give
12 the med guide, and then you have to give the
13 med guide I think it is like once a month.

14 You look at Remicade, and you need
15 to give the med guide prior to every single
16 infusion. Right now, one of the things we are
17 working on ASHP is to literally go through and
18 map this out because our members are saying,
19 "We just need a cheat sheet so we can try to
20 institutionalize these things where we can
21 into our patient admission paperwork, making
22 sure it's integrated into our health records,

1 if they're electronic, and how do we get that.

2 There's questions about shadow
3 records. You know, so when you do get the
4 acknowledgment form, how do you interface it
5 to the medical record to validate?

6 So I think that is what we're
7 looking for reducing burden by simply
8 identifying the different types of drugs and
9 how they are administered, and at what points
10 in the care chain are they being given, so
11 that we can actually start institutionalizing
12 some of the processes, even today, as best as
13 we can.

14 But I would use that as an example
15 with Remicade as a drug that is given
16 frequently in hospitals, and we are
17 anticipating the impact of the ESAs and the
18 different points that we have to provide
19 pieces of information and the frequency.

20 DR. HAUSER: Ronna Hauser from
21 NCPA.

22 I would agree that a lot of this

1 is anticipation. I think that industry is
2 doing a very good job to anticipate what might
3 happen with the increased proliferation of
4 REMS. I think the FDA is doing a wonderful
5 job handling what will happen with an
6 increased proliferation of med guides, you
7 know, taking into consideration the one
8 document solution that the industry has asked
9 for for several years.

10 You know, I know that there's
11 entities right now that exist, too, that NCPA
12 works extremely closely with -- there's
13 Surescripts and Mirixa -- that at the
14 beginning of their existence, you probably had
15 never heard of or thought that they might be
16 able to offer a solution for REMS. But
17 knowing that we see this coming and we see the
18 need for a seamless, integrated solution
19 within the community pharmacy setting, they
20 have worked to make their systems applicable
21 to help solve what we are hoping to head off
22 related to REMS. So, I'm glad we are having

1 these discussions and starting at this point,
2 so we can anticipate what's coming in the
3 future, what we see coming with your increased
4 authority in REMS.

5 DR. BOUGH: Marcie Bough with
6 APhA.

7 One thing to think about for
8 measuring burden that is not requiring
9 healthcare providers to fill out additional
10 paperwork and surveys to capture what the
11 burden actually is, is looking at access
12 standards. When we think of Medicare Part D
13 plans and things about the availability of
14 network pharmacies, we can have a parallel
15 process when we think of the network
16 pharmacies within a REMS program, and what is
17 the patient access? Is it a community-
18 friendly version? Is it something that is
19 limited to the inpatient or the delivery
20 process, or where is the patient receiving
21 this medication?

22 But if we think about access to

1 the medication and ways to look at that from
2 a global perspective from across the country,
3 we might be able to find areas where the
4 burden has become too high and the access
5 standards have decreased. So patients then
6 have trouble receiving, either because the
7 burden, it's too much on the healthcare
8 providers to implement or the REMS itself is
9 too burdensome as a whole to be interoperable
10 and work for the system.

11 But it may be a way to think about
12 looking at some of this that is not survey-
13 driven to those that are implementing the
14 REMS.

15 DR. HOSTETTER: I guess the glib
16 thing to say, too, is that the burden has to
17 be balanced against the benefit. If the
18 benefit is toxicity, as all of you know very
19 well, I think it would be wrong to attribute
20 a reduction in toxicity necessarily to REMS
21 alone.

22 So, whether one would relax or

1 reduce the amount of REMS effort for a drug
2 that showed less toxicity over time would be,
3 obviously, an FDA decision. But I would just
4 point out that, in the case of the drugs I
5 have been talking about, ESAs, there are at
6 least two things that are going to reduce the
7 toxicity, one I think very rightly inspired by
8 the FDA of setting clear guidelines on where
9 the hemoglobin ought to be set, which seemed
10 to be, as much as we know about medicine, as
11 safe as any drug when we keep within those
12 guidelines. I think that it really in truth
13 preceded the REMS effort. So that should
14 reduce toxicity.

15 And then a totally independent
16 economic one, this week ESAs I think became
17 the first drugs that have been bundled into
18 the payment for the treatment. So the
19 economic incentives, or more accurately
20 disincentives to using them will grow among
21 the providers. So there will be less usage.
22 Whether that will be good or bad for the

1 patients we don't know.

2 But those two events, setting
3 clear goals, evidence-based, and economic
4 events, could easily influence toxicity
5 perhaps in good ways, and not necessarily
6 attributable to REMS.

7 MS. TOIGO: Gerald?

8 DR. DAL PAN: Yesterday I asked
9 some of the other groups if they had data on
10 the amount of time, excess time, it takes to
11 implement one of these REMS on a, say, per-
12 prescription or per-patient basis. I was
13 wondering if any of your organizations have
14 surveyed members or have something other than
15 anecdote.

16 MR. CHEN: I will say ASHP has not
17 formally. In preparation for this, we asked,
18 and I think we are in a position we would like
19 to pursue something, but I think taking the
20 benefit of this panel and how we integrate it.

21 But, again, other anecdotal
22 stories is that it takes a lot of time. And

1 probably more importantly, it pulls a
2 pharmacist offline to take care of the one
3 patient for an hour or two hours. When you
4 look at your typical community-based hospital
5 -- it might have 10 pharmacists working, if
6 they're lucky -- you just had a 10 percent
7 patient workload reduction for the rest of the
8 patients in the hospital.

9 So, we know it is a big concern.
10 It is a growing concern among our members. It
11 is probably one of the most frequent questions
12 and calls that I get from our members in the
13 last three or four months, in particular, as
14 they are preparing for just the best practice
15 for the ESA. So, we are prepared to assist in
16 that.

17 DR. BOUGH: APhA is interested in
18 doing some follow-up survey with our members
19 as well. We gathered some information for the
20 opioid REMS discussion last spring. I will
21 look at that data, but we will certainly
22 provide you with some information that we can

1 move forward with that looks at trying to
2 capture some of this data from our members
3 that would be based on just what they're
4 anticipating their time being with
5 implementing the various programs.

6 One of the challenges we have in
7 the pharmacies is that, regardless of the
8 number of REMS that a prescriber might be
9 dealing with, we see all of the REMS in the
10 pharmacy, if they are not required to be
11 specialty-type pharmacies. So, in the
12 community setting, once we lay out which REMS
13 we are talking about, then we can guide them
14 to the amount of time that they are
15 implementing those different programs. So, we
16 will follow up with our members on that.

17 DR. HAUSER: I'm Ronna Hauser from
18 NCPA.

19 We do have anecdotal data that we
20 will be happy to share with the docket. Then
21 I will also make it a point to work with my
22 colleagues within the pharmacy industry to see

1 about any studies out there that may not have
2 been unearthed that we can submit as well to
3 the docket. So, we will take that upon myself
4 to make sure we do that.

5 DR. DAL PAN: Thank you. I think
6 any information you have would really be
7 helpful to us. So I would encourage you to
8 submit it to the docket. Thank you.

9 MS. TOIGO: Claudia?

10 DR. KARWOSKI: For some of the
11 programs, REMS programs, that allow
12 distribution of the drug in the retail
13 setting, in order to reduce the burden, we
14 have certified pharmacies rather than
15 certifying individual pharmacists. What that
16 really entailed was having one individual
17 within the pharmacy that was in charge of sort
18 of training the rest of the staff about the
19 requirements of the REMS.

20 But we also have some information
21 that suggests that some of the processes, and
22 so forth, safeguards are not necessarily being

1 followed, and we're not clear of the real
2 reason for that. Some of it might be that
3 there's a number of programs or perhaps that
4 individual pharmacist may not have enough
5 experience with that program.

6 So, some of the concerns we have
7 is like how to address that, what needs to be
8 done. I think automation would go a long way,
9 but in the absence of having automation in the
10 55,000 pharmacies, I am wondering if you all
11 have any suggestions for how to get that
12 feedback back to the pharmacies and what can
13 be done to address those issues.

14 DR. BOUGH: Well, you raise a good
15 point, that there is variations on how the
16 pharmacists receive information at the
17 pharmacy and how they are being certified with
18 different programs.

19 As we move forward with REMS
20 programs and evolve the process, I think
21 there's opportunities to consider how we tie
22 training and certification to the pharmacist

1 level, instead of just the pharmacy. That
2 discussion has come up in the past. With
3 pharmacists being logged into systems and
4 being able to tie back to an individual
5 identifier, we would be able to do something
6 like that in the future, using, for example,
7 the National Provider Identifier number, NPI
8 number. Not all pharmacists have that, but
9 that could be something that could be a model
10 to move forward.

11 I know some of the other groups
12 have discussed topics on how to identify
13 individual practitioners for that attestation
14 of successfully completing certification. Any
15 of that type of data, regardless if it's to
16 the pharmacy level or to the pharmacist's
17 level, can be housed within a REMS database
18 with the REMS administrator, and then verified
19 seamlessly within a claims adjudication
20 process, either at the front end or the back
21 end of the claims process. So that we
22 wouldn't have to step away and verify any of

1 that. The same holds true with verification
2 prescriber education.

3 So I think as we learn from the
4 past programs and look at opportunities to
5 improve the compliance within types of REMS
6 programs, there's opportunities to change how
7 we are doing that. Maybe it is just the
8 flexibility programs. It may not be the same
9 with every one. But what we want is the
10 processes to be the same. So that if there
11 are requirements for specific education, we
12 are kind of doing it the same way, rather than
13 something different for each different REMS
14 program.

15 DR. HAUSER: Ronna Hauser with
16 NCPA.

17 If you are addressing a specific
18 attestation or things that currently exist
19 today, technologies that are used in the
20 iPLEDGE program, for example, how we attest
21 training related to sudofedrine products, that
22 is at pharmacy level, and the pharmacies have

1 an MPI. That's something that we can
2 obviously report.

3 If we talk about education of a
4 pharmacist or a pharmacy technician, tying
5 that into a certified continuing pharmacy
6 education program. Obviously, there's also
7 ways that industry has been working towards,
8 to make sure all that information could be
9 collated per pharmacist, per pharmacy
10 technician, and reported on.

11 MR. CHEN: And I would like to
12 just add for hospitals, because a lot of these
13 drugs now are moving into all areas of care,
14 that in hospitals we already have a lot of
15 competency requirements of the Joint
16 Commission, looking at patient populations and
17 high-risk medication use in those spaces.

18 Also, one of the concerns, I would
19 say, that we are seeing now is that the use of
20 mandatory education for certain requirements,
21 and its growth in the industry, we are seeing,
22 I think, cross-provider types. Here in the

1 State of Maryland, they have just required for
2 your CE for a pharmacist to, I think it's
3 medication error safety CE. Washington, D.C.,
4 has just recently done that as well.

5 I think the balance of trying to
6 keep track of that for our providers, of what
7 is mandated versus competency developed to
8 ensure safe use, is becoming more in use as a
9 tool. Then do we start squeezing out time for
10 other things that don't have a champion or a
11 mandate for?

12 And also, just as you use for a
13 resource to bring and put on the table,
14 hospitals and health systems have a lot of
15 outpatient pharmacies. Of all the hospitals
16 in the nation, there is probably about 1200
17 that have outpatient community-style, and they
18 are typically very large. For example, Grady
19 Hospital System in Atlanta dispenses as many
20 prescriptions as about 20 traditional
21 community pharmacies.

22 So they are a great resource for

1 large-scale dispensing events with populations
2 that may actually be at higher risk than some
3 of our normal populations that we need to be
4 thinking about.

5 MS. TOIGO: Given that it is
6 lunchtime, it looks like there's no more
7 questions from the panel.

8 So thank you all to our panel for
9 the presenting and for the stimulating
10 question-and-answer session.

11 We will take an hour lunch break
12 and be back at 12:45.

13 Thank you.

14 (Whereupon, the foregoing matter
15 went off the record for lunch at 11:46 a.m.
16 and resumed at 12:49 p.m.)
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1 A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

2 12:49 p.m.

3 MS. TOIGO: Good afternoon,
4 everybody.

5 We are going to get started with
6 panel 4. But before we do, in my quest to
7 have good meetings, I want you to think about
8 if you have said, "Gee, I wish I knew before
9 I got here today," so I have heard some
10 comments about directions and how to get into
11 the building. But any of those things that
12 you are talking among yourselves or you have
13 said, "Gee, I wish they had told me that
14 before I got here," send those to me.

15 We, as taxpayers, have paid for
16 this lovely building. We want to hold
17 meetings here. We want you to look forward to
18 coming to meetings here. So, anything we can
19 do to facilitate this being a good experience,
20 to the extent that we have control, we would
21 like to do that. So, please, share with me
22 those comments.

1 So, panel 4, we are going to
2 continue of our discussion of evaluating the
3 effectiveness of the REMS. We have one, two,
4 three, four, five, six presenters, and then we
5 will have time for discussion.

6 We have two people signed up to
7 speak during the open public session. So, if
8 you are trying to decide whether, if you sign
9 up to speak, that it will keep you here too
10 long, you can see we only have two people. So
11 it is not going to be a long session, if you
12 want an opportunity to speak.

13 So, everybody on this panel, with
14 the exception of Dr. Davis, has been here
15 already and presented and knows the rules.
16 But Dr. Davis probably knows the rules, too.

17 So welcome.

18 Andrew, if you could get us
19 started?

20 MR. EMMETT: Good afternoon,
21 everyone.

22 I'm Andrew Emmett. I'm Director

1 for Science and Regulatory Affairs for BIO,
2 the Biotechnology Industry Organization.

3 Thank you for the opportunity to
4 present on evaluating the effectiveness of
5 REMS programs.

6 In recent months, the first round
7 of assessments have been submitted to the FDA,
8 and FDA sponsors have begun to gain valuable
9 hands-on experience assessing the
10 effectiveness of REMS programs.

11 We would like to offer three
12 recommendations with respect to the assessment
13 and goals and modifications of REMS.

14 First, the post-market
15 modification process should facilitate minor
16 editorial and non-substantive changes to REMS.

17 Second, REMS should not be
18 assessed in absolute terms, and assessments
19 should distinguish between communication-based
20 REMS and elements to assure safe use.

21 And finally, sponsors should not
22 be legally, cannot legally account for third-

1 party compliance with REMS.

2 So, with our first recommendation,
3 an important element of assessing of REMS is
4 to subsequently modify the program to make
5 improvements, of course. While the draft
6 guidance addresses the important issue of how
7 a REMS program should be modified in the post-
8 market timeframe, we are concerned about the
9 suggestion that all REMS modifications,
10 regardless of whether they are substantive
11 changes to the strategy or minor editorial
12 changes to an implementing tool, must be
13 submitted to the prior approval supplement
14 process.

15 We believe that this process will
16 create unnecessary delays in mitigating
17 emerging safety issues and create
18 administrative burdens for FDA and industry
19 when minor changes are needed.

20 As noted this morning, no matter
21 how carefully FDA and the sponsor design a
22 REMS, a sponsor will inevitably need to

1 improve the selected tools over time to allow
2 for effective implementation and best meet the
3 plan's goals.

4 Sponsors need to have flexibility
5 to make timely adjustments to REMS tools, and
6 FDA's limited resources should not be diverted
7 to reviewing supplements making only minor
8 changes.

9 We recommend that the FDA clarify
10 in the final guidance that the agency should
11 review and approve the REMS document governing
12 risk management strategies and that the
13 sponsor should be charged with ensuring that
14 all supporting REMS tools are fully consistent
15 and comply with the approved REMS document.
16 FDA could then exercise general enforcement as
17 warranted.

18 If FDA does not agree with the
19 above recommendation, BIO recommends that the
20 agency adopt a tiered approach to REMS
21 modifications in which sponsors would be
22 permitted to make minor changes to their

1 approved REMS tool through an administrative
2 recording process in advance of FDA's review
3 and approval of the change.

4 Changes falling under this
5 procedure would be limited to technical,
6 managerial, administrative, and minor changes
7 to the approved REMS tools that do not alter
8 the fundamental approved REMS document.

9 FDA could then require that all
10 minor changes be submitted to FDA in some
11 form, such as the next assessment report.

12 Subsequent changes to the REMS
13 strategy should continue to be made through
14 the prior approval supplement process.

15 With respect to our second
16 recommendation, the draft guidance suggests
17 that a proposed REMS assessment plan and the
18 REMS supporting document should include
19 targeted values and that the REMS goals should
20 be stated in absolute terms. We ask that the
21 agency attempt to reconcile its view that REMS
22 goals be ideal outcomes that might not be

1 possible to meet with its view that the
2 concise document in which the goals are
3 contained are enforceable. Sponsors should
4 not be set up for failure by having to commit
5 to ideal goals that may not be achievable.

6 One way of reconciling these
7 concepts is to rely for enforcement purposes
8 on the objectives which sponsors agree should
9 be pragmatic, specific, and measurable.

10 Additionally, there should be a
11 distinction between REMS that contain more
12 routine communication elements and elements to
13 assure safe use. Specifically, we would like
14 to see this distinction emphasized both at the
15 point of defining REMS objectives and also in
16 relation to the REMS assessment.

17 And finally, BIO is concerned
18 about the implications regarding sponsor
19 auditing of the activities of third parties,
20 as discussed in the draft guidance. While
21 PDUFA provides that in certain instances
22 sponsors may be required to take reasonable

1 steps to monitor and evaluate third-party
2 implementation of REMS elements and to work to
3 improve the implementation of such elements by
4 such persons, sponsors should not be held
5 responsible, despite these reasonable steps,
6 for shortcomings of third parties. Sponsors
7 are not legally responsible for the
8 independent decisions or actions of third
9 parties with respect to their drugs, even when
10 these drugs are subject to REMS.

11 There may, of course, be
12 situations where sponsors have information
13 about third-party behavior, and it is
14 appropriate for a REMS assessment to include
15 whatever information is known to the sponsor
16 about third-party decisions and behavior.

17 In addition, monitoring certain
18 third-party behavior and decisions may be
19 constrained by federal and state patient
20 privacy laws.

21 Finally, certification of
22 wholesalers and distributors seems to go

1 beyond reasonable steps to monitor the
2 evaluation and implementation, and a more
3 conventional interpretation of other parties
4 would be those directly assisting healthcare
5 providers, dispensers, patients who work in
6 the healthcare settings such as nurses and
7 pharmacy technicians.

8 So, thank you again for the
9 opportunity to present, and I would be happy
10 to answer questions during the question-and-
11 answer period.

12 MS. TOIGO: Thank you, Mr. Emmett.

13 Our next presenter is Dr. Kelly
14 Davis from the United Bioscience Corporation.
15 Sorry. United BioSource Corporation.

16 DR. DAVIS: Good afternoon. Thank
17 you for the opportunity to speak today about
18 REMS assessments.

19 My name is Kelly Davis, and I'm
20 Vice President, and I'm Vice President of
21 Safety, Epidemiology, and Risk Management at
22 United BioSource Corporation., UBC, where I

1 work as a consultant in drug safety and risk
2 management.

3 UBC has been involved in the
4 design, implementation, and/or evaluation of
5 more than 60 risk minimization programs. I've
6 worked with many different sponsor companies
7 and products across various reviewing
8 divisions. This experience is the background
9 for the points that I will raise today for
10 FDA's consideration.

11 The focus of my presentation will
12 be specific areas where I believe from my
13 experience that clarification and
14 standardization is needed from FDA about REMS
15 assessments.

16 REMS with medication guides are by
17 far the most prevalent type of REMS, followed
18 by REMS that include additional communications
19 to healthcare professionals or communication
20 plans. Both of these types of REMS are
21 focused on education.

22 A standard component of a REMS

1 assessment, then, is to assess how effective
2 these educational interventions are. Surveys
3 to assess knowledge about the specific risks
4 of the product addressed by the REMS are the
5 standard methodology.

6 So, my first request for
7 clarification and consistency relates to
8 determining the appropriate sample size for
9 these assessments. There are two possible
10 approaches. Either target a particular level
11 of understanding and base the sample size on
12 that or select a sample size based on
13 practical factors or precedent and define the
14 precision that the sample would provide at
15 certain hypothetical levels of understanding.

16 As shown on this slide, the table
17 shows an example of the second approach. In
18 this case, for a sample size of 300
19 respondents, various levels of understanding
20 are shown ranging from 50 to 95 percent on the
21 left column, and on the far right the lower
22 bound of the 95 percent confidence interval at

1 the various rates of understanding.

2 So, guidance is needed on the
3 expected sample size for the assessments.
4 Just last month at DIA, an FDA speaker stated,
5 in response to a question, that the expected
6 sample size was 200. But it would be good to
7 see some written guidance on this and also
8 clarification on acceptable reasons for aiming
9 lower, which we have done in particular cases
10 where the uptake has been low or where the
11 product is really indicated for orphan
12 indications.

13 Because REMS safety messages
14 address some of the most important safety
15 information, arguably, the most important
16 safety information about the product, I know
17 that we all hope and expect that the level of
18 understanding will be high, as near to
19 universal as possible.

20 It would be useful for sponsors to
21 understand FDA's expectations around these
22 thresholds. Is 80 percent good enough?

1 Should it be 90 percent?

2 We have done a number of REMS
3 assessments to date. I think we have data on
4 six different products, six different programs
5 with various stakeholder involvement. I can
6 tell you that our mean level of understanding
7 for patients is approaching 80 percent, and
8 our mean level for risk message understanding
9 for healthcare professionals is about 83
10 percent. But you can imagine that the
11 variability from program to program and
12 message to message is wide, ranging from less
13 than 50 percent all the way to 100 percent.

14 So, should the targeted threshold
15 be the same for patients and doctors and other
16 healthcare professionals? And is there a
17 particular level where remediation is
18 automatically expected by FDA? Or is it FDA's
19 view that this may depend on the relative
20 importance of the risk message relative to the
21 overall goals of the REMS.

22 The third area or theme for my

1 comments relates to REMS assessments reports.
2 It seems that it would be possible and helpful
3 to sponsors if FDA would specify the content
4 and format of these reports. We have seen
5 requests for elements to assure safe use
6 programs metrics to be variable from division
7 to division. It's stated in the guidance that
8 status reports on post-marketing requirements
9 studies should be included, but it seems to us
10 that this should only include those post-
11 marketing requirement studies that are related
12 to the goals of the REMS. So, clarification
13 on this point would be helpful.

14 And also, for many REMS,
15 pharmacovigilance reports are also included in
16 the REMS assessments, specifically reports on
17 spontaneous or clinical trial adverse event
18 reports that you are trying to minimize. So,
19 it would be helpful if you could clarify the
20 timing for the cutoffs for those reports. Can
21 companies simply use the most recent PSUR, for
22 example?

1 And finally, a table of contents
2 would also be helpful in forthcoming guidance.

3 So, in summary, this is a list of
4 the suggested areas for greater specificity in
5 the information provided by FDA in the REMS
6 guidance. On the sample for KAB surveys, the
7 only thing I didn't mention on this list is
8 the sponsor's obligation to specifically
9 evaluate patients taking the branded product
10 when a generic version is available.
11 Clarification on that point would be useful.

12 REMS metrics, including thresholds
13 for comprehensions and levels where
14 remediation for educational materials might be
15 needed, and REMS assessment reports
16 standardizing the format and content.

17 If you have questions, I would be
18 happy to answer them during the panel
19 discussion or individually via email, if you
20 would like to contact me that way.

21 Thank you.

22 MS. TOIGO: Thank you, Dr. Davis.

1 Our next presenter is Dr. Stephen
2 Goldman from Stephen Goldman Consulting
3 Services.

4 DR. GOLDMAN: Thanks, Terry.

5 Among the things I did when I was
6 at the FDA of which I'm most proud was serving
7 on the landmark 1999 Task Force on Risk
8 Management, which really established the
9 playbook for how risk management is done, not
10 just in the United States, but worldwide, work
11 I've continued over the past 12 years, both in
12 industry and as a consultant.

13 I'm going to focus on three
14 specific questions that came out of The
15 Federal Register notice: specifying the
16 metrics for determining effectiveness at the
17 time of the REMS approval; how one should
18 monitor the REMS to determine effectiveness,
19 and the third aspect is the concept of using
20 service.

21 I think, frankly, the answer to
22 the first question is a no-brainer, that you

1 must state what the criteria is for success
2 and for effectiveness. An example of that is
3 a study I did and published a few years ago
4 looking at notifications. There were
5 examples, one which I'll show you in a minute,
6 where there was clearly a success in the
7 notification, but the product still came off
8 the market.

9 An example, as Harry Truman, the
10 only thing new is the history you don't know.
11 In 1992, terfenadine had warnings associated
12 with contraindicated medication in certain
13 populations. There was a "Dear Doctor"
14 letter. No, not to healthcare professionals;
15 a "Dear Doctor" letter, over 613,000 folks.
16 Greg Burkhardt at the time working for the
17 agency and his other agency colleagues
18 assessed through pharmacy data to see whether
19 or not the notification had effectiveness.

20 There were two things I found.
21 First of all, reports went down when usually
22 reports go up after notification. And even

1 more importantly, the actual concomitant
2 contraindicated use went down significantly.

3 There were at least two other
4 studies that replicated the same findings,
5 that the notifications clearly were felt to
6 lead to decrease in contraindicated co-
7 prescription. But as the FDA pointed out in
8 its notification, when sought to take
9 terfenadine off the market, it did not go down
10 to zero, nor could it have been expected to.

11 There were four essential
12 categories of risk which I think sometimes is
13 overlooked. You've got drug/drug
14 interactions, like the terfenadine example
15 with cisapride. You've got off-label use,
16 like what happened with bromfenac, a non-
17 steroidal that was not supposed to be used
18 beyond 10 days because of known association
19 with hepatotoxicity.

20 Troglitazone, also associated with
21 hepatotoxicity, had a recommended blood test
22 monitoring program, and teratogenicity like

1 for the retinoids.

2 And medical products differ in
3 perceived benefit/risk, based on the
4 population being treated, availability of
5 other products, whether the adverse event is
6 reversible such as agranulocytosis with
7 Clozaril.

8 Thus, every case must be
9 individualized. You cannot use a cookie-
10 cutter approach.

11 Very briefly, this was an example
12 of a terrific program that was done in
13 Australia concerning flucloxacillin and
14 jaundice. And the point being made here is
15 that a lot of different things were tried
16 before they finally hit on what seemed to be
17 the solution, which is a notification in the
18 pharmacy benefits book and changes in
19 advertising.

20 And the authors themselves
21 cautioned against looking at any one
22 intervention being seen in isolation. That's

1 what the REMS is an organized, complete
2 program with not just one aspect that must be
3 looked at.

4 There's another terrific example
5 that I found done in Belgium about non-
6 compliance concerning bloodstream infections,
7 a very simple, clinically-relevant
8 intervention. As you can see, non-compliance
9 decreased significantly.

10 Lessons learned: risk information
11 intended for healthcare professionals should
12 be clinically-oriented and relevant as
13 possible. Education interventions I fully
14 believe should be done in a care setting to
15 make it clear they have public health impact.
16 And desired results of REMS should be
17 clinically-relevant, definable, and measurable
18 as possible.

19 With the last point about survey
20 data, concerning troglitazone, this was the
21 study that Dr. David Graham of OSC and his
22 colleagues did, which demonstrated, using the

1 tools they had, adherence to the
2 recommendations from liver monitoring, the
3 compliance was dismal.

4 At the same Advisory Committee
5 meeting, survey data was presented which
6 showed a tremendously high level of awareness
7 of the requirements. However, I'm a
8 psychiatrist. And I will point out that
9 knowledge doesn't always follow with action.

10 And there was a subsequent study
11 done by Cluxton and Associates which basically
12 supported the findings of Dr. Graham; namely,
13 that compliance with the recommended system of
14 LFT monitoring was not being complied with.
15 So survey data does tell you what the ideas
16 and the concepts and acceptance is. It
17 doesn't necessarily tell you what the behavior
18 is that is desired.

19 Thank you.

20 MS. TOIGO: Thank you, Dr.
21 Goldman.

22 Next we will hear from Mr. Glenn

1 Naphy, Springboard Associates.

2 MR. NAPHY: Hi. Glenn Naphy with
3 Springboard, a global provider of market
4 research.

5 So, what we're going to do today a
6 little bit is, actually, I'm going to use the
7 term "springboard" off the previous
8 conversation. We are in total agreement that
9 surveys only go part of the way. They are not
10 sufficient.

11 What I have on the next slide is a
12 proposed approach to encompass a two-stage
13 comprehensive approach that optimizes the
14 understanding of the impact. A couple items
15 that we want to put in here is that these are
16 really the ingredients that we have found in
17 looking at a vast array of programs and kind
18 of whittling it down to the nuts and bolts.

19 A couple of things I would point
20 out here is that this is kind of like our
21 roadmap for going forward right now, but each
22 REMS program is different and we need to

1 assess the different things in a different
2 manner.

3 For example, when we are talking
4 about physicians, what specific information do
5 I need to give patients about how to use this
6 medication can be done in a survey. It's
7 really a quick, easy question.

8 However, we would also like to
9 know what is being done to ensure patients
10 remember and act upon it. We have additional
11 systems in place in a physician's office to
12 kind of extend that learning. We heard
13 earlier this morning you only retain 20
14 percent of what you hear the day before, and
15 we need to make sure there our patients
16 remember these important facts as they leave
17 the office.

18 The second component is assessing
19 of a healthcare professional and patient
20 adherence to relevant aspects of each specific
21 ETASU. The identification of barriers to
22 adherence and means for overcoming these

1 barriers cannot be sufficiently obtained in a
2 quantitative survey. So, therefore, we need
3 a qualitative approach and kind of a blended
4 two-approach program.

5 Stage 2 is really an assessment of
6 all pertinent variables. And what I mean by
7 all pertinent variables here are the intended
8 effects as well as the unintended effects.

9 With the knowledge of the stage 1, we are able
10 to then dive into other parts of the areas
11 that may be affected by a REMS or were not
12 anticipated to be affected by REMS, for
13 example, staff expansion for the physician's
14 office. That's an important factor that we
15 need to kind of capture.

16 So, we want to look at, what's the
17 end result that we're really trying to do
18 here? We're trying to improve patient care.

19 So, are we able to get patients back to their
20 workplace, back to supporting their families?
21 Those are elements that we also need to kind
22 of capture.

1 The other thing to kind of
2 complete the loop is really the cost of
3 implementation and monitoring. This could be,
4 also, the manufacturer of the product as well
5 as the healthcare professional. With this, we
6 hope to uncover some of the barriers to
7 effective treatment.

8 Another point that is not directly
9 listed on this slide, but is also important is
10 that we need to also assess the site of care.
11 If physicians run into too many barriers, they
12 may be adhering to all of the components in
13 the REMS program, but may be ushering their
14 patients to be seen at a hospital or a
15 different setting. That's something we also
16 need to encompass when we're evaluating REMS.

17 Thank you very much.

18 MS. TOIGO: Thank you, Mr. Naphy.

19 Our next presentation will be Mr.
20 Kevin Nicholson from the National Association
21 of Chain Drug Stores.

22 MR. NICHOLSON: Good afternoon,

1 and thank you for holding this important
2 meeting.

3 I'm Kevin Nicholson, Vice
4 President, Government Affairs and Pharmacy
5 Advisor for the National Association of Chain
6 Drug Stores. NCDS represents traditional
7 drugstores, supermarkets, and mass merchants
8 with pharmacies.

9 Our more than 150 chain member
10 companies include regional chains with a
11 minimum of four stores to national companies.
12 Our members fill more than 2.5 billion
13 prescriptions yearly -- I realized that
14 yesterday when I spoke I said "million", that
15 was a misstatement, so I want to correct that
16 -- billion prescriptions yearly, which is more
17 than 72 percent of annual prescriptions in the
18 U.S.

19 To help determine the
20 effectiveness of a REMS, FDA should first
21 consider the risks that must be mitigated,
22 which vary widely among affected medications.

1 Considering the wide variance of risks that
2 need to be managed, along with the wide
3 variety of elements to assure safe use that
4 can be used as tools to help manage those
5 risks, we believe it would be difficult to
6 develop standardized metrics and mechanisms to
7 measure those metrics until FDA has more
8 experience with this relatively new REMS
9 authority and the various ETASUs.

10 As I mentioned in response to
11 FDA's questions regarding how ETASUs can be
12 implemented to minimize negative effects on
13 the healthcare delivery system, we believe the
14 best approach to REMS is a cautious and
15 measured approach. We believe that
16 implementing REMS in a stepwise fashion would
17 provide the greatest opportunities for FDA to
18 monitor and assess the various REMS elements.

19 In other words, first establish
20 the baseline requirements that are expected to
21 address the main concerns that FDA feels
22 necessitates the REMS, and then consider

1 moving on to additional requirements, if the
2 initial requirements are not meeting the
3 agency's goals.

4 For example, we are supportive of
5 FDA's proposed draft REMS for long-acting and
6 extended-release opioids because it would
7 implement this class of REMS using a cautious
8 and measured approach.

9 In contrast, we believe that
10 patient registries should be avoided. Patient
11 registries are an example of a problematic
12 ETASU. Should FDA consider requiring such a
13 difficult ETASU, we would urge FDA to work
14 closely with the pharmacy industry and other
15 stakeholders to develop limited programs for
16 that ETASU and evaluate those programs.

17 A limited program would provide
18 FDA with ample opportunity to work out the
19 bugs of that ETASU before mandating that
20 element on a broad scale. Moreover, once the
21 bugs have been worked out, such element could
22 conceivably be applied to other REMS with

1 minimal concern about impact on the healthcare
2 industry.

3 I would like to reinforce that,
4 although pharmacies are not directly
5 responsible to FDA for the design,
6 implementation, and success of a REMS,
7 pharmacies will be subject to the elements of
8 a REMS in order to meet the needs of their
9 patients.

10 As FDA is aware, there are
11 numerous potential REMS elements that
12 pharmacies would be responsible for
13 implementing. FDA should ensure that
14 pharmacies are consulted during the design of
15 such elements.

16 Finally, we thank FDA for making
17 progress toward the development of the one
18 document solution for written prescription
19 information that pharmacies provide to
20 patients. Once finalized and adopted, this
21 should serve as a useful tool to educate
22 patients about their medications and mitigate

1 associated risks, and certainly should be
2 considered, when appropriate, as an element of
3 a REMS.

4 Thank you.

5 MS. TOIGO: Thank you, Mr.
6 Nicholson.

7 And our last presenter is Dr.
8 Richard Wagner from Kaiser Permanente. And
9 this must be the Accutane presentation coming
10 up.

11 DR. WAGNER: Good afternoon.

12 Yes, I kind of feel like the 11
13 o'clock news. I've been teasing people for
14 the last two days. So, we actually do want to
15 share some data today, and I want to let the
16 agency know, and others in the audience, that
17 a poster was presented at ISPOR in May, and
18 that poster is publicly available. I do have
19 copies electronically for folks that want to
20 take a look at it or if someone from the
21 agency would like a copy.

22 But what we want to do is actually

1 meet the burden of trying to demonstrate the
2 effect of a REMS program on health system,
3 both in terms of, hopefully, the improved
4 outcome, but also any unintended consequences.
5 So, we do have some data today.

6 I've got to give my colleagues
7 back at Kaiser Permanente credits. I'm not
8 doing the study. I'm just reporting on some
9 of their data. We have worked closely with
10 our dermatologists on this research project
11 and our pharmacist researchers, and it is an
12 IRB-approved project. So, it kind of meets
13 the standards that we have talked about in
14 terms of protecting patient confidentiality
15 previously. It does get us back into looking
16 at an evaluation of a REMS program, trying to
17 use data from a health system to be
18 influential with the agency and others. And
19 I think it also is of interest to us as a
20 health system in terms of trying to improve
21 our own quality systems.

22 So, we have two decades of

1 experience with isotretinoin and monitoring,
2 both at Kaiser Permanente and through the
3 agency and other health systems. It's one of
4 the 16 deemed REMS, so we're treating it as a
5 REMS, and it's an example of a need that we
6 have talked about previously: establish goals
7 through a process that involves pharmacists
8 and prescribers, in this case primarily
9 dermatologists that prescribe over 90 percent
10 of our isotretinoin prescriptions.

11 We need to evaluate clinical
12 outcomes rigorously, as much as possible be
13 rate-based. So we need a numerator and a
14 denominator to do this effectively. And we
15 want to anticipate and track unintended
16 consequences. That's one of the tenets of
17 quality improvement, is not only track what
18 you're doing to improve quality, but also look
19 for those unintended consequences, and then
20 report outcomes. And as we talked earlier
21 today, be able to adjust the quality system to
22 take into account what we have learned.

1 So, very quickly, again, what we
2 have done since the implementation of iPLEDGE
3 is within the Kaiser Permanente system we have
4 actually tracked our females of childbearing
5 potential. There were over 4,000 treatment
6 courses at Kaiser Permanente Southern
7 California during the study period, 2,582
8 treatment courses during the SMART timeframe,
9 and 1,595 treatment courses during iPLEDGE.
10 These are female patients of childbearing
11 potential.

12 During the SMART program, the rate
13 in Kaiser Permanente was 3.1 per thousand
14 treatment courses during the time of the SMART
15 program. We have previously reported this in
16 the Journal of the American Academy of
17 Dermatology in 2006.

18 However, since iPLEDGE, fetal
19 exposure rates have now changed to 3.76 per
20 thousand treatment courses during the iPLEDGE
21 program. We have actually seen a net
22 worsening of rates, although, as I got to the

1 next slide, because one of the unintended
2 consequences of iPLEDGE implementation I think
3 throughout the country, and certainly within
4 Kaiser Permanent, is a very large reduction in
5 the number of female patients that have
6 prescriptions for isotretinoin, over a 42
7 percent reduction. And although we are
8 gradually returning to previous iPLEDGE level
9 rates, we still have not actually quite gotten
10 back to where we were.

11 Female patients over 21, actually,
12 experienced increased risk post-iPLEDGE, while
13 female patients less than 21 had a significant
14 decrease in risk. So we think this is key
15 finding. We have seen other evidence out
16 there that our younger patients may be better
17 treated by the iPLEDGE program, the patients
18 under 21, seeing a significant reduction in
19 the rate of unintended pregnancy, but we still
20 have a problem in our older patients. So,
21 maybe even inadvertently we have made that
22 worse.

1 So, again, this is a poster
2 presentation. I would be happy to share that
3 poster that has more details, and we are
4 actually pending publication in the clinical
5 journal with peer review that, hopefully, will
6 be picked up sometime before the end of the
7 year.

8 Again, back on everything that we
9 have learned this week or these last couple of
10 days, we need healthcare provider input on
11 REMS design; the recognized potential
12 conflicts of interest if only sponsors are
13 solely responsible for evaluating
14 effectiveness.

15 We still have not seen any reports
16 from the iPLEDGE program since the one report
17 in 2007, and we have been waiting for 2008,
18 2009, and maybe even a 2010 report. We
19 haven't seen it.

20 And we do need to assess the
21 burden on the healthcare system. Others have
22 brought up previously we need to look for

1 unintended consequences. It appears to us
2 that some of our patients have been denied
3 appropriate care with that large, significant
4 reduction in Accutane prescribing.

5 And the application of rate-based
6 metrics for determining effectiveness needs to
7 be considered. So, although we have seen an
8 absolute reduction from eight patients to six
9 patients during this time period, we do need
10 to look at the rate to fully determine
11 effectiveness.

12 And again, I would go back. We
13 have outside agencies that we could consult
14 with.

15 So, I would like to finish my
16 presentation and sit down and take any
17 comments or questions from the panel.

18 MS. TOIGO: Thank you, Dr. Wagner.

19 And we'll start the FDA questions.

20 I just have one question in
21 wearing one of my hats at FDA as a patient
22 advocate and thinking about some of the things

1 we have heard today in terms of the groups
2 involved in developing the plan.

3 I notice you had prescribers and
4 pharmacists, but I didn't see patients. Do
5 you include patients in the groups that are
6 working on developing some of these systems?

7 DR. WAGNER: That's a good
8 question. Not in this particular instance.

9 I would also say that in many
10 ways, though, our physicians are advocates for
11 the patients, and they, of course, directly
12 interact with patients in terms of the iPLEDGE
13 program, the nurses and the medical offices
14 with the patients, too. So, a lot of feedback
15 comes indirectly from patients through nurses
16 and physicians and also through the
17 pharmacists. But we have not engaged patients
18 directly in terms of the program that we have.

19 DR. JENKINS: For Dr. Wagner, your
20 iPLEDGE study is very interesting. It had
21 relatively small numbers. So, I'm wondering,
22 are those differences that you cited

1 statistically significant between 3.1 and 3.76
2 per thousand treatment courses?

3 DR. WAGNER: yes, and I'll show
4 you. I can give you a copy of the poster
5 presentation. It has some more details about
6 the statistical analysis. So, the results I
7 presented are reported in the poster as being
8 statistically-significant.

9 This was a study done primarily
10 for the poster presentation in Kaiser Southern
11 California. We have also combined resources
12 with the folks that we work with in Northern
13 California. So that we are, in essence,
14 doubling the size of the study for the paper
15 that's being submitted for publication. So we
16 are going to end up with something closer to
17 7,000 treatment courses between the
18 approximately 7 million members in Kaiser
19 California.

20 DR. JENKINS: Did you speculate or
21 did the authors speculate on what might have
22 been the reasons for an increased rate of

1 exposure under iPLEDGE in the Kaiser system?

2 Do you have any thoughts about what may have
3 caused that?

4 DR. WAGNER: There is some
5 speculation, and we've got feedback from our
6 dermatologists, in addition to the study
7 authors.

8 One thing is it does appear that
9 the way that iPLEDGE is designed actually is
10 more tailored to what our younger patients
11 need or expect. So, we haven't tested that by
12 survey, but feedback is I think the younger
13 patients are willing to accept maybe a much
14 more structured program, so that that's,
15 again, anecdotal feedback from our clinicians
16 or dermatologists.

17 It does appear that in some ways
18 some speculation, again, as we get to older
19 patients or also patients that have received
20 a second treatment course; they appear to be
21 a little bit more cavalier in terms of
22 actually following the prescribed two courses

1 of birth control. So, it's actually, we
2 believe, a patient behavior issue primarily in
3 our older patients.

4 We can actually go back and
5 demonstrate no patients were pregnant at the
6 time that they received the prescription, but
7 the pregnancies occurred within 30 to 90 days
8 after receiving the last isotretinoin
9 prescription. Clearly, back on patient
10 behavior; clearly, back on compliance with the
11 two forms of birth control.

12 MS. TOIGO: Mwango?

13 DR. KASHOKI: Just to follow up on
14 that, you mentioned that you had noted a
15 decrease in the number of prescriptions. Were
16 you able to collect information as to whether
17 or not this was because of a change to
18 prescribing for the patients for whom the drug
19 is technically approved, and so an improvement
20 in prescribing practices or something
21 different?

22 DR. WAGNER: I think it is

1 probably multifold. Clearly, the initial
2 impact of iPLEDGE was disruptive. So, the
3 normal processes of care during the early
4 stages of implementation were disrupted. That
5 typically happens in many other programs that
6 you implement when you have a significant
7 change.

8 That persisted during year one and
9 two. So, it's gotten better. What we have
10 clearly identified, and the poster has
11 examples of it, that it does appear that the
12 patients that are currently in the iPLEDGE
13 program in our system were actually somewhat
14 slightly sicker. They have had more courses
15 of other anti-acne products. They have other
16 indicators that they may be even slightly
17 sicker from a dermatologic perspective than
18 the other patients. So we may be taking care
19 of a higher-risk group of patients. So some
20 early evidence of that with our study.

21 But we do believe, separate than
22 that, that I didn't report on it, but it is

1 actually reported separately, our male
2 patients also experience about a 20-plus
3 percent reduction in prescriptions during that
4 same time period. Again, they have gradually
5 started to come back. We are still down a
6 little bit. So, we have had that unintended
7 consequences on male patients, too, in terms
8 of reduction in Accutane or isotretinoin
9 prescriptions for the male patients, not as
10 great as the female patients. So we have had
11 a disproportionate impact on female patients.

12 DR. JENKINS: So, to take you up
13 on your suggestion about consulting with the
14 providers and the healthcare systems in
15 designing REMS, do you have advice on how you
16 would recommend that iPLEDGE be modified to
17 better address the goals or the needs of
18 closed systems like Kaiser?

19 DR. WAGNER: Well, one thing, and
20 we have mentioned it earlier, if we could
21 eliminate the amount of time spent on having
22 to enroll our male patients, which we actually

1 feel has relatively little value in terms of
2 pregnancy prevention, obviously. There may be
3 some reasons to have male patients in the
4 system, but it does take time to enroll them.

5 I think, actually, we can live
6 with iPLEDGE in terms of the success for our
7 younger patients, that more strict required
8 program that iPLEDGE is now put in, in terms
9 of the web-based approach, kind of the
10 followup in that younger group. It does
11 actually appear to us that there may be some
12 success there, and we should really understand
13 for that younger patient exactly what are
14 those elements of success.

15 The older patient, we really have
16 to understand what's going on with our older
17 patients because they clearly have not bought
18 into the two forms of birth control or somehow
19 they forget, or there's some other behavioral
20 type of intervention that we should engage in.
21 And I'm not quite sure what that would be, but
22 this is relatively new data for us.

1 Our previous paper in 2006 also
2 reported a higher rate of pregnancies in our
3 older patients, especially our patients in the
4 30-to-39 age band. It is really quite
5 interesting to us that these older patients
6 are not using the two forms of birth control
7 because you would think in some ways, being
8 more mature, they would actually get it. And
9 some reason there's that difference between
10 our older patients and younger patients.

11 So, I don't actually have a
12 solution. We should talk.

13 MS. TOIGO: Claudia?

14 DR. KARWOSKI: One more question
15 regarding the 42 percent reduction in female
16 patients post-iPLEDGE. Can you give us your
17 thoughts on why that is? Do you think it's
18 the burden of the program? Or is maybe more
19 careful selection of patients, you know, maybe
20 physicians selecting out or deciding not to
21 treat those patients that they may determine
22 might be at higher risk?

1 DR. WAGNER: Yes, we think we're
2 actually seeing slightly sicker patients, so
3 to speak, based on other parameters. So that
4 there is a small adjustment in the risk of the
5 patient that's being treated right now,
6 especially the female patients.

7 The initial assessment was the
8 implementation of the program was very
9 difficult and took folks several weeks, maybe
10 even months, to really come up to speed. So,
11 an initial gap was just that initial
12 implementation.

13 In some ways, we understand that.
14 We have other programs that we implement, and
15 there's sometimes these gaps as you come up o
16 a new program in terms of effective use of the
17 program.

18 But over time that this sustained
19 reduction has actually been in place, it was
20 actually troublesome to us, as we are trying
21 to actually reach out and take care of all our
22 patients appropriately. And again, on our

1 female patients, this disproportion, that 40-
2 plus percent reduction, is even significantly
3 more than the reduction we see in our male
4 patients. So, we don't prefer for any
5 reduction, but that has actually
6 disproportionate on our female patients.

7 We think it is back to the actual
8 steps they have to go through in the program.
9 Again, it is going to be something that we
10 have teased out for the paper, but it is also
11 an assessment that we need to do, I think
12 using maybe a survey or other followup means
13 with patients that would be pending.

14 MS. TOIGO: Mwango?

15 DR. KASHOKI: This question is for
16 Dr. Goldman.

17 Earlier we have heard suggestions
18 for standardization of REMS. One suggestion
19 was even perhaps to standardize based on the
20 type of risk. The discussion we had was
21 around teratogenicity.

22 But in your presentation, you make

1 a different point, saying that REMS is
2 different because of the difference in
3 risk/benefit profile for each product;
4 therefore, we should not apply a cookie-cutter
5 approach, and definitely shouldn't do that in
6 terms of our REMS assessment.

7 So, what were your thoughts, given
8 the previous recommendation about
9 standardization and how would that apply to
10 assessment?

11 DR. GOLDMAN: I have no problem
12 with standardization if it doesn't become a
13 lockstep and if it does not allow for
14 knowledge of the underlying disease state,
15 knowledge of the underlying population being
16 treated.

17 The data I presented, a lot of
18 that was from studies that I have done. And
19 one of them came about because there was this
20 tacit understanding that "Dear Healthcare
21 Professional" letters didn't work. And I
22 didn't believe they didn't work. It was not

1 my experience at MedWatch; it was not my
2 experience outside.

3 So, I classified the four
4 different categories for exactly what is being
5 presented now. That's teratogenicity. And
6 the behavior you want would be prevention of
7 pregnancy by patient compliance. That's very
8 different than asking prescribers not to co-
9 prescribe contraindicated meds. That's
10 different than asking them to use a monitoring
11 program for LFTs. It's very different than
12 not prescribing med longer than 10 days in the
13 case of bromfenac. So, I think that that's
14 one aspect that has to be looked at is, what
15 is the risk that is being evaluated?

16 Secondly, there is no doubt that
17 there are products that have stayed on the
18 market with very severe toxicities because
19 they offer a benefit that others would not and
20 because of the disease state being treated and
21 alternatives in terms of that.

22 And I did the Clozapine program.

1 A psychiatrist, I can tell you there was very
2 good buy-in from the psychiatry community
3 because it was a novel agent, the first one
4 approved for treatment-resistant
5 schizophrenia. The program was set up and
6 yielded terrific data that would not have been
7 gotten any other way. As a matter of fact, it
8 showed that the monitoring program could be
9 less strenuous because the data that came in
10 was so good.

11 So, what I am advocating for is
12 not not having standards or a template, but
13 being able to individualize the REMS based on
14 disease state, online population knowledge
15 about particular behaviors, and utilizing
16 that, which would also force, though, the kind
17 of evaluations that are being done.

18 I just mentioned to Glenn, when it
19 comes to survey data, CDRH uses survey data to
20 evaluate compliance with use standards.
21 That's a terrific way of using that because
22 it's actually looking at acceptance of a use

1 standard and evaluating it. That's different
2 than asking someone if they're complying with
3 a monitoring program, because, as I showed you
4 from FDA's own data, knowledge and saying what
5 you do know doesn't necessarily translate into
6 the action taken based on that.

7 MS. TOIGO: Dr. Davis?

8 DR. DAVIS: I would like to
9 comment about the standardization versus
10 customization because I think both are
11 important.

12 Just going back to the situation
13 for teratogenicity, for example, I think there
14 are definitely areas where standardization
15 could be considered and would improve programs
16 and make them more usable. For example,
17 pretty much across many different programs
18 that have to do with teratogenicity the
19 definitions for women of childbearing
20 potential are different. Another example is
21 the definitions for appropriate, reliable
22 methods of contraception are different.

1 It seems to me that those are
2 things that could really be standardized and
3 make these programs more user-friendly.

4 Thank you.

5 DR. KARWOSKI: The first speaker
6 talked about not pre-specifying or not, I
7 guess, setting absolute terms for success when
8 we approve a REMS. Then I've heard other
9 thoughts or mixed messages from the other
10 speakers saying, yes, we should absolutely do
11 it at the times; we should specify criteria
12 for success.

13 So, I think we are sort of
14 struggling now with what to do. Then, if we
15 do take that sort of approach of pre-
16 specifying, should that be standardized across
17 REMS and make sure we have sort of a one size?
18 You know we target 80 percent for objectives
19 and meeting goals, or is this all sort of done
20 on a case-by-case basis?

21 MR. EMMETT: In our
22 recommendation, it was that we remedy the

1 apparent disconnect between establishing pre-
2 specified, targeted goals for assessment
3 versus FDA's enforcement and compliance
4 approach.

5 We certainly have no problems with
6 performance-based standards for REMS
7 assessment. Of course, that's appropriate and
8 goes back to the riskMAP guidance as an
9 appropriate mechanism.

10 But within FDA's enforcement and
11 compliance activities, it's important to
12 clarify how FDA will be assessing absolute or
13 targeted goals, and we have requested
14 clarification on that.

15 DR. GOLDMAN: May I comment on
16 that? It did very much dovetail with the data
17 I showed you on terfenadine, and there's a lot
18 of other examples with that.

19 There have been programs that
20 clearly worked, if you take a look at, let's
21 say, contraindicated prescribing or
22 contraindicated population being prescribed.

1 If you're going to establish from the
2 beginning that there's going to be no
3 contraindicated prescriptions, you might as
4 well not even start the program because it's
5 not going to happen. Or you have to go to the
6 most restrictive access program.

7 You know, again, you have to look
8 at the public health impact. You've got to
9 take a look at the product. You've got to
10 take a look at the severity of the disease
11 state, the availability of other meds or lack
12 of availability of that.

13 That's, I think, what I'm trying
14 to get across here, is that with the standards
15 and definitions, it's one thing, but trying to
16 make a blanket statement as to absolute versus
17 another is different in terms of that.

18 MS. TOIGO: Suzanne?

19 DR. BARONE: I have a question for
20 Mr. Emmett.

21 You talked about that sponsors
22 should not be legally responsible for

1 independent decisions or actions of third
2 parties. Then you went on to mention
3 distributors.

4 Can you comment, or I want you to
5 talk about this a little bit more, the
6 difference between those parties that you have
7 contracts with, such as distributors, versus
8 those parties that you don't have contracts
9 with, but certify. Can you talk about that?

10 MR. EMMETT: Sure. I would be
11 happy to.

12 You know, I think with respect to
13 REMS programs, there is a difficulty here in
14 that neither FDA nor sponsors have authority
15 to regulate the practice of medicine. That is
16 one of the challenges that we continually face
17 when implementing REMS programs.

18 Of course, in the statute there is
19 the requirement to monitor and evaluate
20 compliance with the REMS programs and to also
21 monitor and evaluate other parties. We take
22 other parties to really mean those downstream

1 entities, such as hospitals, infusion sites,
2 pharmacies, where the product is dispensed.

3 We feel that wholesalers and
4 distributors really seem to go beyond that
5 description of other parties, and it raises
6 some logistical challenges for both the
7 wholesalers and the manufacturers for those
8 certification requirements and monitoring and
9 evaluation.

10 DR. BARONE: So, can I just follow
11 up? So, if you have a REMS that requires
12 certification of infusion sites, how do you
13 assure that the drug, if you don't have any
14 control over your wholesalers or
15 distributors,, unless you're going to
16 distribute the drug yourself, how do you
17 control whether that drug is going only to
18 those sites that have been certified by your
19 companies?

20 MR. EMMETT: Well, I think that's
21 a very good point. Of course, there's a
22 certain amount of monitoring with your

1 business partners which is going to take
2 place. But it is a question of certification
3 of those business partners rather than basic
4 monitoring.

5 DR. BARONE: I think that's one of
6 the issues that compliance has been seeing, is
7 that your contracts need to be very clear
8 then. And you would monitor those contracts
9 just as you would any other contract. It is
10 one of the things. I don't think it is a
11 surprise that we do inspect the REMS.

12 So, I just wanted to comment that
13 I think that you do have some responsibility
14 to monitor.

15 MR. EMMETT: We'll take that back
16 to our membership and discuss that point
17 further. Thank you.

18 MS. TOIGO: Keith?

19 DR. WEBBER: With information that
20 comes out of an evaluation of a REMS, it seems
21 it would be useful to share that with others.
22 Do you all feel that this would be able to be

1 publicly-available information that comes out
2 of the evaluation of REMS for specific
3 products or specific sites?

4 DR. WAGNER: Yes, and I think,
5 actually, part of the reason we engaged in
6 this research project, which has now taken the
7 better part of two years to collect the data
8 and prepare the analysis, the study design, is
9 to actually share this information publicly,
10 which we have done at ISPOR previously, and
11 then combine it with our colleague from
12 Northern California, put it into a peer review
13 clinical journal, hopefully, for publication
14 later this year.

15 And it should stand the test of
16 peer review. It should be rigorous. It
17 should be statistically-significant. It
18 should be scientifically-valid. All of the
19 quality of this effort should be very high.

20 Also, internally, now that we have
21 this data, since we just presented it in May,
22 we are actually going back to our

1 dermatologists. Back to Dr. Jenkins'
2 question, we need to maybe sit down with the
3 dermatologists and figure out what would be
4 strategies to implement for our older patients
5 that seem to be less successful on a rate
6 basis than our younger patients with iPLEDGE.
7 Are there some new strategies that we can put
8 in place to help them be more successful?

9 And so we haven't actually come up
10 with those strategies. But now that we have
11 the data, we can actually start to think
12 through, what would be possible new strategies
13 for implementation? And also, then, others
14 outside of Kaiser Permanente can use this data
15 because there may be other thoughts that would
16 come from outside the organization that would
17 actually help us think through, what are new
18 strategies that would be put in place to help
19 our older patients be more successful? And
20 using older patients that are 20 to 40, and
21 I'm much older than they are, but, you know,
22 our patients in that 20-to-40 range seem to be

1 less successful with iPLEDGE than our younger
2 patients less than 21.

3 DR. GOLDMAN: I use every example
4 that I can find, in the literature or we
5 posted. For example, there was terrific
6 literature on the actual writing of a
7 notification, the format used.

8 I noticed the FDA, which I'm
9 delighted to see is using more Q&As, which is
10 a great format and has been shown repeatedly
11 to be good both for consumers and healthcare
12 professionals. So, I certainly would advocate
13 -- it's wonderful that you're publishing this.
14 I'm intrigued by it.

15 I wish we had a centralized
16 database, which has been talked about. I
17 think I congratulate the companies that are
18 publishing on this.

19 But I will point out there is a
20 tremendous literature on this that's outside
21 of pharmaceutical and medical devices. That's
22 in marketing, and it's in comprehension and

1 other things. There's a lot of activity going
2 on that really could be utilized in relation
3 to what we're doing and certainly applied that
4 way.

5 MS. TOIGO: Dr. Davis?

6 DR. DAVIS: My interpretation of
7 your question was, would sponsors be willing
8 to publish REMS assessment reports? I would
9 say that there could be certain situations
10 where a very brief explanation could be given,
11 especially if changes were made.

12 So, for example, in the REMS
13 website there are new little tags on all the
14 approved REMS. It will say "new" or "new
15 information". Perhaps there could be a little
16 explanation saying why the change was made, if
17 a modification was needed on the basis of the
18 REMS assessments. But I think that,
19 generally, that kind of information would need
20 to be fairly brief.

21 MR. EMMETT: And I'll just add, in
22 the spirit of quality systems and continual

1 improvement of REMS, we certainly think
2 feedback data, sharing that with our trading
3 partners is an important element of that to
4 ensure that the system is continually
5 improving.

6 With respect to publicly
7 disclosing the assessments or company
8 assessment data, we will raise that question
9 with our membership, but I think it would be
10 important to note that, if there's any
11 potentially competitive commercial information
12 included, that that would need to be redacted
13 or addressed.

14 MS. TOIGO: One more question,
15 and, Dr. Jenkins, I think it's yours.

16 DR. JENKINS: I'll slip in a
17 comment and a question or maybe it's just two
18 comments.

19 Through the miracle of technology,
20 meaning BlackBerrys, one of my staff raised a
21 question about Mr. Wagner's presentation about
22 the iPLEDGE study, and it's probably not

1 something you can address here. But they
2 questioned whether you have ascertained that
3 the ascertainment of events wasn't different
4 between the two time periods. So, with the
5 stricter procedures under iPLEDGE, are you
6 sure that the higher rate of reporting wasn't
7 because you were doing a better job of
8 ascertaining actual events than maybe you were
9 under SMART? And you probably don't have an
10 answer for that, but I just wanted to share
11 that staff back in the office brought that up.

12 I wanted to also follow up on Mr.
13 Emmett's comments about the third parties.
14 I'm concerned because the logical conclusion
15 of the position that you are advocating for is
16 that, if we have a product that we think needs
17 restricted distribution in order to be safely
18 marketed, then it couldn't be marketed in the
19 normal distribution chain if we can't be
20 confident that only those people who are part
21 of the program will be getting access to the
22 drug. So, that either leads to a central

1 pharmacy-type distribution system, where you
2 distribute it yourself as the manufacturer,
3 you have a single designated pharmacy, or it
4 means you can't be marketed.

5 So, there are consequences for
6 saying that you can't control the third
7 parties if it needs restricted distribution.
8 And one of the things we have heard is don't
9 take these products out of the community
10 pharmacies; don't use central pharmacies for
11 these products.

12 So you can address it, if we have
13 time, but just a couple of comments to put out
14 there.

15 MS. TOIGO: Dr. Davis?

16 DR. DAVIS: I would just comment
17 that in many of the elements to assure safe
18 use programs that we run these relationships
19 with distributors are handled through strict
20 contractual arrangements with distributors.

21 Then, in addition to that, for
22 many programs we double-check back to make

1 sure that there aren't patients who are
2 getting the product or prescribers who are
3 prescribing outside those programs through
4 sort of an audit mechanism.

5 MR. EMMETT: And I would just add
6 that, if for some reason there's a third party
7 who is failing to comply with a REMS, the
8 default option would be, first, to identify
9 why is that REMS element, that tool, not
10 proving to be effective; how can we modify
11 that to ensure that they are compliant before
12 falling back on enforcement mechanisms?

13 MS. TOIGO: Okay. Because we are
14 going to leave this topic, evaluating the
15 effectiveness of the REMS, and you won't have
16 another opportunity, but being cognizant that
17 we wanted to stay close to time, does anyone
18 have a burning question?

19 (No response.)

20 Okay. Well, panel, thank you very
21 much for your presentations and your
22 participation.

1 And now we're going to switch
2 gears and move on to topic No. 5, which is the
3 effect of REMS on generics.

4 We have two presenters for this
5 session.

6 Are you ready, Gordon?

7 Okay, our first presenter on panel
8 5 is Gordon Johnson, and he is representing
9 the Generic Pharmaceutical Manufacturers
10 Association.

11 MR. JOHNSTON: Thank you, Terry.

12 Good afternoon, everybody.

13 My name, again, is Gordon
14 Johnston, the Vice President of Regulatory
15 Science for the Generic Pharmaceutical
16 Association, which is a group in the U.S. that
17 represents the generic manufacturers.

18 We will just have a few comments
19 and points to consider regarding avoiding some
20 of the adverse impacts of REMS on the
21 availability of generic drugs.

22 First of all, we recognize the

1 complexity of REMS implementation and the
2 challenges that both FDA and the stakeholders
3 must confront. I think we're all on a steep
4 learning curve when it comes to optimizing
5 many of the aspects related to implementation.

6 With that said, the Generic
7 Pharmaceutical Association supports FDA's
8 implementation of REMS requirements. We
9 firmly believe that the REMS program will
10 advance patient safety, and we support REMS
11 programs to promote patient safety.

12 Nevertheless, from the inception
13 of REMS programs, there have been some
14 concerns about the potential impact on the
15 generic industry. In the legislation,
16 Congress specifically recognized the potential
17 for companies to use REMS as a way to delay
18 generics from entering the market. Thus, the
19 statutory provision provides that no holder of
20 an approved REMS-covered application can use
21 REMS to block or delay generic approval.

22 In addition, Congress directed FDA

1 to determine whether the burden of creating a
2 shared REMS program would outweigh the
3 benefit, taking into consideration the impact
4 on healthcare providers, patients, the ANDA
5 applicant, and the holder of the referenced
6 drug product.

7 So, we understand and agree that
8 the first goal must be patient safety, and we
9 urge the agency to keep the impact on the
10 availability of generic drugs in mind, as
11 Congress intended.

12 I'm going to highlight just a few
13 key areas that we want to have a dialog on,
14 and I think areas that we believe to be
15 perhaps the most significant to the generic
16 industry.

17 The first one would be blocking
18 access to samples needed for bioequivalency
19 testing. REMS restricted distribution
20 requirements should not prevent an ANDA
21 applicant from obtaining samples of a
22 reference listed drug when needed to conduct

1 bioequivalence testing.

2 There have been instances when
3 innovator companies have been able to use
4 restricted distribution systems to deny
5 generic companies access to samples needed to
6 undertake bioequivalence testing. This is
7 obviously an unintended and very unfortunate
8 result, and we ask FDA to work with us to
9 address this issue in a manner that considers
10 the process that will ensure proprietary
11 information and confidentiality of ANDAs would
12 not be disclosed.

13 The next major topic is on
14 governance. I think there's two areas here,
15 governance of the REMS program when the
16 innovator REMS is already in existence. The
17 second would be when the REMS program becomes
18 available after generic products are approved.

19 Generic companies should have an
20 equal role in the governance of REMS programs
21 in which they participate. If generics are on
22 the market when the program is being

1 developed, they should have an equal industry
2 say in the development of the REMS. If
3 generics come to market later, they should
4 have an equitable role in the operation of any
5 REMS programs that they join.

6 There is a potential of an
7 imbalance of power bestowed upon a company
8 that has already developed a REMS. A role in
9 governance is important because if the
10 innovator leaves the market, the generics must
11 continue the program.

12 Moreover, fairness dictates the
13 companies sharing in the cost of the program
14 have a role in this governance, sharing costs
15 in a way that is appropriate, equitable, and
16 transparent.

17 We believe that FDA's policy is
18 that a single REMS program should cover the
19 brand and generic products. This approach has
20 advantages in terms of effectiveness of the
21 REMS program and in terms of keeping costs
22 low. We recommend that FDA pay careful

1 attention to ensuring the costs are
2 transparent and shared in an equitable manner.

3 The next item is limiting
4 education requirements of a REMS program by
5 the brand sales force. Certainly, brand and
6 generic industries have significantly
7 different marketing models, and therefore,
8 these differences should be considered when
9 developing education programs that might be
10 required as part of any REMS.

11 In terms of the cost
12 considerations, again, we clearly support the
13 use of REMS to ensure patient safety, and the
14 FDA should take steps to ensure that the REMS
15 programs are not developed without
16 consideration of cost-effectiveness.

17 So, in conclusion, we appreciate
18 this opportunity to present today and look
19 forward to working with the agency as we move
20 towards implementation.

21 Thank you.

22 MS. TOIGO: Thank you, Gordon.

1 Our next presenter is Mitchell
2 Cohen from Kaiser Permanente.

3 MR. COHEN: Good afternoon again.

4 I'm Mitch Cohen, Senior Counsel
5 with Kaiser Permanente.

6 I want to thank the FDA again for
7 inviting us to this forum and giving us an
8 opportunity to present.

9 Kaiser Permanente is an integrated
10 healthcare delivery system. We have
11 hospitals. We have many healthcare providers,
12 physicians, pharmacists, and we are also a
13 health plan.

14 As I think I indicated yesterday,
15 on an annual basis our pharmacies dispense
16 more than 100 million prescriptions. And we
17 also have our own specialty pharmacy and try
18 to do work directly, as best we can, through
19 our specialty pharmacy for REMS products and
20 other products that fall within that specialty
21 pharmacy category.

22 I spoke yesterday and said that

1 there were three key points, three bullets
2 that we wanted to emphasize: transparency,
3 involvement of healthcare professionals,
4 sharing and evaluation of data from ETASU and
5 confidentiality.

6 There's a fourth point, and that's
7 competition. That fourth point is, obviously,
8 the one here that we want to talk about.

9 We think when there is an impact,
10 when REMS impacts or takes away from
11 competition, that that can have a burden on
12 patient access to product and on the
13 healthcare delivery system.

14 There's clearly a balancing that
15 you need to do, that we need to do, between
16 competition and patient safety, and we
17 recognize that.

18 But, interestingly, I think much
19 of the last two days have been very focused on
20 process. One thing I think we need to think
21 about, and hope that the agency will, is that
22 the process not be used in itself to

1 manipulate the competitive market for
2 pharmaceuticals and for biologics.

3 At Kaiser Permanente, we have a
4 high use of generics. More than 80 percent of
5 our prescriptions are generic products. And
6 we have great success from a quality-of-care
7 point of view in the use of generics.

8 We have been disturbed in what we
9 have heard and learned about manipulation by
10 some companies of using REMS to keep generics
11 or delay generic entry into the market, and we
12 think that that's a particular concern. And
13 it's seen, for example, the citizen petition
14 that was filed by Dr. Reddy.

15 The other area, though, in
16 competition that I don't want to be lost here,
17 because I think it has been brought up several
18 times by many here, and again going back to
19 there's a balancing clearly from a patient
20 safety point of view between safety and
21 competition, is the distribution, the idea
22 here that there may be restricted or limited

1 distribution networks for REMS products for
2 certain specialty pharmaceuticals.

3 In our own system, we recognize
4 that there is a need for a specialty pharmacy
5 in many cases that has to be part of the
6 distribution process. But what we have seen
7 is that in many cases, when there's a use of
8 an exclusive or maybe two specialty
9 pharmacies, that many organized systems like
10 Kaiser Permanente or like the University of
11 Illinois, who spoke very, I thought,
12 eloquently yesterday about their inability to
13 bring product in and to manage it within their
14 own system, that it has an adverse impact on
15 patient care. And it has an impact on
16 competition, and here's the competition piece
17 to it.

18 There's the fact, of course, that
19 we can't get access. But from an anti-
20 competitive point of view, from a legal point
21 of view, it also often leads to an increase in
22 cost. What we have seen is that for those

1 that there's an exclusive distribution channel
2 or a very limited distribution channel, it's
3 a premium for a wholesale acquisition cost
4 that and certainly others must have to pay for
5 those particular drugs.

6 And I would add, again, as our
7 colleagues or the representatives from the
8 University of Illinois said yesterday, not
9 necessarily any improvement in the quality of
10 the care that is presented to patients. In
11 fact, some limitations, sometimes delay. We,
12 like the University of Illinois, and I think
13 others, have similar kind of examples out
14 there.

15 Another point I wanted to raise
16 again on the similar vein is that some
17 companies that do not even have REMS have
18 said, and those that do have REMS say, it is
19 the FDA that is telling us we must use a
20 restricted distribution system. Sometimes we
21 can check and see whether or not that is true
22 through your website. Other times we can't.

1 So, often, because there's not
2 that direct dialog at times with the FDA on
3 these, we don't know the truth of that matter.
4 Often, people, again, point to the FDA.

5 I would point out Kaiser
6 Permanente is clearly a large, organized
7 system, but if we have challenges here, I can
8 only imagine that the individual physician or
9 the smaller practice has the same kind of, in
10 fact, perhaps a greater challenge. We at
11 least have the ability to identify and, when
12 we can, to respond.

13 So, there are three general
14 suggestions or recommendations for the FDA.
15 One is, as we have said earlier, a continued
16 and greater transparency and thought for what
17 programs really need to be through restricted
18 networks and which can be more broadly
19 distributed through other pharmacy systems.

20 An explicit focus, when you're
21 looking at REMS and the development,
22 implementation, and assessment, is what impact

1 are they having competition, and is that a
2 negative to patient access and the healthcare
3 delivery system?

4 And finally, frankly, in
5 understanding that using your enforcement
6 authority and working with others like the
7 Federal Trade Commission to evaluate when
8 there are anti-competitive effects out there.

9 Thank you, and I appreciate any
10 questions.

11 MS. TOIGO: Thank you, Mr. Cohen.

12 FDA questions? Jane Axelrad?

13 MS. AXELRAD: Actually, I want to
14 make a statement as opposed to asking a
15 question, because it may not be widely known,
16 and I want to make sure that it gets on the
17 record, what we have been doing in terms of
18 trying to make sure that REMS are not used to
19 block or delay generic competition.

20 No. 1, we do take it into account
21 when we write the REMS, and I don't think that
22 any of the REMS with restricted distribution

1 programs per se would block generic
2 competition. Where we have found cases in
3 which sponsors have tried to use the REMS to
4 block generics, we have been willing to write
5 letters on behalf of the generic companies
6 saying what the parameters were in terms of
7 them satisfying our concerns about setting up
8 a program for handling, for example, samples
9 to conduct bioprevalent studies, so that both
10 they and the sponsors are aware that we don't
11 think that the REMS is a barrier to getting
12 those samples.

13 We have also been in conversations
14 with the Federal Trade Commission about this
15 issue and have discussed with them how we
16 might make sure that REMS are not used to
17 block or delay generic competition.

18 So, I just wanted to say that we
19 have been quite active in this area and are
20 doing what we can, and we will be continuing
21 to do it.

22 We also, where there have been

1 issues in terms of setting up a single shared
2 system with a drug that was already on the
3 market, we have been actively involved in
4 trying to get all the parties together and
5 getting them to play nicely together to the
6 point of actually convening meetings and
7 sitting in the meetings to try to get them to
8 work together well.

9 And again, we are looking for ways
10 that we can do that better because it is
11 extremely resource-intensive. Obviously, we
12 can't do that for every program to make sure
13 that the sponsors play well together.

14 MS. TOIGO: Any questions? Oh,
15 I'm sorry, go ahead, Gordon.

16 MR. JOHNSTON: Terry, just a
17 comment. We do recognize the agency has done
18 a lot and put a lot of effort into trying to
19 facilitate discussions.

20 You know, both the carrot and the
21 stick that FDA holds can be pretty powerful.
22 Certainly we appreciate from the generic

1 industry perspective those efforts that we
2 have seen to date. So, thank you.

3 MR. COHEN: And I just wanted to
4 add, if it isn't clear, how much we really do
5 appreciate the amount of transparency we have
6 seen over the last several years. One of the
7 ways we are able to understand what's in a
8 REMS and the distribution system, and what's
9 been represented to us by the sponsors, is
10 what you're putting out there. So, that's
11 actually quite helpful. Clearly, this kind of
12 forum where you are listening is appreciated
13 as well.

14 MS. TOIGO: Thank you.

15 Keith, you must have a question.

16 (Laughter.)

17 DR. WEBBER: Yes, I have a couple
18 of questions.

19 First of all, with regard to
20 potential inequities in educational programs
21 with the REMS, what management or mitigation
22 strategies do you see would need to be put in

1 place to deal with that risk? And what's FDA
2 role in that process versus outside folks? I
3 know the FTC was mentioned, but others perhaps
4 as well.

5 MR. JOHNSTON: Just to clarify,
6 was the first question what could FDA do in
7 terms of REMS programs that might rely on use
8 of a sales force? Did I understand your
9 question correctly?

10 DR. WEBBER: Yes, I think that's
11 basically the question. I think there's sales
12 forces, but also other educational aspects
13 that go along with the REMS that need to be
14 administered equitably.

15 MR. JOHNSTON: It seems with REMS
16 each one is somewhat of a case-by-case basis.
17 Clearly, the generic industry does not have a
18 sales force. So, looking at other potential
19 pools of individuals that could provide this
20 training, be it third parties in some cases,
21 are there areas where technology could provide
22 some of that training? I think we would have

1 to explore all of those areas, but we do
2 realize the difference between the brand
3 industry with a well-established sales force
4 that can take on that role versus the generic
5 industry. Really just asking that the agency
6 be conscious about that when those discussions
7 take place.

8 MS. TOIGO: A followup, Keith?

9 DR. WEBBER: But just no specific
10 recommendations as far as what our role is,
11 other than just to be cognizant of it?

12 MR. JOHNSTON: Well, in reality,
13 that's probably it. And I'm not trying to be
14 glib about it, but the fact is, once that's
15 recognized, we can, I think, collaboratively
16 explore what other options are there on the
17 table for education.

18 I think it does call on our
19 industry to put ideas and recommendations when
20 those REMS programs come up. So, depending on
21 the intensity of the program and that type of
22 thing, it would probably in some ways dictate

1 recommendations.

2 So, I don't have any specific
3 models that I could suggest here today.

4 MR. COHEN: Well, if I could make
5 another pitch for healthcare providers, I
6 think to the extent that you have got multiple
7 sponsors or product manufacturers now, that
8 the extent that you can consult with those of
9 us who do continuing education and patient
10 education, that there may be other ways in
11 which we can educate those who need to be
12 educated, rather than simply relying on the
13 manufacturer. That might be a way in which we
14 can help facilitate some of the education.

15 MS. TOIGO: Mwango?

16 DR. KASHOKI: Ms. Axelrad just
17 outlined a couple of steps that have been
18 taken to try to prevent or limit the amount of
19 blocking that an innovator might do to
20 generics. Were you looking for additional
21 steps that FDA could possibly take, whether --
22 I'm just throwing things out there --

1 explicitly having language in REMS for a
2 product which might be difficult because
3 sometimes you can't anticipate whether or not
4 a generic is going to come on for a particular
5 product, or guidance, or were those steps that
6 were just described sufficient?

7 MR. JOHNSTON: One of the
8 responses from the innovator industry has been
9 that distribution outside of the prescribed
10 closed system would not be permitted;
11 therefore, they could not provide samples to
12 generic companies.

13 If the agency could make clear if
14 there is a process set up to provide those
15 samples under supply chain controls to a
16 generic manufacturer, that clarity may
17 eliminate that argument by the individuals at
18 the closed REMS systems.

19 MS. TOIGO: Claudia?

20 DR. KARWOSKI: So we have helped
21 facilitate having generic companies work with
22 innovators to develop single shared systems.

1 We have a little bit of experience.

2 I guess, as we gain experience, do
3 you see the companies taking more of a sort of
4 proactive approach about contacting each other
5 and attempting to work together without
6 requiring FDA to sort of facilitate that?

7 MR. JOHNSTON: Well, I think
8 that's a very fair comment. Part of what's
9 occurring, I think, in the generic industry,
10 as I mentioned, is a steep learning curve. We
11 are gaining some experience. To date, there's
12 been a lot of interaction with FDA, but I do
13 believe, as our industry gets more familiar
14 with expectations and interactions with their
15 brand counterpart, that that may take place.
16 So, I think that's a very fair statement.

17 MS. TOIGO: Keith, another
18 question?

19 DR. WEBBER: Yes, this is for
20 Gordon Johnston.

21 In your presentation, you were
22 talking about governance of REMS. I just

1 wanted to clarify if there's any distinction
2 between -- you had said that, when setting up
3 a new REMS when there's a generic already on
4 the market or generics on the market, along
5 with the brand-name product, that there should
6 be an equal governance. And if it's a generic
7 comes on the market for a product where there
8 is already a REMS in place, that it would be
9 equitable.

10 I'm just wondering, is there a
11 distinction between those two words or is that
12 just --

13 MR. JOHNSTON: A very sharp ear.

14 Really there's not a distinction.
15 It's looking for, I guess, equal interaction
16 on either a REMS that's being developed
17 collaboratively between brand and generic
18 after both are in the marketplace and a REMS
19 is established.

20 In the former case, when the REMS
21 is already established before generics are
22 approved, clearly, the generic will not be

1 involved in the development of that REMS. So,
2 there's no governance or no input on the
3 development of the REMS, but it's really
4 downstream, then, in management and the
5 operation of that REMS from that point forward
6 after the generic companies have invested in
7 the REMS. We would look at it as an equal
8 part in management of the REMS as opposed to
9 when you're developing a REMS and implementing
10 that REMS when both brand and generics are in
11 the market.

12 MS. TOIGO: Any more questions?

13 (No response.)

14 Okay, we'll move on to our last
15 panel, and let it be known that FDA didn't
16 fill up the time with questions on that few
17 remaining minutes.

18 Okay. For topic 6, we are on
19 protection of patient information, and we have
20 two presenters for this panel, Kevin Nicholson
21 from the National Association of Chain Drug
22 Stores, and Lori Potter from our friends at

1 Kaiser Foundation Health Plan.

2 MR. NICHOLSON: Good afternoon,
3 and thank you again.

4 Again, I am Kevin Nicholson with
5 the National Association of Chain Drug Stores.

6 With respect to patient privacy
7 concerns related to elements to assure safe
8 use that include patient enrollment and
9 patient registries, we would ask FDA to
10 consult with privacy experts within the
11 Department of Health and Human Services and
12 FDA's sister agency, the Office for Civil
13 Rights.

14 As FDA may be aware, OCR, the
15 Office for Civil Rights, just a few weeks ago,
16 published proposed rules that implement the
17 new privacy provisions of the Health
18 Information Technology for Economic and
19 Clinical Health, HITECH Act, which is the most
20 substantial modification to the HIPAA privacy
21 rules since it became effective.

22 HIPAA and HITECH have created a

1 complex and all-encompassing regime that
2 protects the privacy and security of patients'
3 sensitive health information. Moreover, the
4 penalties for violating these rules are
5 substantial and include the authority for
6 states' attorneys general to enforce and
7 impose significant fines in addition to
8 federal fines and penalties.

9 The reach of HIPAA and HITECH
10 includes all healthcare providers as well as
11 anyone with whom they share or disclose
12 patients' sensitive health information, and
13 all agents and subcontractors and sub-
14 subcontractors, and sub-sub-subcontractors, et
15 cetera, et cetera.

16 The practical effect is that
17 anyone who receives sensitive patient
18 information that originated from a healthcare
19 provider is already subject to the
20 jurisdiction of HHS and states' attorneys
21 general with respect to privacy and security
22 requirements.

1 With all of this in mind, we urge
2 FDA not to seek to impose additional privacy
3 or security restrictions upon healthcare
4 providers or their business associates and
5 subcontractors, et cetera, but, rather, to
6 work with OCR to clarify and address any
7 privacy concerns that might arise from the
8 various elements to assure safe use.

9 Thank you.

10 MS. TOIGO: Thank you, Mr.
11 Nicholson.

12 Ms. Potter?

13 MS. POTTER: Good afternoon again.

14 I am Lori Potter with Kaiser
15 Permanente, counsel in the Government
16 Relations Department.

17 I want to thank FDA for giving us
18 the opportunity to address the issue of data
19 confidentiality.

20 As I think those of you who were
21 here yesterday know, Kaiser Permanente
22 submitted a citizen petition where we raised

1 the issue of data confidentiality late last
2 year. We raised this issue based on our
3 experience with REMS at Kaiser, in particular,
4 REMS that include elements to assure safe use.
5 Because, as you all know, those are the REMS
6 where there are often patient registries,
7 there is some safety monitoring. There are
8 potentially a lot of data that is collected.

9 And we realize that there is an
10 importance to collecting data in a REMS
11 program, but, again, we think that that
12 importance of data, that need for data needs
13 to be balanced with patient privacy concerns,
14 as the earliest panelist brought up.

15 One of the things that we wanted
16 to note in our citizen petition is that we
17 think that there needs to be some overall
18 recognition that the collection of PHI
19 relative to a REMS needs to be really directed
20 towards the purpose of those REMS, to the
21 goals of the REMS, and not be broader
22 authorizations for disclosure of data.

1 We think that in our experience we
2 have seen the broad authorizations that are
3 requested by some of the drug manufacturers
4 really will potentially lead to risks to
5 patient privacy, in particular, when those
6 authorizations allow broader disclosures to
7 third parties for various purposes.

8 We think that when you look to the
9 new privacy regime, and those of us who are
10 covered entities under HIPAA are very aware of
11 the new regulations and the legislation
12 pending in Congress that provide these patient
13 protections, that you see the real ability
14 under the current to control that information
15 flow. We also think that HIPAA includes
16 certain provisions that would support these
17 safety activities, for instance, the public
18 health exception under HIPAA which allows
19 parties like Kaiser, covered entities and
20 other providers, to disclose information to
21 FDA for safety monitoring purposes, but it
22 doesn't provide for that broader disclosure

1 which includes risks to patient privacy.

2 So, we believe that FDA, when they
3 look at the statute for the REMS, while
4 privacy is not an element that is specifically
5 called out, we think that some of the language
6 that the REMS, not the unduly burdensome to
7 patient access, can be interpreted more
8 broadly to cover the issue of patient privacy.

9 We also believe that while,
10 clearly, there is a need for documentation for
11 monitoring safety activities, and certainly
12 for some of the provider certification
13 programs, we think that there needs to be a
14 real recognition that patient privacy needs to
15 be protected. There's a need to develop
16 confidentiality, sort of a confidentiality
17 recognition around a REMS program.

18 We think that there needs to be a
19 real assurance that there are overbroad
20 authorizations that are sought by companies.
21 We have actually noted in our own experience
22 that we have been confronted with very broad

1 authorizations, and there are REMS that are
2 set up for a particular program that really
3 don't include a registry or any collection of
4 data. So, we think that is actually a misuse
5 of the program and potentially misleading to
6 patients and providers out there who are
7 concerned about these privacy risks.

8 We also think that there needs to
9 be some additional requirements or additional
10 recognition, rather, built into the program,
11 that there may be manufacturers who are
12 seeking data and claiming that it is required
13 by a REMS when, in fact, there is not a
14 requirement for those particular data.

15 And in particular, we applaud FDA
16 for their efforts toward greater transparency
17 because one of the tools that we are able to
18 use is we can take a look at the concise REMS
19 that are posted and understand that there
20 would not be a requirement for these
21 additional data to be released, in particular,
22 to be released to third parties.

1 So, in conclusion, I again ask
2 that FDA and in their workings on the REMS
3 program really pay attention to the privacy
4 risks, engage providers, understand that
5 patients are concerned about these risks, and
6 that the laws do have ways to address the
7 risks.

8 And I'll conclude there, and I
9 thank you. I will look forward to answering
10 questions.

11 MS. TOIGO: Thank you, Ms. Potter.

12 Questions from the FDA panel?

13 (No response.)

14 I don't think we have any privacy
15 experts on our panel here. So, you can see
16 with the lack of questions.

17 You have a question? Yes, go
18 ahead. A comment?

19 MR. NICHOLSON: I have a comment.

20 MS. TOIGO: Sure.

21 MR. NICHOLSON: I just want to
22 comment that my presentation and Ms. Potter's

1 is not really inconsistent. It's just that
2 NACDS also does have concerns with
3 information, with potentially providers having
4 to sign authorization requirements that seek
5 information from patients that may not
6 necessarily be required or, you know, be
7 necessary for the operation of the REMS.

8 So, I would support her comments
9 as well, that there does need to be some sort
10 of oversight in ensuring that anyone who is
11 requesting an authorization, that the
12 information that is being requested, the
13 patient information that is being requested
14 isn't beyond what is necessary for the
15 operation of the REMS.

16 And to a certain extent, that has
17 been addressed in the HIPAA and the HITECH
18 rules with the requirement that only the
19 minimum necessary information be shared to
20 meet the goal of the purpose of sharing the
21 information. However, one limitation of that
22 is that it pretty much leaves that decision up

1 to the contracting parties to decide how much
2 information needs to be shared.

3 So, I guess what I am trying to
4 say is that there probably is an opportunity
5 at some point to get some guidance from OCR on
6 that, on how much information should be shared
7 with respect to a REMS.

8 MS. AXELRAD: Yes, do you see
9 anything inherent in the restricted
10 distribution programs that we have, and
11 particularly the ones that have patient
12 enrollment or registries of some sort, that
13 you find would be directly in conflict, if
14 used properly, if the information that was
15 obtained from that to follow up on adverse
16 events, for example, to determine whether the
17 program is working, do you see any inherent
18 conflicts with the new statute?

19 I know there have been abuses. We
20 heard yesterday about some abuses of it, but
21 that is different than having something that
22 is inherently in conflict based on what we

1 have been doing.

2 MR. NICHOLSON: Do you want to
3 answer first?

4 MS. POTTER: No.

5 MR. NICHOLSON: No, I don't. I
6 don't see -- I mean that's one of the reasons
7 I wanted to speak on this topic today, is that
8 I do want to point out that I don't see any
9 inherent conflicts or problems.

10 I do think that the structure of
11 HIPAA and HITECH do envision this type of
12 operation. So, I just think that perhaps some
13 guidance might be necessary.

14 MS. POTTER: Yes, I also think
15 that, because HIPAA does provide some
16 disclosure without authorization for safety
17 monitoring, in particular, for safety
18 monitoring either by the FDA or by FDA0-
19 regulated entities, that I think that would
20 encompass a number of the activities that are
21 included in a REMS, where you wouldn't need
22 this additional authorization for information

1 that could be, then, broadly disclosed to
2 third parties.

3 I think that's really where the
4 issue that we have raised really lies, and
5 that is that you have patients and providers
6 who are asked to sign very broad
7 authorizations for further disclosure beyond
8 the purpose of a REMS, beyond the goals of
9 those programs, the safety monitoring programs
10 or the patient registries.

11 Then, really, our argument would
12 be that, then, there are no protections for
13 how that data gets further used because the
14 patients have authorized it, and therefore,
15 it's pretty much open for any kind of
16 disclosure that would be done by the
17 manufacturer at that point.

18 I do want to make a further
19 comment about HITECH. That is that Mr.
20 Nicholson is correct that there is a real
21 significant change in the privacy provisions
22 that have been enacted under HITECH and that

1 they have extended those privacy rule
2 provisions to business associates. But,
3 again, that requires that a covered entity has
4 signed a contract with a business associate,
5 and then that is what implicates those further
6 provisions under HITECH about how you can use
7 and disclose information.

8 One of the concerns that we have
9 really involves these very broad disclosure
10 requests that we get from manufacturers, when,
11 frankly, we think they are not necessary.
12 When we, as Kaiser, can evaluate these
13 requests, we can negotiate, we can push back,
14 we can understand because we have the
15 resources, and, frankly, we deal with a lot of
16 these programs. So that we can make our way
17 through the requests and potentially end up
18 with a better solution for our patients and
19 for our providers.

20 But when we look at the overall
21 REMS programs out there and how they may be
22 implemented in the community, we wonder what

1 happens at the individual provider level when
2 manufacturers are giving them HIPAA releases
3 to then provide to their patients to sign over
4 broad access to their data.

5 MS. AXELRAD: Yes, just to follow
6 up on what you have just said, I'm searching
7 for what role FDA needs to play in all of
8 this. I can see that when we write our
9 restricted distribution program, to the extent
10 that we are requiring the collection of
11 information, we need to make sure that the
12 collection of information, and patient-
13 specific information in particular, is
14 necessary to the workings of the program.

15 But we may not see the privacy
16 authorizations that the manufacturers are
17 sending to the individual providers. I am not
18 sure what role we can play in making sure that
19 those authorizations are within scope, any
20 more than we would be involved in any other
21 interactions between manufacturers and
22 providers or the collection of information in

1 provider offices that are really unrelated to
2 REMS.

3 MS. POTTER: Yes, and I understand
4 that that's a challenge for FDA. I think one
5 of the things that we had suggested was
6 certainly in discussions, and we have been
7 talking over the last couple of days about
8 bringing providers into these discussions or
9 the early design of a REMS program, where
10 certainly the privacy concerns could be
11 raised.

12 The other point to make is that in
13 your Federal Register notice you have asked
14 for specific factors that may not have been
15 addressed specifically in the statute. And
16 one of our points is that, while privacy is
17 not specifically enumerated, we do see it --
18 you can sort of broadly interpret that
19 language perhaps to see it as an undue burden
20 on patient access when patients are faced with
21 having to sign away broad access to their data
22 in order to get a needed treatment.

1 We think that that really is not a
2 good situation and that perhaps it could be
3 part of a guidance or certainly an educational
4 process that happens in your conversations
5 with the drug manufacturers, and then,
6 obviously, including providers in the mix.
7 Because we are very sensitive to those privacy
8 concerns. I think it would make a huge
9 difference in terms of mitigating some,
10 frankly, of the abuses that we have seen with
11 these broad disclosures.

12 MS. TOIGO: Suzanne?

13 DR. BARONE: If you are aware of
14 any specific language in any of the
15 attachments to any of our approved REMS, we
16 would appreciate if there is any language in
17 any of those that you submit and tell us which
18 ones or what language bothers you.

19 In some cases, we have that
20 patient assistance program built in where a
21 company wants to do that or the insurance,
22 especially if they are using a specialty

1 pharmacy. So there are some of those
2 concerns. But if you have specifics that are
3 approved and up on the website as part of a
4 REMS, we would be interested in knowing that.

5 MS. POTTER: And you know, we're
6 not mentioning names here, but we do have
7 examples, because we deal with a lot of REMS,
8 of specific requests for patient information
9 for broad disclosures that sometimes are
10 represented as being part of a REMS when, in
11 fact, they aren't. Or drug manufacturers have
12 come to us and claimed that there are REMS and
13 they have instituted a REMS program, and they
14 claim that it includes this requirement to
15 collect data, when, in fact, they don't as
16 well.

17 So, you know, I think there needs
18 to be some education on these issues.
19 Certainly there's been, as both of us have
20 talked about, some real changes in the
21 regulation, in the legislation. There's
22 pending legislation in Congress right now that

1 would further tighten up privacy protections.

2 We know there's a lot of consumer
3 concern out there because, in fact, one of the
4 things that we hear, I work a lot in the State
5 of California and some of their privacy groups
6 related to electronic health records. One of
7 the issues that's almost always brought up is
8 from patients who are concerned about the
9 kinds of marketing or promotional materials
10 they get from drug manufacturers after they've
11 gotten a prescription or they have been
12 involved in some sort of program, in
13 particular, some safety programs.

14 So, there is some consumer
15 awareness and concern out there, and we wanted
16 to raise that issue to FDA.

17 MS. TOIGO: Thank you, Ms. Potter
18 and Mr. Nicholson.

19 I think that concludes our final
20 panel and final of six topics, on protection
21 of patient information.

22 We do have, or at least after

1 lunch we had two speakers scheduled to speak
2 in the open public session. I didn't get
3 their names, though, but it looks like Kristen
4 has their names.

5 So, if you could come up to the
6 table here?

7 I recognize Dr. Schnoll. But who
8 else? Okay, we have three.

9 We have John Chaneler from MarcRx.
10 I may have not got that correct. Sid Schnoll
11 from Pinney Associates, and Brian Gallagher
12 from the American Pharmacists Association.

13 So, we will follow the same rules
14 here, five minutes for your comments, and our
15 FDA panelists may have a question or two for
16 you after your presentation.

17 You're in the hot seat first. So,
18 you get to go first.

19 Do you want to tell us a specific
20 topic or, if it's just general, then just go
21 right into your presentation.

22 DR. SCHNOLL: Sid Schnoll from

1 Pinney Associates.

2 I'm going to talk about the
3 metrics this afternoon.

4 A couple of things that I wanted
5 to address. One, I really believe that the
6 issue around goals, that goals can be
7 aspirational, but only if objectives are
8 measurable that are added to those goals.
9 Otherwise, we really don't understand them.

10 And I think, as Dr. Davis
11 mentioned, that it's worthwhile to develop
12 some standards related to those objectives,
13 but they should be based on the risk. So, you
14 might want 100 percent to be able to answer
15 questions if the risk is severe, but maybe 80-
16 85 percent if the risk is not severe.

17 The other thing is that we should
18 be able to measure the burden or lack of
19 burden associated with a REMS by looking at
20 changes in prescribing behavior. Prescribing
21 behaviors may go up or down. But in order to
22 really understand why those behaviors are

1 changing, it will be necessary to do some
2 focus groups or surveys with the prescribers
3 to understand what made them change that
4 behavior.

5 In relation to education, as
6 somebody with the letters "M.D." after my
7 name, I can tell you that one of the reasons
8 I got there was because I could answer
9 questions when it came to knowledge
10 assessment. M.D.'s do that very well.

11 But one of the things that is not
12 very clear is if education really changes our
13 behavior. There have been a lot of studies in
14 relation to continuing education to try to
15 look at this, and it really is not clear
16 whether the education does change behavior.
17 We need to develop a way to assess that. That
18 is the only way we will really know if the
19 training and education of prescribers achieves
20 the outcome that we want.

21 In terms of patient education, med
22 guides and other things, certainly we need to

1 do comprehension testing, literacy testing, on
2 these items. When these things are translated
3 into other languages, literal translations are
4 not enough. We have to take into
5 consideration cultural differences that exist
6 and make sure that translation is adequately
7 comprehended by the population involved.

8 One of the things that might be
9 useful in this, and I know this is a different
10 branch of the FDA, but actual use studies that
11 are done on labels for OTC products may be
12 something that can be used to fully understand
13 what is going on.

14 Another issue that we mentioned
15 earlier was standardization of measurement
16 systems to allow some assessment across REMS
17 to look at the various elements and determine
18 whether or not they are appropriate for the
19 outcomes desired.

20 When looking at how to assess a
21 REMS, I think we also have to consider that we
22 may have to develop totally new systems for

1 measurement, things that we haven't thought
2 about, and approach them in a different way.

3 There are some systems that we can
4 look at. Certainly claims databases could be
5 a way of assessing REMS. But there are
6 prescription drug monitoring programs that
7 many of the states have now, and for some
8 products they can be used, but a lot of them
9 don't allow access to the information. So, we
10 need to be able to get them to do that.

11 Something I mentioned last week, I
12 think for many of the areas we need to bring
13 together a number of private, federal
14 agencies, other stakeholders to really fully
15 appreciate where we are going and how to get
16 there with the REMS.

17 All the data that are collected I
18 think need to be timely and product-specific,
19 and a lot of measurement systems don't permit
20 that, particularly things like overdose and
21 deaths associated with various
22 pharmaceuticals.

1 I think as we move forward with
2 this, I would like to quote a person who I
3 think probably knew a lot about numbers and
4 was a very wise man, Albert Einstein. And he
5 said, "Not everything that counts can be
6 counted, and not everything that can be
7 counted counts." And I think we have to keep
8 that in mind as we move forward.

9 Thank you very much.

10 MS. TOIGO: Thank you, Dr.
11 Schnoll.

12 Our next speaker is Brian
13 Gallagher from the American Pharmacists
14 Association.

15 MR. GALLAGHER: Thanks to the
16 panel for holding this session and for
17 allowing me a few minutes to speak.

18 In listening to the discussion
19 this morning in the first panel, when some
20 interesting observations were made in terms of
21 the tension between trying to have a uniform
22 standard that would apply to everybody and

1 Kaiser's request for flexibility and
2 innovation, in thinking about that, a
3 potential solution occurred to me that I
4 shared with some of the panel members during
5 one of the breaks. And it was suggested to me
6 that I come up here to put it on the record,
7 so everybody could discuss it and think about
8 it.

9 And that solution would be a
10 potential middle ground that balances those
11 two things. What I would suggest is building
12 in a waiver program into the REMS program for
13 innovations. So that if the REMS was approved
14 and groups like Kaiser or something in a
15 controlled environment wanted to come forward
16 with some type of innovation that they wanted
17 to try that would meet or exceed the
18 standards, that they be allowed to do that, so
19 that those innovations could then be
20 incorporated later on.

21 And a number of the comments that
22 Kaiser raised, some safeguards came to mind,

1 too. To avoid the exception potentially
2 swallowing the rule, it seems to me that if
3 you adopted an IRB-type approach for approval
4 of this, that the FDA could approve or set up
5 some type of approval mechanism for the
6 standards in the waiver. That would be some
7 safeguards. There should also be a
8 requirement built in there that the results be
9 shared, so that it could be adapted across the
10 whole industry.

11 The benefits of this, it seems to
12 me, would be to maintain a uniform system that
13 some of the panelists expressed a need for and
14 a single standard of care while also allowing
15 for testing innovation in a sort of controlled
16 incubator-type environment.

17 It would eliminate activities that
18 don't work. So it would decrease that burden
19 on providers like my members, and it would
20 provide a controlled methodology for
21 continuous quality improvement.

22 So I would just ask the panel to

1 potentially consider that. Thank you.

2 MS. TOIGO: Thank you, Mr.
3 Gallagher, for sharing those comments.

4 And our last speaker is John
5 Cheneler from MarcRx.

6 MR. CHENELE: Thank you. There's
7 nothing like being the last one to actually
8 keep everything going.

9 The reason that I wanted to speak
10 is I wanted to follow up with some comments
11 that I heard over the last two days and what
12 I've heard for the three years since this
13 comment was first proposed in Congress, and
14 we've all watched it somewhat evolve and
15 somewhat grow into what will soon be an
16 actionable plan and actionable item for all of
17 us to deal with.

18 I would like for all of us to do
19 what we talk about when we get together at
20 groups in our offices, either FDA, sponsors,
21 those of us in different companies. We are
22 all talking about thinking out of the box. I

1 want us all to think of, how do we think out
2 of the box?

3 There were a couple of things that
4 were said. Just most recently, Dr. Pinney
5 (sic) mentioned something; Dr. Goldman
6 mentioned them, about using some new ideas and
7 some new techniques and there's new analytics.

8 What I am going to talk about is
9 social media. Because whether we like it or
10 not, the social media is discussing everything
11 that we do and everything that a drug does in
12 the marketplace. As we develop all of these
13 ideas and plans to go forward with the REMS,
14 the marketplace will discuss everything we do
15 and monitor us.

16 I use as an example -- I would
17 like to digress. Last week was a monumental
18 week for Facebook. For any of us that are on
19 Facebook, we joined 500 million users. I want
20 to repeat that number; 500 million users are
21 on Facebook. That would be the equivalent of
22 every man, woman, and child in North America

1 communicating personal information on Facebook
2 to a group of people.

3 I also want to go back and think
4 of something that happened a year ago. A year
5 ago, a blockbuster movie came out that
6 everyone anticipated was going to just drive
7 sales like no tomorrow. It was about this
8 weekend last year. It opened up in the
9 Midwest and the East Coast on a Friday
10 evening. By 10 o'clock, there had been enough
11 tweets and text sent that that movie died. On
12 the West Coast, no one went to it. That's the
13 power of social media. People communicate in
14 ways that we have never even dreamed of.

15 And this is not just the 15-year-
16 old in high school. These are adults our age,
17 older, younger. It crosses the spectrum.

18 I go back, 500 million Facebook
19 users. A lot of people are communicating.

20 As this market evolves, the social
21 media market, communication for what's
22 happening on the drugs will continue. The

1 retail industry, the CPG industry, the
2 political markets, the auto industry, they are
3 monitoring social media, and they are seeing,
4 through social media, webcrawling and patented
5 technologies. They can use advanced analytics
6 and understand what's happening with the users
7 and the non-users.

8 There are websites today where I
9 can go to, any one of us can go to and read
10 hundreds of actual users' comments about a
11 drug. The same drugs that we're talking about
12 in REMS, folks are talking about it out there.
13 It's going on today and it's not going to slow
14 down. It's going to keep growing.

15 I would like to ask the FDA panel,
16 as you develop your thought processes and help
17 us, keep in mind that three years ago very few
18 people were on Facebook. Now half a billion
19 are on it.

20 The market will continue to
21 evolve. Social media comments will continue
22 to evolve. And we must be acknowledgeable

1 that we, as practitioners in the
2 pharmaceutical world, in various aspects, we
3 have to monitor what is going on.

4 It behooves us to ask the sponsors
5 and all the players in this to constantly and
6 vigilantly market themselves while they are
7 monitoring what's being said out in the
8 market. This is the first level of trend
9 analysis that we can see adverse reactions
10 long before we start to see serious effects in
11 the marketplace.

12 Thank you.

13 MS. TOIGO: Thank you for your
14 presentation.

15 And I'll ask the FDA panel if
16 there are any questions for any of our
17 speakers.

18 (No response.)

19 Okay. Thank you for sharing your
20 comments.

21 And it looks to me like we've got
22 to the end of the agenda, which means I now

1 turn it over to Jane Axelrad, whose meeting
2 this is, to share her final comments.

3 MS. AXELRAD: First of all, I
4 wanted to say that we really appreciate all of
5 the input that we received during what I think
6 was a very productive two-day meeting.

7 I want to thank all of our
8 presenters for being willing to share their
9 views about this important topic and our FDA
10 panelists for asking some very good questions,
11 I think, and developing a fairly good record
12 about what has been going on and what the
13 perceptions are about our implementation of
14 the REMS program.

15 I also want to thank Terry for
16 doing such an excellent job of moderating the
17 program and keeping us on time and organized,
18 and for all of the various people that put
19 together the meeting and dealt with all of the
20 logistics.

21 Over the course of the past two
22 days, I think several themes emerged.

1 First of all, REMS are a necessary
2 and important part of ensuring safe use of
3 drugs that might, absent effective REMS,
4 otherwise be unavailable.

5 While REMS address specific
6 serious risks of important medications, the
7 programs often have unintended consequences
8 that should be addressed. They place a burden
9 on various parts of the healthcare system,
10 including prescribers, pharmacists,
11 distributors, and hospitals. They could
12 deprive patients of access to important
13 medications, if they are not properly
14 constructed.

15 Among the unintended consequences
16 of our programs I think are the paperwork
17 burdens that the multiplicity of unique
18 systems place on prescriber practices,
19 pharmacies, and the healthcare system. For
20 example, one of our speakers said that keeping
21 track of prescriber certifications in multiple
22 programs can require a medical center to move

1 literally thousands of pieces of paper. And
2 we have heard from a number of speakers that
3 multiple systems also can place significant
4 burdens on pharmacy practices and affect
5 workflow and the pharmacists' ability to serve
6 their patients.

7 REMS programs can also, we heard,
8 pose challenges in ensuring continuity of care
9 to patients as patients move from inpatient
10 facilities to outpatient or home care and
11 possibly back again.

12 Medication guides as part of REMS
13 were cited frequently as being burdensome on
14 the healthcare system, although consumers and
15 patients strongly support the expanded
16 availability of useful patient information.

17 We heard suggestions for
18 improvement to patient information by
19 consolidating the various forms of information
20 into a single useful document that takes into
21 account the health literacy of the recipients.

22 We heard that there is a need to

1 convey in the REMS program, in the medication
2 guides and in other REMS documents, the fact
3 that there are benefits associated with a drug
4 as well as the risks, and to present the
5 benefits and risks in a balanced way.

6 And this afternoon we heard that
7 FDA has a role to play in ensuring that REMS
8 are not used to block generic competition.

9 We heard a number of different
10 solutions suggested to some of these issues.
11 One of the frequently-mentioned solutions was
12 that involvement of prescribers, pharmacists,
13 and patients in the development of REMS would
14 be a way to make sure that REMS programs
15 fulfill the purposes for which they are
16 developed with perhaps less unintended
17 consequences.

18 Several speakers suggested that
19 FDA convene an advisory panel to provide
20 advice on the design of individual REMS
21 programs.

22 Another proposed solution was the

1 development of templates and increased
2 standardization of REMS programs to reduce the
3 burden on the healthcare system of
4 implementing those programs.

5 Best practices might also include
6 tying REMS into existing electronic pharmacy
7 systems and electronic health records that are
8 increasingly used in medical practices, and
9 particularly in larger medical centers.

10 We also heard about the
11 incorporation of scientific principles such as
12 failure modes and effects analyses that can
13 help determine when a REMS is needed and how
14 to select elements of a REMS so that it's
15 targeted to addressing specific risks.

16 We also heard that effectiveness
17 of REMS elements should be assessed, and
18 elements that are not effective should be
19 discarded. Several speakers suggested
20 increased transparency about assessments of
21 individual REMS that would be useful, so that
22 others can learn about the experience that is

1 happening across the industry.

2 As part of our next steps, we are
3 going to be considering all of the input that
4 we received at the meeting, including any
5 written comments that can be submitted to the
6 docket up to and through August 31st.

7 One of the things we are going to
8 do is examine our program to see whether some
9 of the suggestions that we have heard can be
10 incorporated into REMS that are already under
11 development. We will be looking at risk
12 management programs that are already in place
13 with an eye towards increased standardization
14 of REMS. And we are going to be reaching out
15 to stakeholders about the design of REMS to
16 further discuss how to better integrate REMS
17 into the healthcare system.

18 We will look forward to working
19 with all of you in the future to draw on the
20 analogy that Dr. Woodcock opened the meeting
21 with, to build a house, that is,
22 implementation of our REMS program, in a way

1 that meets the needs of all the stakeholders.

2 And thank you all for coming.

3 (Applause.)

4 MS. TOIGO: That concludes our
5 meeting. Thank you.

6 Safe travels.

7 And if you have any
8 recommendations, certainly send them to me.

9 (Whereupon, at 2:49 p.m., the
10 proceedings in the above-entitled matter were
11 adjourned.)

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