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Food and Drug Administration

Advisory Committee on FDA Risk Communication

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P R O C E E D I N G S (8:10 a.m.)

Agenda Item: Call to Order and Conflict of Interest Statement

DR. PETERS: Good morning. I would like to welcome everyone to what I believe is the 13th meeting of the FDA's Risk Communication Advisory Committee. My name is Ellen Peters and I'm the chair of the committee. This is my first meeting in two years and my first meeting as chair of the committee. It's absolutely a pleasure to be back, to see some familiar faces, as well as some new faces, and I'm very much looking forward to our discussion over the next couple of days.

At this point, let me turn it over to Dr. Lee Zwanziger, the designated federal officer.

DR. ZWANZIGER: Thank you, Dr. Peters.

Good morning to the members of the Risk Communication Advisory Committee, members of the public, the press, and the FDA staff. Welcome to this meeting. We welcome especially our new RCAC members, Dr. Peters and also Drs. Engelberg, Freimuth, and Hallman, and today's temporary voting member, Dr. Shonna Yin, and Dr. Sandra Milligan, from the RCAC industry representative pool.

The following announcement addresses the issue of conflict of interest with respect to this meeting and is made a part of the public record to preclude even the

appearance of such at this meeting.

The FDA has determined that members of this committee are in compliance with federal ethics and conflict-of-interest laws. Today's agenda includes two topics. First, the committee will discuss the results of a literature review, as required in the Patient Protection and Affordable Care Act, about communicating quantitative risk and benefit information in prescription drug promotional labeling and print advertising. This is a particular matter of general applicability to pharmaceutical firms. Based on the agenda for today's meeting and all financial interests reported, all members may participate fully in today's deliberations.

Two members from the regular roster had to be absent just due to schedule conflicts, Dr. Fagerlin and Mr. Schwitzer.

The Act calls for reviewing all available scientific literature in consultation with experts. The FDA has commissioned a literature review and sought advice on it from experts, including current and former committee members and special government employee consultants, as we continue to do in today's meeting. We look forward to this discussion.

The second topic today is on outreach activities in FDA's Office of Special Health Issues. This topic is a

non-particular matter, so interests in firms regulated by the FDA present the potential for conflict of interest. Should the discussion turn to any area of potential conflict not already on the agenda, participants are aware of the need to identify conflicts pertaining to them and refrain from participating, and their statements and the exclusions will be noted for the record.

We do have a period set aside for open public comment each day, listed in the agenda. There is a sign-up sheet for last-minute inspirations outside. Please see one of my colleagues at the sign-in table outside if you wish to speak.

The entire meeting is being broadcast by Internet and transcribed, and the transcript will be posted on our Web site. Please remember to turn on and speak into the microphones every time you are recognized to speak and turn them off when you're not speaking. Also I would suggest we turn cell phones and other devices to silent mode.

Thank you.

DR. PETERS: At this point, why don't we go ahead and have the standing members of the committee introduce themselves. It looks like Dr. Wolf might not have been able to make it yet. Perhaps we could start with Dr. Sokoya Finch.

Agenda Item: Introductions of Committee Members

MS. FINCH: Good morning. My name is Sokoya Finch. I'm with Florida Family Network in Tallahassee, Florida. We cover health disparities, as well as health literacy and social justice issues.

DR. ENGELBERG: Good morning. My name is Moshe Engelberg. I head up a company named ResearchWorks, headquartered in San Diego. We do what most people call social marketing, a mix of health communication and marketing, for a variety of organizations, with a focus on public health.

DR. BROWN: Good morning. My name is Mary Brown. I'm a health communications specialist with the University of Arizona College of Pharmacy, as well as having my own firm. I study health communication, patient literacy, development of health literacy materials.

DR. HUNTLEY-FENNER: Good morning. My name is Gavin Huntley-Fenner. I have my own science and engineering consulting firm, where I look at issues relating to human factors and risk communication.

DR. REYNA: I'm Valerie Reyna. I'm a professor at Cornell University in human development, psychology, cognitive science, and a few other programs. I do research on memory and risky decision making across the lifespan.

DR. PETERS: As I mentioned before, I'm Dr. Ellen

Peters. I'm on faculty at Ohio State University, in the psychology department. I study issues around how individuals process information and how that information processing makes a difference to decisions. Recently I have been very focused on issues around numeracy.

DR. BREWER: Noel Brewer. I'm on faculty at the University of North Carolina, in the Gillings School of Global Public Health. I study how people make decisions and I focus on how they make decisions about medical tests and about vaccinations. I also more recently have started studying patient harms due to medical tests.

DR. PAUL: Good morning. I'm Dr. Kala Paul. I'm a neurologist by training. I'm president of the Corvallis Group, which is a company that specializes in risk communication for pharmaceutical and device products.

DR. FREIMUTH: Good morning. I'm Vicki Freimuth. I direct the Center for Health and Risk Communication at the University of Georgia. I was formerly director of communication at CDC.

DR. ANDREWS: Good morning. I'm Craig Andrews. I'm professor and Kellstadt Chair in Marketing at Marquette University in Milwaukee, Wisconsin. My focus is on advertising and public health issues.

DR. COL: My name is Nananda Col. I'm an internist and I have an appointment at the University of

New England in Maine. My work is on mathematical modeling of risk and developing shared decision-making approaches to help patients make more informed decisions.

DR. HALLMAN: Good morning. I'm Dr. Bill Hallman. I'm a psychologist. I'm chair of the Department of Human Ecology and I'm director of the Food Policy Institute at Rutgers, The State University of New Jersey. My area is risk perception, especially related to microbial risk and food safety risks.

DR. YIN: Good morning. My name is Shonna Yin. I'm a general pediatrician and a researcher focusing on issues of health literacy, trying to develop and evaluate strategies to improve parent understanding of various issues, with a particular focus on medication. I'm trying to decrease medication errors.

DR. PETERS: These are the present members of the standing committee.

And, Lee, of course, correct me in anything I say incorrectly here.

The committee is constituted to be without standing industry representatives. But at every meeting that I know of, at least with this particular committee, we have had the fortune to have either one or two industry representatives join us and provide their important perspectives. I believe we have one industry

representative here. If you could introduce yourself?

DR. MILLIGAN: Good morning. I'm Dr. Sandra Milligan. I'm with Amgen out in California, in the regulatory affairs department. I'm honored to be here today as the industry rep for the RCAC.

DR. PETERS: Lee, I believe you are going to do a welcome and a meeting overview.

My apologies. We have another gentleman sitting at the table. We missed the introductions. Dr. Abrams is with the Food and Drug Administration. If you could introduce yourself, please?

MR. ABRAMS: Sure. Tom Abrams, director of the Office of Prescription Drug Promotion in the Center for Drug Evaluation and Research at the Food and Drug Administration.

DR. PETERS: Thank you.

**Agenda Item: FDA Welcome, Meeting Overview, and
SPRC Update**

DR. ZWANZIGER: Good morning again. I'm changing hats now. I'm also serving as the acting director for risk communication since the retirement of my former supervisor, Nancy Ostrove, whom many of you know.

I want to give you a quick overview of some recent work that we have been doing or work in progress.

Many of you are already very familiar with the

strategic plan for risk communication that FDA issued in September of 2009, following discussions with this committee. That plan was structured around three goals, to improve how FDA communications about regulated products: strengthening science, enhancing our capacity, and optimizing our policies. We have further elaborated those in 14 strategies, including one that I'm going to give some illustrations of today on streamlining processes for conducting communication research and testing.

One of the works in progress that we have mentioned in passing several times is our effort at developing generic clearances for faster Office of Management and Budget review of FDA research and compliance with the Paperwork Reduction Act. One feature -- maybe it's even an artifact -- of the system is that we can only submit one study at any given time under generic clearance to speed research review approach. Our solution was to create multiple generic clearances so that we basically more pipelines into OMB. Our office has been helping to do this. This is what we hope will be a service for researchers throughout the agency. Brian Lappin developed one for the Center for Tobacco Products. We have had a whole series that have been completed and a few still in progress by Miriam Campbell, building more generic clearance avenues. I have listed those here. We have

generic clearances specific for the various centers and a few also generally available for qualitative research and, we hope, soon one on general usability studies.

Another work in progress that you have heard mentioned is our internal testing network. As recommended by the RCAC, FDA is informally testing messages when short of time and resources. The objective here is to catch the big red flags in draft communications using a network of volunteers, FDA employees from other parts of the agency than developed the communication in question. A recent example that we are proud of is the November 8th launch of our Web site on sharps disposal. If you want to take a look at it, it's up. I couldn't get to the Web site right now. We found through informal testing recommendations for revising the language, highlighting some content with respect to others, and generally shortening things, and changes were made prior to the launch, including a more descriptive title on the Web page, emphasis on a two-step disposal process, and fewer navigation headers. So we feel like people all across the agency are pitching in to help improve our risk communication.

Another work in progress is a focus group effort. This is actually a two-phase focus group effort. It's nearing completion of the second phase. This is also a project headed by Brian Lappin. It is a key project

featured in FDA Track. You can see the progress that we're making on this project if you go to FDA's FDA Track Web site.

The project aims to get feedback from members of the public of varying education levels, from both around this area and also elsewhere -- in this case, Texas -- to get comments and thoughts on different formulations of FDA messages on the risks and benefits of prescription drugs. The focus groups have all met and the final report is in the works. We expect it next spring sometime.

Another work in progress, much nearer its beginning phases, is in our staff headed primarily here by Miriam Campbell. We are developing a study to compare types of videos, styles of videos, communicating messages, in this case on sunscreen. We chose that because of its wide applicability. We contracted out to have done a Web-based survey using an Internet panel. The sample will include a range of health literacy, education, and older ages of participants.

We hope that that will inform us going forward as to making a choice as to styles of videos we might want to develop.

I want to just mention a subject near and dear to all of our hearts, the book *Communicating Risks and Benefits: An Evidence-Based User's Guide*. We have been

working very hard this fall to get final changes and approval for a second print run and distribution by GPO. That now is on the cusp of going out the door. I'm very excited to have that be distributed by the Government Printing Office staff. Meanwhile, we do have some copies from the first print run left. If anybody wants one, this would be a great time to ask. We'll be happy to give them to you or mail them to you if that would be more convenient.

Finally, I just want to mention that we have such an exciting meeting lined up today and tomorrow. You heard just briefly about today's literature review. I just wanted to mention that, like all literature reviews, it had to come to an end, and more material is always being published. So if you know of relevant articles that you think we should look at, you can send them to me at the Risk Communication Advisory Committee address, and I will get them to the subject-matter experts for their review.

Our second session today will be an overview and discussion with our Office of Special Health Issues.

Tomorrow is also going to be great, with presentations by Dr. Reyna and a couple of guest speakers. So I hope you will be back.

Thank you very much.

DR. PETERS: Thank you, Lee. That was terrific.

Having been absent from the committee for a couple of years -- go ahead.

DR. COL: I was curious about the survey comparing three styles of video for effectiveness and impact. What do you mean by "styles"?

DR. ZWANZIGER: One using a cartoon, one using voice, sort of a straight presentation, and -- Miriam, what did we call our third style?

This is Miriam Campbell, who is on this project.

DR. CAMPBELL: There are three very differing styles of videos. The first is a cartoon. The second is a live individual, including a spokesman from FDA. The third is multimedia, very fast-paced, including both live actions and cartoons -- very up-to-date.

They are very different. We are going to test the three for effectiveness by age and by literacy, and try to determine a more effective means of producing videos on any topic, basically, from this.

DR. PETERS: Craig?

DR. ANDREWS: I saw a couple other panel members looking my way on this. Could we ask who the spokesperson is? This has come up before at our meetings.

DR. CAMPBELL: The spokesperson is a dermatologist from FDA.

DR. PETERS: Are there other questions from the

committee members? Moshe.

DR. ENGELBERG: Is one intent of the Paperwork Reduction Act to also expedite OMB review and approval?

DR. ZWANZIGER: OMB administers the Paperwork Reduction Act, and one intent of the generic clearances is to facilitate OMB review and approval, yes. And they do seem to help, incidentally.

DR. PETERS: That was actually going to be my question. Do you think this is actually speeding up the process at this point or you have some hope that it will?

DR. ZWANZIGER: Yes.

DR. PETERS: That's great. That's actually a huge, huge -- from the time that I was here, back in 2007, 2008, that is a huge step forward. I'm very impressed that FDA has started to work out some of these issues. The testing of communication that will now be possible is very different, given that you are going to be able to do this faster, at least for some projects.

Mary, did I see your hand up?

DR. BROWN: I was just curious how you came to choose those particular three styles in your study, the video styles.

DR. ZWANZIGER: We had them available already. We had some videos produced and one that was in production. So we thought it was a good time to start some evaluation.

DR. PETERS: Noel and then Kala.

DR. BREWER: Can you just say a little bit, on the videos, about what you mean by effectiveness and impact? I would love to know more about that.

DR. CAMPBELL: We'll be doing an Internet survey in which individuals will be allowed to view two of the three videos, one after another. Because there are three videos, we'll have six groups. Each video will be seen by two of the groups first and then we'll have an opportunity to ask follow-up questions about impact in terms of whether it's memorable to them and what was memorable and what was favored and what wasn't favored, and which was their favorite and which one helped them learn more, basically by following up with them in terms of what they do remember from them.

DR. BREWER: I'm wondering if there are other measures. What you just described would sometimes be called process measures, in the sense that there would be a process evaluation to determine how many people would watch something or how well they liked it or an appeal to an audience. That might be different than trying to affect outcomes of the sort that are intended to be affected by the video, such as understanding or changes in knowledge or other measures. I'm just wondering if that's also of interest.

DR. CAMPBELL: Of course it's of interest, but designing a study that is going to actually follow up people to see whether it has an impact on their actual behavior is not something we could afford at this time.

DR. BREWER: Would you want to change intentions to change behavior? Is that also relevant?

DR. CAMPBELL: That's very difficult to assess.

DR. BREWER: Could you just ask, "Do you intend to do blank," to see whether it differs among the three groups?

DR. CAMPBELL: Yes. In fact, that's part of the questionnaire.

DR. BREWER: Thank you very much.

DR. PETERS: Kala?

DR. PAUL: Noel asked my questions.

DR. PETERS: Perfect. Any other questions for Lee?

(No response)

DR. ZWANZIGER: Thank you all, and thank you, Miriam.

DR. PETERS: I have to say, if I could for just a moment, having been absent, as I said, from the committee for two years, I think there has actually been a tremendous amount of progress over the last couple of years in taking steps towards helping FDA to do better testing and faster

testing, which is very important -- faster testing of the risk communications. I think the general clearance hopefully will make a huge difference. I think developing that network of volunteers -- that was something that was mentioned sometime in our first year of the committee. It was mentioned as maybe this would be a step that FDA could take in order to generate more and earlier research to improve communication, where perhaps OMB clearance wasn't possible at the moment, but that kind of introductory feedback could end up making a huge difference. And it sounds like it actually might be. I think that's just terrific. I want to applaud FDA for actually following through on some of the advice and some of the discussions that we have had here, and actually putting it to action. I think that's terrific.

Lee mentioned a number of these different things that have been happening vis-à-vis the strategic plan. As she also mentioned, you can find the strategic plan for risk communication online if you're interested. You can also track the progress. Lee will give updates of the progress at each and every meeting, and she and, in the past, Nancy have been doing that for quite some time. If you're interested, you can actually go back into the minutes of the various meetings and look at how much progress has been made over the approximately four years

that this committee has been here.

Most, if not all, of FDA committees are advisory in nature. Our committee is no different. Our committee is advisory in nature. FDA comes to us for advice on some specific issues. We're going to see an example of that this afternoon around MedWatch. But we're also tasked by Congress to do some things. Today is going to be one of our mandated tasks. It's really quite an interesting task that we're going to be taking a look at this morning. We are going to hear about and then discuss implications of this literature review about communicating quantitative risk and benefit information in prescription drug promotional labeling and print advertising.

At this point, I would like to welcome Thomas Abrams one more time. Please welcome him to the stand to do his thing. Thank you.

**Agenda Item: Session I: Literature Review and
H.R. 3507**

**Introduction and Overview of FDA's Analysis of
H.R. 3507**

MR. ABRAMS: Good morning, everyone. Thank you, Dr. Peters.

First, FDA would like to thank Dr. Peters and the committee for discussing this topic. As Dr. Peters mentioned, it's an important topic to the agency and to

public health. We also appreciate the guidance and advice that you will provide based on your expertise and experience.

To give you a little background, in March of 2010, President Obama signed into law the Patient Protection and Affordable Care Act. This is also known as ACA. So if somebody refers to ACA, it's an acronym for the whole bill.

There's one section in this bill, Section 3507, which requires FDA to determine whether the addition of quantitative summaries of benefits and risks of prescription drugs in a standardized format to promotional labeling and print advertisements of prescription drugs would improve health care decision making by clinicians, patients, and consumers. This format that they are referring to is similar to a drug-facts label on over-the-counter drug cartons and labeling.

In making this determination, the bill directed FDA to review all available scientific evidence and research on decision making and social and cognitive psychology, and also directed us to consult with manufacturers and consumers, experts in health literacy, and other representatives and experts.

As part of FDA's response to this requirement, we contracted with RTI International to do a complete and

objective review of science-based studies related to the communication of quantitative benefit and risk information. Dr. McCormack and Dr. West will present their findings to the committee and to the public today.

Today FDA is seeking input from experts on this committee and from the public. We look forward to hearing from the committee about the research that has been reviewed. We also will use this information from the literature review to make an assessment of next steps as far as this requirement by Congress. So we will use the information from the literature review. We will use the recommendations from the committee. We will use the data from our own research studies. We will make the decisions about the appropriateness of including this information in promotional labeling and print advertising.

Please note that today's discussion will focus on promotional labeling and print advertising. It will not address patient medication information, PMIs. This is a very large and extensive initiative that FDA is undertaking, but that's outside the scope of this meeting this morning.

I would like to thank everyone attending this meeting and the committee for this discussion. We look forward to a very productive and lively discussion.

Thank you.

DR. PETERS: Thank you very much.

Are there any questions for Dr. Abrams at this time?

(No response)

Thank you. I very much appreciate your time to introduce this important topic. I think that at this point we'll go ahead and introduce, I believe, Lauren McCormack and Suzanne West.

Suzanne, I believe that you will be presenting the results from the literature review.

Agenda Item: Communication of Prescription Drug Quantitative Benefit and Risk Summaries in Promotional Labeling or Print Advertising: A Literature Review

DR. WEST: Actually, I will be presenting the first part of the literature review and Lauren McCormack, my colleague and health literacy expert, will be presenting the results.

I thank you very much for being here, and I thank the committee for allowing us to present this information. My name is Suzanne West. I was the project director for this project. I appreciate the fact that FDA did fund this. The literature review took about an 11-month period. We're also very grateful to Helen Sullivan and Amie O'Donoghue for their very helpful comments throughout the process.

The overarching question, as has been indicated earlier, is whether the addition of quantitative information for drug advertising impacts informed decision making and whether there are particular communication formats that will assist in informed decision making. So that's what we'll be addressing today.

I want to give you a little bit of background on the requirements that FDA has put forward from the Food, Drug, and Cosmetic Act regarding promotional materials. Promotional materials should be accurate, brief, and balanced. For print advertising, the regulations require a brief summary. For broadcast ads, they are required to have either a brief summary or a combination of a major statement of the product's risks and side effects, as well as a means for consumers to access information contained in the packaging.

However, we know that even if an ad meets or exceeds the minimum requirements set forth by FDA, the ad may not be in a particular format sufficient to be understandable to the consumers, to the broad audience that's out there listening to this or reading this information. There are no uniform standards for the presentation of risk information in print ads.

We know that several years ago there were some studies that compared the information in a variety of

different ads. They found that there was inadequate risk information, inaccurate efficacy information, and there was imbalance.

This slide shows different ways of showing quantitative information. The premise is, if quantitative information is valuable for informed decision making, what is the best format for presenting it? As you know, FDA has been considering this for some time. We heard earlier about the document that was prepared by many members of the RCAC, *Communicating Risks and Benefits: An Evidence-Based User's Guide*. There is an entire chapter devoted to this that was written by Drs. Fagerlin and Peters. It's a very interesting chapter. The report came out in August, and our review was pretty much done by May. It is really relevant to say, is our literature review complete? Another paper came out soon after that, after we completed our literature search. That was done by FDA's Dr. Akin. So we know that we need to at least reference those two papers in our report.

The literature suggests that how information is presented can impact informed decision making in several different ways. For a person to be able to make an informed decision about an advertised prescription drug, they need to be provided with adequate, high-quality, relevant, unbiased information. When you're thinking about

DTC ads, you think that the information has to provide information on risks and benefits, so that a person can make an appropriate consideration of the risks and the benefits to make an informed decision.

But even if a person is provided with accurate and unbiased information, we know that risk and benefit information is not adequately understood.

What are some other issues? Framing is important. Any element of an ad that limits or inappropriately skews consumers' perception of drug effectiveness or risk could affect consumers' ability to make an informed choice. We have to make sure that the presentation of choices is not value-based, that it's value-neutral. Qualitative information is difficult to convey appropriately. We know that. But it's critical for communicating the magnitude of risks and benefits. The use of standard definitions for outcomes that occur over time is needed because outcomes, and therefore preferences, do change over time.

These are the two questions that we derived for the literature review. Congress is specifically interested in whether adding quantitative summaries on the benefits and risks of prescription drugs, in some standardized format, is valuable and would improve health-care decision making but not only consumers, but clinicians and patients.

If you look at these two questions, they seem fairly simply phrased. They seem fairly direct. It took us a really long time to get to these two questions. It was not straightforward. We are very fortunate to have worked with a wonderful technical-expert panel, who helped us get there. I'll talk a little bit more about that in a minute.

The possible relevant variables that we considered in our review: We felt that the outcomes that we needed to consider were knowledge, information format and style preferences, perceived risks and benefits, behavioral intention, and ultimately behavior -- did they use the sunscreen, for example? But we also knew that there were important potential moderators:

- Health literacy, which is defined in a systematic review, coauthored by Dr. McCormack from RTI, as the degree to which individuals can obtain, process, understand, and communicate about health-related information needed to make informed health decisions.

- Numeracy, as studied by Dr. Peters, is also very important. It's the ability to understand, use, and attach meaning to numbers. It is a component of health literacy. It's an important and independent contributor to comprehension and decision making.

Numeracy is really important when we think about

whether or not to include quantitative information about risks and benefits in promotional materials. In order for a person to be able to understand numbers, they have to have some basic level of numeracy. Many don't have numerical competence.

- The other potential moderator is socioeconomic status. Ensminger and colleagues define socioeconomic status as having both material resources and education. Those at lower SES levels would be expected to perform poorly on key information-engagement tasks.

We were looking for these moderators as we reviewed the literature.

Quantitative information: We prepared a handout. All of you should have a copy of that handout in your packets. I can't go through it in detail, obviously, because we don't have the time right now, but I do want to at least give you some basic foundation.

We defined quantitative information as empirically quantifiable evidence which can be described using numeric or non-numeric formats. On this slide you can see a range of different ways of presenting numeric and non-numeric information. We have probabilities that range from zero to 1. We have natural frequencies and simple frequencies. We provide an example of a simple frequency here: One out of every three women reported experiencing a

side effect. We have percentages. As the handout shows, we also have more complex numerical formats, such as absolute and relative risk reduction -- both important for communicating risk and benefit. Then number needed to treat, sometimes also considered as number needed to harm, is valued by clinicians typically.

Then we have the non-numeric, which is on the right-hand side of the slide. That's "often," "rarely," those sorts of descriptors, which mean one thing to me and another thing to you. Then there is visual. On the flip side of the handout we have a variety of different visual formats, many of which we'll be talking about later today.

We used a systematic review approach to the literature. We began in a typical format, where you define your key questions and then you go through the process of refining your key questions. You do some simple literature searches to see how easy it's going to be, how you need to refine your questions a little bit more, et cetera. We provided this very basic background to our technical expert panel, which consisted of five academics who were very well known in the health literacy area. We provided this information and put together a two-hour structured telephone call, where we asked them to help us with our questions, help us to focus them more clearly and more appropriately to the questions that we needed to address

for the ACA legislation. The subject headings, as many of you know, are not conducive to identifying a targeted literature base. The literature is vast. So their help was really necessary.

What they were able to do was to help us not only refine our key questions, but they came up with particular search terms that we could use. We looked for information on knowledge and comprehension, perceived risk and/or benefit, attitudes and perceptions, behaviors and behavioral intention, decisions and decision making, emotional response, information seeking. By using the medical subject headings from PubMed and by using text words, we identified 550 citations. We were very fortunate that the TEP provided us with about 100 citations that they felt would be particularly relevant to this literature. By going through many of the papers given to us by the TEP that we knew were important, we looked at their bibliographies another 100 papers. So we started out with 759 articles. Some of them were duplicated. It came down to the point where we had 674 citations to review for these two key questions.

In typical systematic review approaches, what you do is develop your key questions and then you have your inclusion and you have your exclusion criteria. What we have here are our inclusion criteria, contrasted by the two

different key questions. For each of those 674 citations, we had two researchers independently review the titles and the abstracts. What we did was a very broad-brush cut, where it includes or excludes. We were very conservative. It had to be really out of the ballpark for us to exclude it. What we found was that it was very difficult to identify truly valuable studies, studies that should be included in our literature review, just by reviewing the titles and the abstracts.

For key question 1, which was particularly important -- that was kind of the crux of our review -- we wanted to identify as many of them as possible. We didn't put any limits on it, not by geography or anything else. The other point that was very difficult was to actually find whether we were comparing numeric to non-numeric information, which was what we were looking for in this research -- papers that contrasted "often" and "never" with 20 percent increased risk or something like that. We had to go to the methods. We actually had to review what their intervention was. That was quite time consuming.

So we identified all of the key question 1 studies. The key question 2 studies, as you can see from the study settings and geography, we limited to the United States and New Zealand, because these are the two countries that have DTC advertising. We searched from 1990 until

February 23, 2011 -- that's why it's important; if there are papers that have been published since February 23, we need to know about them -- only English. Again, key question 1 was looking at numeric versus non-numeric. Key question 2 was looking at the formats. The various formats that are on the back page of the handout -- it shows you the different formats that we were looking at.

What is very important for you to realize is that there are quite a few studies on format. We needed to limit it in some way. The way in which we limited it was that the studies had to talk about medication use, they had to refer to US or New Zealand populations, and they had to have some evaluative or randomized design.

We started with 674 citations. If you do the math, you can see that right off the bat we eliminated about 526. But it really wasn't right off the bat. It was really over a very iterative process. Again, as I said before, we did it very conservatively. When we were uncertain as to whether we should include an article or not include it, we had team members review it as well, and we had a final decision made for each of the questionable articles.

As you can see, we had about 30 background articles that were important because they provided a foundational piece for our background to bring up in the

review, but they weren't the studies, the actual comparative studies, that we were looking for. Then we had 11 really good review articles, the articles that were reviewed in our hand searches. But we came down to about 107 studies that we included. They were included for either key question 1, key question 2, or both. Anything that had key question 1 in it we definitely took. We had 13 studies that were only key question 1, the comparative or non-numeric and numeric information. Sixteen studies had both, comparing non-numeric to numeric, as well as format evaluations. We had 23 for key question 2. Those were the format papers. The ones that were excluded were excluded based on geography, non-drug, and they weren't evaluative in design.

That concludes my section. I'll turn it over to Dr. McCormack, who will give you the findings.

DR. PETERS: Before you turn it over, I wonder if you might be willing to stand up there for just a moment so we can check on any kinds of clarifying questions that people on the committee might have. Nan and then Kala.

DR. COL: Thank you. I have several questions.

One is, how was the technical expert panel chosen. There seem to be several areas of expertise that might have been very helpful to include on that panel.

The search criteria -- the journals that were

included were the core clinical journals, plus an additional 14 journals that were apparently the most frequently publishing risk communication. How were those 14 journals identified? What were they? I don't see them listed.

I'm asking these questions because I see there is a lot of literature that I'm aware of that wasn't included in this. I don't fully understand what that was.

DR. WEST: In terms of the technical expert panel, what we did was look at the individuals that we knew who were well-versed in health literacy. I think we list the technical expert panel members in our report. We wanted to limit it to a smaller group, for the simple reason that we really needed to engage them in conversation. It was really more of a -- these were the people that we could include. We vetted it with FDA. These five were the ones that we approached and who agreed to participate.

Do you have a follow-up on that?

DR. COL: No. I would just suggest that in the future -- small is good, but it seems that having a broader representation of specific skill sets might be more useful in ensuring completeness.

The other question is how these 14 journals were chosen and why you decided to base your literature around

the key clinical journals, which typically, in my experience, don't publish these things. How were those selected? I'm trying to understand why so many articles were omitted from your lit search.

DR. WEST: What I didn't show you were all of the iterative PubMed searches that we did. In some of them, we started with 5,000 citations. We had a very finite amount of time to go through these articles. What we did was we tried to identify which was the best search approach for identifying the key articles. As you can see, we did identify 674 and we did get down to about 100 that were relevant. We had to make sure that they met our key questions and that they met our inclusion/exclusion criteria. We were looking for comparative studies. We weren't looking for summaries or reviews or those sorts of things.

DR. COL: I'm still -- what were the 14 journals that you added? How did you come up with that particular list of 14 journals?

DR. WEST: I'm blanking on what the 14 journals are. I don't have it at hand right now. It's certainly something that I can provide for you. But these were journals that we talked about with our TEP. These are the journals where many of the TEP publications that they had given us were. There isn't a list, like the core medical

journals, that are the core health literacy journals. So we went to the journals that we felt were most appropriate.

DR. COL: I'll just add that I think that if you had a broader representation from TEP, then you might have been able to bring in a broader number of journals and probably would have had a more replicable search strategy.

DR. WEST: Okay.

DR. PETERS: Nan, if I could, though, it sounds like there are a variety of very useful sources, and perhaps specific citations even, that could be really helpful in terms of answering these questions, if you could get those to Lee.

DR. COL: Sure. But what I'm trying to get at is, as you are getting these other searches that are coming in, I think, as you find articles that were not included, what would be useful is to track what journals they were in and then including those journals, so there could be an iterative, replicable process for identifying journals that are carrying these things rather than relying on an arbitrarily chosen five-member TEP panel. If you looked at the other journal articles that were brought in, put it to a broader audience of people who look at risk communication from perhaps a more quantitative modeling perspective or other perspectives, and then see if those met your criteria -- what journals were those studies being

published in -- and then redo the search in those specific journals, I think you would have a replicable, systematic review.

DR. WEST: And my colleague Lauren was actually kind of -- we were just discussing, as you were mentioning that -- what we did is, we did our search. We came up with the articles that we thought were most relevant. Then what we did was, we looked for -- we saw the journals that those articles were published in. Those were the journals that we selected for inclusion in our literature search. It was not just medical decision making or this or that. It was actually an informed choice of the 14.

Our literature search is published as an appendix in the report. I believe that it would have the journals listed. I just don't have them off the top of my head.

DR. PETERS: We weren't able to find the journals listed --

DR. REYNA: At the very end of the report -- it begins on page 74, all the way through 78 -- you can see some of the journal titles quoted there. That has most of them.

DR. COL: But a list of the 14 journals, a table that says --

DR. REYNA: Yes, that would be nice, too. But you can see them on those pages.

DR. WEST: I guess I'm hoping that it's clear that we did use more than 14 journals. We did use the core literature.

DR. PETERS: Nan, I think it would be greatly appreciated if some of the pieces that you think are missing -- if you could get those to Lee.

At this point, if Nan is done, we have Kala, Craig, and then Valerie.

DR. PAUL: This question is related to your choice of staying with those articles that dealt with medication use. There's a very rich literature on risk communication outside of medication. I was wondering why that, in particular, was excluded and if you could speak to the choice of medication only.

DR. WEST: It's actually a very good issue. As I indicated earlier, this review was actually a fast review. Many systematic reviews or literature reviews can take over a year and a half. That was number one. We had to identify a way of getting down to about 50 articles. That's what we had proposed to FDA, and so we were using our search strategies to get to that point.

DR. ANDREWS: In her defense, this sounds very similar to meta-analyses, where you set out criteria and things are excluded. All of us have had our research excluded because of certain factors. You understand those

things.

But I concur with Kala that there's a lot to learn from other disciplines beyond just maybe medical use -- for example, human factors, consumer research, nutrition. But I just want to concur with what she said.

DR. WEST: I agree. Let me make clear that for key question 1, we included all of the literature. It was not limited by medication use. We didn't have that many studies. We had a study on PCBs included in key question 1. So that indicates that we actually didn't just focus on medications. It was key question 2 where we had to limit the scope.

DR. ANDREWS: And that can be difficult if you are analyzing just the abstract and the title, I suspect. All of us can think of research where maybe if you drill down and look at the methods and some of the stimuli, they, in fact, were testing these sorts of things.

DR. PETERS: Are you referring to key question 1 at that point?

DR. ANDREWS: Yes.

DR. PETERS: Valerie?

DR. REYNA: I think some excellent points have been made. I do want to clarify one thing, however, from just my perspective. I think probably the choice of the term "arbitrary" to describe the expert panel is not what

was intended. I think the expert panel, instead, is a set of folks who publish extensively in the peer-reviewed literature. I'm sure we all agree that what we really probably mean is something like "systematic." We want to ensure the systematicity and inclusiveness of the literature review. It looks there were efforts, certainly, within the time constraints and budget constraints, to do some of that. I just wanted to point that out.

The other thing I would say is that I would encourage in all literature reviews to use Medline and Web of Science, in addition to PubMed, which is a kind of technical detail, but it's useful sometimes.

DR. WEST: We're finding that more and more with some of our evidence-based practice work.

DR. PETERS: Valerie, thank you on the arbitrariness of the TEP. Having been one of the members, I appreciate the comment that perhaps more systematic would have helped. But it was not arbitrary.

At this point we have Noel and then Kala.

DR. BREWER: Hello from another part of the Research Triangle. Nice to see you here.

There are a couple of things it would have helped to know a bit more about. One of them is the study quality, how good some of these studies that were done are. Having only experiments certainly places the bar in a

certain place. Studies below a certain quality you just sort of sweep out. I didn't get a sense from reading the report -- it might be that I just didn't read it carefully enough to get that, but that was one thing that I wanted to understand better as a result of it.

A second point is that I was -- I appreciate now the difficulty that you have, the time constraint that you have. But including only published studies has its own limitations. I think I understand why you did it. Including unpublished studies has a whole other set of limitations. That was on my mind.

One other comment I have, and then I have a question for you.

The comment is that it would be nice to know whether these truly are RCTs -- for example, if you have within-subjects designs, whether they truly randomize the order. That actually will make it a randomized trial, whereas simply having a within-subjects design that's not truly randomized will then not be an experiment.

DR. WEST: And again, what we need to do is look at key question 1 apart from key question 2. For key question 1, we included all of the literature we could possibly find, whether it was an RCT, whether it was observational studies -- everything. As you can see, we didn't have that many. For key question 2, we actually did

have that requirement, that it be a randomized study.

You referred, Noel, to quality. We did not do a quality assessment on these articles. Part of the reason for that is that we knew we couldn't exclude any key questions. We could have perhaps done a quality evaluation, but the studies were really very different. If you are familiar at all with any of the studies, if you looked at the evidence tables, they are so very different that even setting up some quality criteria is actually fairly difficult to do. We spent a fair amount of time internally thinking about that.

DR. BREWER: Indeed. And I appreciate that, having done a number of systematic reviews myself. At some point, you could spend a whole day -- even just coming down with criteria for quality, you could spend two months or three months reviewing the literature on that. I totally appreciate that. But maybe just some sort of acknowledgment or some discussion, for example, of the construct validity of the measures used, the construct validity of the manipulations, the representativeness of the sampling and the statistical conclusion validity -- you have the causality piece covered, but there are three other kinds of validity that are particularly important to address, at least in passing.

DR. WEST: We can't expect you to have looked at

all of the studies that we did evidence tables for or all of the evidence tables. But to address that concern, we did put bottom lines on. In those bottom lines on the evidence tables, that's where we put the limitations of the studies and that sort of thing. But we didn't feel comfortable enough to say, this is a good study or this is a poor study. We felt that limitations were all that we really could do at this point.

DR. BREWER: Sure, and I think that's fair. I just want to encourage you to consider -- and again, given time and resource constraints -- including more explicitly a comment on each of those three kinds of validity that I was not able to extract from the current evidence table. Sometimes that can simply reflect a sample size or a sampling approach. Probably they are all convenience samples.

Let me ask for one piece of data that I would really love to see in the report. I think it would be simple. I would love to know how many of the final studies you reviewed were recommended ad hoc by other sources and how many came from the systematic review. Just a count of that would be really instructive for understanding several things. One is how much the panel caused you to lean in one direction, and then how extensive your review terms ended up allowing you to be.

DR. WEST: Right. I guess what we could do is say how many papers actually turned up in both sources.

DR. BREWER: That would be great.

DR. WEST: And that was part of what we were doing as we were doing our reviews. What we would do is a PubMed search and we would say, were five key articles found in that search? If we didn't find those five key articles, we knew that the search wasn't valuable and we had to go and revamp it.

You can't imagine how difficult this search was. I keep saying that, but I'll take a comparison of drugs in a particular disease for an evidence review any time, not health literacy.

DR. BREWER: I hear you. The appendix that you provided with your search terms is especially instructive and very helpful. I really like the transparency of that. It is very difficult to do these searches.

There's the work by Eggers (phonetic), which suggests that there are problems using a single database for a source, and there's bias in that. That work is a little dated. I think these databases are becoming so complete that in many cases you can get most of what you need from a single source. So I think in some ways your search is -- there are some real strengths to the search approach you took, is what I'm saying.

DR. WEST: I appreciate that.

DR. BREWER: Thank you very much.

DR. PETERS: I think Kala might have a question.

I think at that point we'll stop the questions and go on to the next presentation.

DR. PAUL: Suzanne, thank you for revisiting this. This is still related to the key questions. If you go back to your slide where you present the key question statements -- this may be the source of my confusion -- the statement for key question 1 specifically indicates that only medication interventions were looked at. Key question 2, which is the one that I would have expected to be broader, which was the general presentation of quantitative information anywhere it shows up in risk communication, would have been the one that I would have expected to have gone to the general literature. I wonder if you could revisit those for me in terms of the thought process. You said that key question 1 saw all the general literature.

DR. WEST: That's right.

DR. PAUL: But it states medication interventions.

DR. WEST: Because the focus was to inform medical interventions. But we weren't just focusing on medical interventions. Section 3507 is where these questions were derived from. It was that legislation. We

were trying to inform helping the FDA come up with the risks and benefits -- or how to deal with quantitative information on benefits and risks. That's why I say we had in key question 1 a PCB, polychlorinated biphenyls, as a particular study in here, because it compared numeric to non-numeric information. Anything that had non-numeric to numeric, that kind of a comparison, we included. It could have been screening information. It wasn't just drugs.

DR. PAUL: I'm just looking at the way the question is stated. What you are saying is that your search went beyond the bounds of the question.

DR. WEST: Yes.

DR. PAUL: Okay, that's fine.

The second one: Our concern still remains about all that vast literature that we think is out there. You have already answered --

DR. WEST: But we had to focus it on medications to limit it.

DR. PAUL: Thank you.

DR. PETERS: Thank you very much, Suzanne. If other questions about clarification of the methods come up, we can ask them again perhaps, after Lauren McCormack presents the results of the survey.

I think what the discussion has pointed out is, as with any kind of meta-analysis like this, there are huge

opportunities to make it bigger and there are always some limitations to what can be done. I believe we have a pretty good understanding at this point of how they went about doing this particular meta-analysis.

DR. MCCORMACK: Good morning, everyone. I'm Lauren McCormack, at RTI.

I would like to provide a little bit more information about the expert panel, just to supplement what Sue said. In addition to health literacy expertise, some of the panel members also had areas of expertise in medical decision making, risk communication -- Brian's work at Michigan -- health plan decision making, and Paul Han's work in uncertainty. So in addition, there were those areas covered broadly under the medical decision making kind of rubric. I just wanted to provide that supplemental information.

This first slide talks about a broad-brush overview of the 52 studies that we looked at. Thirty-seven of them focused on prescription drugs, either real drugs or, in some cases, hypothetical drugs in hypothetical situations. The topics, as Sue was alluding to, really were across the board -- in addition to the drugs, decisions about immunizations and other screenings, risk of disease, treatment decisions, environmental health issues. There was one study on fish consumption, for example, and

risks associated with that. Diverse populations, but mostly adults -- there were some studies, as many of you have probably seen, with students, those people who use the Internet -- other studies with those. Jurors, people in public places -- sometimes they were recruited there -- parents were also the populations.

Most of the studies dealt with patient populations and consumer populations, as opposed to clinicians. You recall that in the key questions clinicians are included. But by and large it was focused on patients and consumers.

Another way to characterize the studies, as Sue was alluding to, is that several looked at both numeric and non-numeric information. Not as many looked at both of those in combination. That is an area for potential future research, looking at the combination of both numeric and non-numeric together to see the synergies there. There were a lot of studies that looked at numeric presentation and different ways to manipulate that.

More studies tended to look at risk information only, as opposed to benefit information only or both risks and benefits. Again, another area to look at in future research is the combination of risks and benefits, and the impact on the outcomes. Including both risks and benefits would help with the balanced nature. A lot of people

presume that there is a benefit to medical care and interventions, and are not aware that there might be harms associated with that. For a balanced approach, both harms and benefits -- and I just lost my slides here.

DR. PETERS: Do you want to take a break until we get them back?

(Technical problem with slides)

DR. PETERS: Are there other questions that we could ask in the meantime that might be helpful?

DR. REYNA: One point I was going to raise at some point -- now seems like a good time -- again, with great respect for the arduous nature of these tasks. I very much understand. The review that I wrote in *Psychological Bulletin*, for example, took three years and multiple people. So I understand the effort involved.

I would, however, point out that without assessment of the quality of the methodology of studies, one cannot really reach conclusions. I know you can be descriptive, and the descriptions certainly help. It's a baseline to begin with. But, for example, if you have 10 studies and five of them are pro and five of them are con, but the five pro studies are all bad studies, then 100 percent of the evidence really supports con. I just wanted to underline the crucial nature of methodological quality in just being able to form a conclusion or to reach an

inference about the nature of the research.

DR. MCCORMACK: Thank you. That's an excellent point. We appreciate and totally agree with the need to assess study quality. You'll see when we get my slides back up that we look at the limitations of the some of the studies, including being non-randomized, use of convenient samples, low sample size, low response rates in some cases -- not in every case, but in some of the studies. So it's not to say that we ignored those issues when we were reviewing the studies. As Sue said, we acknowledged some of the limitations in what we call the bottom-line portion of the evidence table for interpretation and considered those, to some degree, in selecting studies. That is our ultimate preference when we do systematic reviews. RTI, being an evidence-based practice center, does those kinds of studies all the time, and we like to do systematic reviews.

The major constraints here were the time we had to do it and, of course, the scope of the funding available. Those were two major constraints, the major one primarily being speed.

We understand the need to do that and didn't completely ignore that in selecting studies.

DR. PETERS: Given what I think is a very good point that Valerie has made and that Noel made earlier, I

wonder to what extent you could use the analysis you have already done about quality and bring that into the report a little bit more, in terms of looking at questions where you couldn't reach any kind of a conclusion. But maybe you can, to Valerie's point. Maybe you can use the evidence that you have already assessed around quality and draw a firmer conclusion. I don't know what the answer to that is, but I suspect that you guys might be able to do that fairly quickly.

DR. MCCORMACK: Yes, I think that's something that we can do. We have the information and the evidence tables already. To some extent, we have factored that into which studies we felt leaned themselves to drawing conclusions. When I have a chance to present, I'll try to touch on that in my remarks.

DR. PETERS: Great. We appreciate that. Mary and then Moshe.

DR. BROWN: I'm just wondering about the plan for incorporating more research. You spoke about constraints. Were you planning on adding more research and going back and reconsidering your conclusions?

DR. MCCORMACK: I don't know the answer to that at this point.

PARTICIPANT: We have asked in the questions for the committee if you have any additional topics or articles

that you feel are important to this topic, and we are going to revise this literature review. Also this literature review is only one part of our response to H.R. 3507. We can take other factors into account, including the recommendations from this committee.

DR. PETERS: Moshe, I wonder if you might be able to hold off on your question, because I think we're ready to go at this point.

DR. ENGELBERG: Yes. No problem.

DR. ZWANZIGER: I just want to issue a quick apology to everybody who is tuned into Adobe Connect. We're having repeated crashes, and then we have to restart it. We're really sorry about this. We'll keep trying to stay connected.

Meanwhile, I guess we are back in business here. Sorry for the delay.

DR. MCCORMACK: No problem. Thank you.

So we had the 52 studies and needed some way to organize them. We developed a framework, sort of a health communication continuum here, beginning with preferences for information format and style. As many of you know, preferences are subject to change and are subjective themselves -- but nonetheless, important to study and look at people's preferences for information. We also looked at a group of studies, the largest being on knowledge and

comprehension. Knowledge is often recognized as being necessary but not necessarily sufficient for behavior change, which is somewhat the ultimate endpoint. We also looked at studies of perceived risks and benefits, of side effects, intended effects, risk of disease, perceived risk being a very important intermediate variable on its way to behavioral intentions and behaviors, which we included. There were not as many studies for perceived risk and behavioral intentions as there were for the other two. I'll give you the specific numbers as I go forward for each of these categories.

For the rest of the presentation, what I'm going to do is walk through each of these four outcome categories. I'll give you some examples and I'll also give you some of the major findings. We'll show you specific studies that enumerate them.

There were various studies in the information format and style preferences comparing numeric and non-numeric, things looking at frequencies, percentages, graphics, absolute risk, relative risk -- lots of different options for what people prefer here. One of the things to be watching out for when you're looking at different ways to format is ordering effects. It's important to try to randomize -- and some of the studies did this; not all the studies did this -- to make sure you randomize in which

order people see the different formats.

It can also cause issues of information overload, something else to be on the lookout for. People will say, "I've seen enough. I'm going to choose the last one, and that's what I prefer." These are some things that we try to be on the lookout for when we are looking to address the points about quality, to the extent that people paid attention to things like order effects and overload in their designs.

There was a general preference for numeric information, particularly among the higher-educated, in our studies. The one I'll look at with you is the Knapp, Raynor, and Berry study in 2004.

This one was looking at two methods of presenting risk information to patients about the side effects of medication. The European Union developed verbal risk scales using five different non-numeric terms. The terms are "very common," "common," "uncommon," "rare," and "very rare." Just think for a moment: If someone told you that it's common that you would have a side effect for a drug, think about what percentage you would put on that for the likelihood that you, as an individual, would get that side effect. This is essentially what this study was about, looking at that issue, as well as the satisfaction with information presented in the words as opposed to the

numbers. So this study is sort of like a twofer. It's looking at preferences, as well as risk perceptions. We have two of these here.

I'll move on here and show you some real examples.

Both individual groups -- that is, the numeric and non-numeric -- received information about this particular drug. These were patients, 120 patients, who were actually taking this drug. So that also raises the question, if they were taking this drug already, what did they know about it? What preconceived information did they bring to the table? I do not believe that was addressed in the study. Nonetheless, patients on this drug -- those in the numeric group had the information that this is a rare side effect of the medicine, and for those in the numeric group, this side effect occurs in 0.04 percent -- that is, 4 in 10,000 people who take this medicine. Both groups received the information at the top: This particular drug is associated with some side effects. It can cause pancreatitis.

By and large, people had a preference for the numeric information. They felt that this was more satisfying for them. I will point out that satisfaction is one of those variables that is subject to ceiling effects sometimes. That's something to keep in mind.

I will also mention that in this study there was a greater negative perception of risk, people overestimating their risk. Among the non-numeric group in particular, 18 percent of those thought that they would get the side effect versus 2 percent of the people with the numeric.

Overall, as I said earlier, people are more satisfied with the information when it contained numeric data.

With respect to preferences overall, there was a pattern across the 17 studies that we looked at. Our little pie chart in the top left-hand corner shows the number of studies that were in this particular outcome category out of the 52. People generally favored numeric presentation of risks and benefits, particularly when compared to simple verbal descriptions like the one I showed you in the example.

With respect to numeracy, a couple of studies looked at numeracy. Not all studies looked at numeracy or health literacy issues. One that did showed that people with lower numeracy had lower trust in the information, which could potentially affect their preferences, as well as other outcomes.

So the bottom-line question is, how do these preferences translate into other outcomes? A nice study

would be to do some multilevel modeling where you could look at preferences and how that moves into some of the other outcomes.

We turn to our next category, knowledge and comprehension. As many of you know, exposure to information does not necessarily translate into knowledge. That's why it's important to look at different formats and different ways of presenting the information, to see which one is more likely to affect this outcome. We looked both at the type of format, and whether that had a positive impact on knowledge in general -- do they gain more knowledge generally -- and we also looked in some studies at the actual accuracy of the knowledge and information that they gained. Some specific studies looked at that. There was one study that looked at framing of the information and whether it was presented -- a survival versus mortality curve, and how that affected knowledge.

The Schwartz et al. 2009 study is the one that I'll be showing you now. This is actually two studies in one. It's two randomized trials by Schwartz, Woloshin, and Welch. This was in the *Annals*, and it was using a drug facts box to communicate drug benefits and harm information. What they did was to create this drug facts box. I'm showing you two slides right here. The first one, as you might have surmised, is about heartburn. You

the same pictures of those burgers, dogs, et cetera, that potentially cause heartburn, the same cover information for both the control group and the treatment group, down below. The difference was in the right-hand panel here on the top. That information about the drug, Amcid, is presented in a narrative, or non-numeric, format. In the drug facts box, it's presented in a more structured fashion, if you will. It includes information. It's looking at a particular drug called PRIDCLO. One of the things that the drug facts box does is, it shows the information that fewer people had a heart attack on this drug. So it actually shows results, which is not something that you see typically in some of the existing drug ads. It's actually, how well did it work? It also includes information about side effects, both symptom side effects and life-threatening side effects.

People were asked a series of knowledge questions. The people who received the quantitative information were more likely to have higher knowledge scores relative to the people who received the narrative information.

There was a question as well: Imagine if you had heartburn. If you could take either of these two drugs for free, which one would you take? They showed Amcid, as well as another drug called Maxdrol. Maxdrol had greater

benefits, but similar side effects. People who received the quantitative information were more likely to pick the correct drug, which is the one that had fewer side effects.

As noted here, the drug facts box was associated with more accurate understanding of the side effects and benefits of the different medications.

So in summary, for knowledge, there were advantages to some of the numeric formats in terms of accuracy of information and knowledge gained. There were some studies that showed some advantage to non-numeric formats that I do want to mention as well. This is particularly when describing relative differences. The non-numeric studies resulted in more accurate knowledge about comparing. If you had drugs A, B, C, D -- a lot of different drugs -- if you had the non-numeric information given, it helped people understand that A is better than B, B is better than C, C is better than D. When there are multiple options, those kinds of findings were advantageous for the non-numeric formats.

One might ask the question, should you include both numeric and non-numeric? There were a few studies that did make that recommendation. It seems that there is some merit to consider that option. You have to counterbalance that with information overload and the potential impact on cognitive load.

There were a few studies that also showed that graphics increased comprehension, possibly because of decreasing cognitive load, possibly freeing up working memory to allow focus on gaining comprehension. There are also studies that showed that visual aids seemed best for helping the low-numeracy group, particularly with gist knowledge.

Perceived risks and benefits is the third category. Most of these studies -- you can see there are 12 of them here -- looked at personal risks and benefits as opposed to public health risk or community-level risk. These are focusing on the individual. Again there's a range of studies looking at the main effects of presentation format on perceived risk, trying to look at how people engage with the information, and trying to explore some of the reasons why non-numeric helps people have more realistic risk perceptions.

The example study is sort of as companion study to the one I showed you earlier. As opposed to looking at patients, this study by Berry et al. looked at the public. One of the things they were worried about was whether it was just in patients they would find the results that they found, so they wanted to replicate the study with an over-the-counter drug and looking at patients. They had 188 volunteers, recruited in public places. I think we're

aware of some of the limitations of convenient samples. They did randomize the people into four experimental conditions after they recruited their sample. They also looked at what someone should do if they have the side effect. Should you seek help immediately or as soon as possible? Those were the two different recommendations for what to do. They looked at that as well.

This was for a stiff neck, the condition. The non-numeric group had higher perceptions of risk compared to the numeric group. Here is the information that they saw, which was in a leaflet: This effect is common in people who take these tablets. "Common" is the word there. Numeric: This effect occurs in 6 percent of people -- that is, 6 in every 100 -- who take these tablets.

In addition to higher risk perceptions among the group on the right, they were also less likely to take the medication, however you want to interpret that.

Patients here are more likely to perceive greater likely side effects, more risks to health, and greater side effect severity as well.

In summary, for these 12 studies, format did affect assessments of personal risk, with the non-numeric having more extreme risk perceptions -- in some cases, gross overestimates of their actual level of risk. It could be that the numeric presentation allowed increased

precision.

Also I'll briefly mention that some studies looked at presenting absolute numbers -- 48 out of 100. People tended to have more accurate risk perceptions when presented like that, as opposed to in a frequency band, with something like 1 in 10, where they had to do the math, the 2 in 20, et cetera.

Those with higher numeracy were less likely to have skewed risk perception -- once again, numeracy showing that it is an important moderator.

The last category is behavior and behavioral intentions -- again, a range of studies that were looked at here. The outcomes specifically were taking medications, participating in a trial, in a few studies, and then also looking at measures of informed decision making. An example there is feeling informed. Some of the work to operationalize what informed decision making means, some work by Mullen and colleagues in the cancer research -- he has looked at some different measures -- we considered those as well. I'll show you a study in a moment that looks at feeling informed.

This one is by Man-Son-Hing, Annette O'Connor, and colleagues, looking at "The effect of qualitative versus quantitative presentation of probability estimates on patient decision making: a randomized trial." When we

saw this study, this was sort of easier, at first glance, to say this was going to fit in the inclusion criteria, because it really had a lot of what we were looking for in terms of the comparators and the randomized trial element to it. This focused on stroke prevention. I will show you how they presented the information here.

They looked at different drug choices for stroke prevention, as well as no medication as being an option, aspirin and warfarin, another. As you can see here, the probability of stroke risk when you use the non-numeric information -- moderate, low, and then, with aspirin, between moderate and low. They also used pictographs to show the probability of stroke risk and side effects, which is severe bleeding, presenting that with numeric information.

They divided up their participants into low- and moderate-risk participants. Those moderate-risk participants were more likely to make an actual choice at the extremes. What that means is either no medication or warfarin, fewer people choosing aspirin. Their main outcome related to informed decision making was whether people reported feeling informed. They used the decisional conflict scale by Annette O'Connor and colleagues. Only the subscale on informed showed a difference for those who got the numeric information. None of the other subscales

on the decisional conflict outcome were significant in the study.

In summary, when we looked at the 14 studies in the behavioral intentions and behavior area, we were not able to draw conclusions about patterns. There was not a consistent pattern that we saw emerging in this body of evidence that we looked at. So we do not offer a conclusion here, as opposed to the other areas. The numeric format prompted some decisions in studies, possibly because of reduced uncertainty associated with precision, with the information.

There was a paucity of studies with behavioral outcomes, just to note.

To summarize the four areas and our overall observations and conclusions, the numeric information had a positive on various outcomes. These tended to be at the left-hand side of the continuum, with less focus on behavior and behavioral intentions. What that suggests is the need for more longitudinal studies, in which more time can be allowed so you can actually look at people's behaviors over time. This impact of numeric information, and providing it, is consistent with some work done by the IPDAS group, which is the International Patient Decision Aids Standards group, which recommends presentation of quantitative information.

These slides summarize the results here. We were able to draw some conclusions and observations that numeric had some advantages over non-numeric, particularly with respect to descriptive labels, as shown here, less ability to say anything with certainty about whether probabilities are better than frequencies, frequencies are better than percentages -- not able to offer that kind of conclusion at this time, nor would we be able to say whether there were visuals that were better than others in terms of those choices. So there is some more work to be done, because no format structure or graphical approach emerged as superior. There was a range of quality, as we have noted, throughout the studies and study outcomes used.

There were a couple of studies on intervention framing and looking at the impact of that and some recommendations in the literature about the pros and cons of using framing. So that's another important consideration.

I think I have mentioned several times the studies that looked at numeracy and some of the varied effects and moderating effects that variable places on what we looked at.

The limitations, in addition to the ones that I alluded to earlier in terms of study design -- some of them are listed here. One of the things that was very absent

was any theoretical foundation for many of the studies. These are nicely designed experiments, cognitive psychology, social psychology, experimental psychology. They are great for looking at that, things done in the labs, small samples. But the theory wasn't there. I think there is a lot that can be done to advance the state of the science with a theoretical foundation.

DR. PETERS: We are actually at a decision point ourselves here. It actually is just past time for our break. We can either take a few clarifying questions that people are burning to ask --

PARTICIPANT: Is she done?

DR. PETERS: I just assumed you were.

DR. MCCORMACK: I'm pretty much there. I think I've covered everything. I'm fine.

**Agenda Item: Committee Questions and Discussion,
Session I**

DR. PETERS: Thank you very much for the excellent presentation and also for the excellent review that you guys did. I think there's a tremendous amount of work that was done, and very quickly, I know, having been a small part very early on in your process. So I appreciate that first, in terms of just doing that.

At this point, my question becomes relevant. Do we want to have Lauren stay up there for a moment while we

ask a few clarifying questions that people are burning to ask? I'm seeing some yeses. Why don't we go ahead and ask some clarifying questions at the moment? We're going to take a break fairly soon. We can always continue with more clarifying questions afterwards.

Nan and then Craig and then Vicki.

DR. COL: Thank you. I was just struck by one of the conclusions here. I guess the broader question is, given the paucity of data, it must have been very difficult to come to any conclusion. But one of them was that non-numeric leads to more extreme risk perception. I was actually dumbfounded by looking at the -- this is how the non-numeric translation of numeric -- which is actually the descriptors of numbers that are used. There's one example where you say 6 percent is translated into a "common" side effect, in one example you cited. In another one it said 10 percent is translated into "rarely" experiencing a side effect.

If 6 percent is common, how is, in another study, 10 percent rare? It seems perhaps that this conclusion that non-numeric leads to more extreme risk perception is that the use of non-numeric labels introduces a huge opportunity for the investigator to introduce bias by assigning labels such as "rare," "common," "uncommon," and that that conclusion may not be driven by the data, but may

be driven by what appears to be an arbitrary -- and I, in fact, do mean the term "arbitrary" -- use of labels. Actually, it may not be arbitrary; it may be intentionally biased, where they are trying to downplay the risks in one case and exaggerate -- but this could be driven by labels. I don't know -- is there any data on how these labels are derived? It seems that that conclusion is dependent on that.

DR. MCCORMACK: Those labels were recommended by the European Union. They defined "very common" as more than 10 percent, "common" as 1 to 10 percent, "uncommon" as less than 1 percent, and then "rare" and "very rare" go down from there. That's what the EU recommended, and investigators over there in the UK were looking at.

DR. COL: I guess I'm pointing out that there is inconsistency, because 6 percent is called common and then 10 percent is called rare. So it actually seems to be a directional problem within these studies, so they are not adhered to. Maybe that's a quality indicator we should be looking at.

DR. MCCORMACK: Yes, 6 percent is common, and that falls between 1 and 10 percent. The other one was below 1 percent, and that was rare.

DR. COL: But here it says 10 percent of women reported nausea, and the verbal description is, women

rarely experienced nausea. A couple of slides later, on your slide entitled "Observations and Conclusions," 10 percent translates to rarely.

DR. WEST: There isn't a translation there. These are just examples. We gave a probability of .2. We gave 10 percent of women experiencing nausea. That was just an example. Then for a descriptive, that was another example -- "women rarely." We could have said "women often." It's not supposed to be a direct translation there. They are just examples.

DR. PETERS: If I could ask just a follow-up question, my understanding is, from the studies, that when the studies were done, of the ones that you cited, I believe they were all using the European Union labels, and so there was consistency across the studies, not necessarily in the example slide that was given. I believe that's correct.

You guys really don't want a break. We have Craig, Vicki, Gavin, Valerie, Bill, and Shonna.

DR. ANDREWS: Thanks, Lauren. I just recall things from the past -- this is from the Federal Trade Commission, when we were analyzing different advertising, as well as disclosures. A lot of studies will excise things to show them to different consumers or various samples. I was going to ask you about the realism factor

in information overload. This is critical, I believe, when you talk about brief summary information, fast-paced commercials. Did you look at that as a factor -- in other words, studies that would look at that as far as placing it into the real context, where there is a lot of information overload? These things may work, they may work great, but when you add all the information, then the conclusion is that maybe that's not going to work out.

I remember a few years ago there were issues about, disclosures don't work, warnings don't work. In fact, you have loaded up everything in there to make it certain that it's not going to work.

Anyway, that's not an important question.

DR. MCCORMACK: So are you alluding to the fact that there could be publication bias, lack of detail in amount of information presented in studies -- omitted -- that you can't get a complete picture?

DR. ANDREWS: Earlier Noel was talking about validity issues. This is more external validity, generalizability. In the context that they will actually appear -- in other words, if they are swamped by all sorts of information that usually is included in these brief summaries, what effect would that have? Again, if you excise this out and show this in a small experiment, yes, you might find that. But in the context of realism and the

actual print summary or in a commercial, that might be very different. I was just wondering if some of the studies would tease that out. Or did you find that in any of the studies?

DR. MCCORMACK: I think very few of the studies teased out the effect of the specific information in the larger context of the information that people would get, which is a hard thing to measure, number one. It would be great to be able to do that, to present a more realistic scenario, and to be able to have greater external validity for some of the studies. I think your point is well-taken. Very few of the studies, if any, looked at prescription drug ads, actual television -- a limited number, if any. Many of these things looked at decision aids and manipulations of information -- again, small studies, experimental design. There is more research to be done, I think.

DR. ANDREWS: A quick follow-up: Did any also incorporate multiple studies at all, rather than just showing the results of a single study? In other words, here are the results of this clinical trial, rather than multiple trials.

DR. MCCORMACK: Meta-analyses, for example.

DR. ANDREWS: And sharing those numerical results.

DR. MCCORMACK: These are 52 individual studies as opposed to -- so I agree.

DR. PETERS: I actually would like to add to that. There have been at least a few studies done by Schwartz and Woloshin where they have done it, not in a TV ad, but they have done it within the context of print advertising. Some of this has been done in a more realistic context. There certainly have been studies looking at the very important point you bring up -- and I believe Noel might have brought it up earlier -- on cognitive overload and this idea that less can be more.

DR. ANDREWS: I think Lou Morris had done a number of studies as well, going back.

DR. PETERS: Yes.

I am actually going to take an executive decision here. We have a number of questions still outstanding. I have the list of people who have those questions. But at this point let's go ahead and break. We're going to break for 15 minutes.

Before we break, Lee has something to say.

DR. ZWANZIGER: Thank you, Dr. Peters.

I'm going to ask people to do something that I know is hard. Please don't pursue your clarifying questions during the break. Wait until we can do it in the transcript so everybody gets to benefit. Thank you.

(Brief recess)

DR. PETERS: If I could take one moment, we have had one additional member join us, Dr. Michael Wolf. I wonder, Michael, if you might like to introduce yourself.

DR. WOLF: Sure. Michael Wolf. I'm an associate professor of medicine, associate division chief at Northwestern University. I also direct the health literacy and learning program, linking our School of Education and School of Medicine.

DR. PETERS: Thank you very much. I appreciate that.

At this point, where we're asking some clarifying questions around the presentations that were given by the RTI folks on their very interesting review.

At some point -- we do need to keep track of time, to some extent -- we do need to also roll up our sleeves and get to the questions that CDER, the Center for Drug Evaluation and Research, has posed to us. They go beyond this literature review. It has to do more with the complexity of information that FDA has to face.

But for now, why don't we go ahead and continue with some clarifying questions. I believe, Vicki, you might have been next.

DR. FREIMUTH: Thank you. My question relates to Nan's earlier question. When I saw the 6 percent being

equivalent to "common" -- and I heard that these are terms that have been defined. But I do wonder if there has been audience research done behind those terms to see what perceptions are of this language. It really was just intuitively surprising to me that 6 percent was considered common.

Does anyone know that, whether these European Union terms of equivalencies, percentages, language have actually been subjected to any testing?

DR. REYNA: That was exactly the nature of the comment I was going to make. There's a whole corpus of research on how probability terms are interpreted. People such as David Budescu and Thomas Wallsten and a host of other people have done research reviews on that. To make a very short summary of that research, the interpretations are variable, as you might expect.

There are also some recommendations from that literature. I was looking that up once I got server connection here. For example, there is a recent -- Budescu, Broomell, and Por, "Improving communication of uncertainty in the reports of the Intergovernmental Panel on Climate Change." So some of this usage has been applied in settings. I know that some of the recommendations -- I'm not sure if the European Union recommendations are directly based on this research, but I know that other

recommendations for risk communication and probability term communication have been based on this research. And it's highly rigorous research.

DR. MCCORMACK: Just to add to that, in response to your question, Vicki, we completely agree with the need for pretesting interventions, in addition to pretesting surveys before they are fielded, because of the open interpretation of questions when people see certain terms that might mean one thing to one person and one thing to another person. I think, in part, that's what motivated the researchers to do this study, because they saw these labels -- I'm speculating -- and wanted to know how people interpreted the labels, and therefore that's why they did this research.

DR. PETERS: Gavin.

DR. HUNTLEY-FENNER: I have a couple of questions, one relating to gaps in the literature and the other relating to the theory point.

What I think I've heard is that you found that there were gaps in numeric studies, looking at both numeric and non-numeric studies. Second would be studies looking at both the risks and benefits. The third group was studies looking at behavioral outcomes. I wanted to know if that's correct and whether there are any additional gaps in the literature that you have identified.

The second thing is, I know you had to sort of cull your materials pretty significantly. I was wondering if you went back and looked through things you got rid of to see whether the gaps were artifacts related to the culling process or whether these are really, truly missing -- gaps in the research.

DR. MCCORMACK: Your first question about the types of gaps -- you are correct. There are some gaps particularly with behavior and behavioral intentions, because those are harder to study. They are at the end of the continuum, so fewer studies there. You are also correct in that there were fewer studies that we found with respect to presenting both risks and benefits, more studies presenting risks alone. One could infer that that is not a balanced presentation of the information. So limits and gaps in our review for those particular areas. There could be other studies out there that look at those things. Again, if they did not meet the exclusion and inclusion criteria that we set up, then we couldn't include them.

Just to reiterate, we had more exclusion criteria for key question 2 as opposed to key question 1. For key question 2, we limited it to drug studies, only those in the US and New Zealand, and only included randomized designs, whereas key question 1 was more open and inclusive. There was even one study in there with focus

groups, both qualitative and quantitative.

Hopefully I have answered that question.

Did we go back, was your other question, to look at the studies that we excluded? No.

DR. HUNTLEY-FENNER: I just wanted to get your sense of whether you thought these were artifacts or you think that they are really gaps in the literature. It sounds like you think they are really gaps in the literature.

The second question had to do with the theoretical foundation issue. There are some areas of research where this is a pretty significant problem. In every case there is usually some kind of implicit theory that the majority of the field is operating under. I was wondering if you have a sense of that. What is the implicit theory at work that would give rise to the kinds of studies that you have observed?

DR. MCCORMACK: There are a number of theories out there that one could think about that are important for designing a study, for developing your intervention, for choosing which outcomes to look at. That answer could take probably a long time, and I think it would be a really fun day to spend thinking about designing a study from different fields -- psychology, health communication fields. We could spend the day together.

Some of the studies that tended to look more at the behavioral intentions included things -- self-efficacy, which is common in some of the theories. I would think that that would be one variable, that if we want to get to that endpoint on the continuum, to behavior, we would also want to look at the self-efficacy, confidence in being able to make decisions related to drugs and which drug to take.

I'll just give you an example of a variable, as opposed to choosing a particular theory, so I don't miss a particular one or choose the wrong theory. There are so many out there that could inform study design.

DR. HUNTLEY-FENNER: I understand. I guess we'll have to discuss that later.

I think one of the interesting things that I'm observing is that when you see gaps in the literature, they usually reflect some underlying understanding of the way the behavioral process works. It could be that there is an expectation that behavioral outcomes are directly related to these precursors. Really, if you understand the factors that contribute to risk perception or attitude change, then you pretty much capture the primary drivers of behavioral change and maybe identify a ceiling in terms of what can be expected out of behavioral change. That theory may or may not be correct, but I guess that would account for why you wouldn't necessarily want to invest in looking at

behavioral change in detail.

DR. MCCORMACK: The other gap that I'll mention, since your question hit on that, is that, although we looked at 37 studies on prescription drugs, most of the studies were not on drug advertising. Thinking about external validity and transferring the information from that body of literature to drug advertising is something that needs attention and thought, to think which of these study findings can transfer. There was one study looking at prescription drugs, but it looked at the composition of the information in the ad, which tended to focus more on providing risk at the expense of benefit. Benefit information was either absent or very small, detailed information. That didn't make the cut, because it didn't have any outcomes in the study. It just looked at the prescription drug ad and its composition.

There are things to be learned from those as well.

DR. PETERS: Thank you, Lauren, also for being sensitive to our time here today. While we do need to ask these questions of clarification -- it's very important for the committee to know that -- we also do need to get on to some questions that CDER has posed.

I do want to add, though, that in our session tomorrow morning we will actually be talking about some of

these theoretical issues. Dr. Reyna will present some about her fuzzy-trace theory, which can be considered one of the core foundational theories within judgment and decision making, and in particular in this area. So tomorrow, I think, we're going to hit more on that question. I'm looking forward to that session tomorrow.

I did want to mention, as long as we're talking about gaps, a gap that I at least saw in the literature review. It had to do with who uses the most prescription drugs. It's not 20-year-olds. It's older adults. It's people who are 65 and older who, at least on a per-capita basis, are the primary users of prescription drugs. It seems to me as if a consideration of aging was a limitation of this review and probably of the studies themselves. In particular, I would think that less numerate older adults are a group that has not been considered here and are a very important group to consider.

Again, we're just on questions of clarification at this point. At this point we are going to get some more questions for clarification from Valerie, Bill, Shonna, and then Sokoya.

DR. REYNA: Actually, it's a very nice segue to the most recent comment. On pages 11 and 12 of the literature review you do discuss theory and you discuss Marty Fishbein's theory of reasoned action, and also theory

of planned behavior is implicitly referenced here. I should say that, on the one hand, I think that these expected-value class of theories -- and this is one of a class of theories -- that mention things like self-efficacy and so on have a great deal of empirical support. There is a more recent update that Marty Fishbein contributed in 2008 to a special issue of *Medical Decision Making* that I think is on point. But I should say that the claim that they are sufficient is one that I know that Marty -- may he rest in peace -- certainly made -- he thought the job was done and all we needed to do was implement. But I think there's a good empirical argument for the job not being done by those theories -- namely, that they account for a significant portion of the variance, but nowhere near 100 percent of the variance. There have been theoretical developments since the theory of reasoned action and since the theory of planned behavior, both theories that emphasize affect, as well as theories that emphasize mental representations and so on.

So I think the claim that this is sufficient certainly was made by the adherents, but unless you're accounting for 100 percent of the variance -- if you're talking about 30 percent of the variance, it's not completely sufficient to explain behavior.

DR. PETERS: If we could go on with Bill, Shonna,

Sokoya, and then Nan.

DR. HALLMAN: I have actually two short questions, with perhaps long answers.

Most of the information that you presented here today has to do with descriptions of likelihood. I'm wondering about the interaction between likelihood and the severity of the side effect that likelihood is the subject of. What do the studies suggest about that?

DR. MCCORMACK: There was one study that looked at increased risk perceptions, both the probability of risk being higher with non-numeric information and also the severity. At least that one study looked at that.

DR. HALLMAN: Which you noted here, but only probability information was given and a conclusion on the part of the consumer about severity was reached.

DR. MCCORMACK: Yes. We didn't show all that information in the visual. We just showed you the one example of how they were presenting the probability. But in the back of our report, there are evidence tables which provide additional information about what was in the interventions that might have that.

DR. HALLMAN: I guess I would suggest that one of the gaps in the literature is looking at this interaction between perceived likelihood and severity. I'm struck by some of the television advertisements that verbally

quantify a rare but serious side effect of whatever the drug is.

The other one is about the total number of side effects and what people conclude from that. They have to do a kind of joint probability in their heads. If you're really just getting the gist of this, if there are nine possible side effects, are you more likely to decide that you are susceptible to at least one of those, even if they are jointly very, very small? What does the literature say?

DR. MCCORMACK: We did not look at that specifically. I do recall one study that elected to focus on the top couple of side effects, even though there might have been nine or 10 potential. They were considering issues of information overload. So that's the way they strategized.

DR. HALLMAN: Thank you.

DR. PETERS: Shonna.

DR. YIN: I recognize that this literature review took a lot of work. I want to applaud that.

I want to go back to some of the comments other people have made about the gaps in the literature and the need to go back and try to add additional literature to this review, especially since it's hard for us to draw conclusions, especially around key question 2, about what

type of format is the best way to present the information. I was wondering specifically about these excluded papers. You said there were 55 that were excluded because they were not done in the US or New Zealand and they didn't involve medication use, et cetera. I was wondering in terms of the breakdown of the number of articles that were excluded because of medication use versus the fact of location, versus the strength of the study, if it was randomized or not. I wonder if it's possible to go back, if it's feasible to go back and look at those 55 and then see where things fall at that point in terms of the conclusions that can be drawn.

DR. WEST: Actually, we do have that information. Of the 55, 31 were not drug, 7 were not randomized, and 17 were not US or New Zealand. There were quite a few studies from Germany, as I remember, and maybe the Netherlands that we did not include. That's why the number is 17.

DR. PETERS: Sokoya, Nan, and then Noel.

MS. FINCH: My question is around your relevant variables, health literacy. I was just wondering, did any of your studies or your health literacy review include the literacy levels, as well as touching upon the cultural diversity of America, the patients and the general public that will be accessing this information? I wanted to know, if so, what type of impact did you see through the studies

on behavior change as it relates to patient decision making around the advertisement and how that information may change their behaviors?

DR. MCCORMACK: To your first question on health literacy, there were studies that looked at health literacy. More tended to look at numeracy specifically. Those who looked at health literacy used the TOFA (phonetic) or the REALM, in some cases, to operationalize health literacy.

With respect to attention on cultural diversity, because many of the studies had samples of around 200 -- they did power calculations and estimated that that was about what they needed to get their study -- lab studies, studies done in clinics, studies done at the mall, convenience samples. There was one that was an RDD randomized, controlled trial that did more systematic sampling. My point is that there were not a lot of subgroup analyses who included use of culture.

MS. FINCH: So would you say that's a gap?

DR. MCCORMACK: I think that's fair to say, yes.

MS. FINCH: Do you think that as you continue on, you can look at closing the gap?

DR. MCCORMACK: I think that the body of evidence that exists out there -- more studies could be done on that because of the gap. That's a consideration for researchers

abroad, to think about including that in their studies.

MS. FINCH: Just one more comment to that. Right now this nation is over 60 percent minority as the majority. We have all been looking at trying to incorporate the second language, which is Spanish, as being culturally sensitive as it relates to information and so on. Other companies or other federal agencies, like the women's health, the National Office of Minority Health, have been looking at translation of other materials in other cultures, in other languages to be able to accommodate that set of individuals. But my concern is, as we look at H.R. 3507, that it's inclusive of the population and the needs, and that the research and the lit review does a fair reflection of the majority, so that H.R. 3507 will be successful in all ways that they are able to be.

DR. PETERS: Thank you, Sokoya. I think those are some very important points that you are bringing up.

At this point, let's go to Nan, Noel, Moshe. Then at that point we're going to transition and start to talk about some of the questions that CDER has posed, because it's what we have to roll our sleeves up on, rather than just putting RTI on the spot. So Nan, at this point.

DR. COL: I have a short comment and then a longer gap.

The first one is on your conclusion about numeric

being preferable to non-numeric. I think it might be helpful if you distinguish non-numeric into the descriptive terms versus the graphical. I think that the conclusion that you are referring that's supported is that the numeric trumps words like "common" or "rare." I may be mistaken, but I don't think you are intending to say that numeric trumps graphical. If you intend to say both, maybe you could just tease that out in the conclusions. I was a little confused.

But I want to talk about gaps, following up on Bill's excellent comment about severity. The other thing that I'm missing here is the denominator in most of the literature. I'm wearing my risk modeling hat here. All the examples are, a 10 percent change of this, a 20 percent chance of this. It's over what timeframe? Is it a chance of nausea? When is the onset? What is the timeframe of the onset? What is the timeframe of the duration? If patients are going to make informed decisions about the risks and benefits, they need to understand the complexities of timing. This dimension -- for instance, we talk about a five-year risk of breast cancer. What about a 10-year risk, 20-year risk? These are risks that change over time. The function of the risk is not always linear. They are often increased, decreased, exponential at certain times. It's critical, if patients are going to make

informed decisions, that they understand the timing.

I haven't seen that in the risk literature. I'm not sure if you encountered that, but it seems to me an important gap.

DR. MCCORMACK: Excellent comment. I'll take the last one first. Several studies presented information differently, with different timeframes -- five-year survival risk, two-year probabilities of X, Y, Z. There were some studies that considered that. The Woloshin one that I presented using the Cochrane Collaboration data, real data on two-year risk probabilities for what they presented. To make a fully informed decision, yes, that would be helpful for people to know, the context and the timeframe.

Your first question had to do with whether we were able to tease out a conclusion with respect to visual information. I think this slide may get at that question. Our focus was on drawing conclusions with respect to descriptive labels versus visuals and the comparison between --

DR. COL: It was more just how your conclusion was worded. I think the implication -- since that's going to be the take-home message that a lot of people will only read -- when people hear non-numeric, I think most people will think graphical or visual. I think what you actually

intended -- I think -- was the descriptive words, that numbers were better. I think just being more explicit about that in your language would help.

DR. MCCORMACK: There was a lot of attention on what we meant by numeric versus non-numeric amongst the team and with our FDA colleagues to make sure we were all on the same page about these labels. We can double-check to make sure, if it's not clear here or in our slides, that it is clear in the report heretofore.

DR. PETERS: I think actually your previous slide gets at Nan's question. The previous slide is specific to what Nan asked. You compared numeric to descriptive labels. In your next slide you look at a slightly different question. I believe this is what Nan is asking about.

I think it is, and I think it's a really important question. I have to admit, personally, I would not have thought about the visuals that they talk about as being non-numeric, because there are numbers embedded in them. I personally found -- and it sounds like there is some agreement here -- that calling these kinds of visuals non-numeric isn't really quite right, because there are numbers in them. I think what you really studied is the impact of what most people would agree was numeric information, whether it's probabilities, frequencies, and

percentages -- you compared those to the descriptive labels -- for example, the European Union's, that's one. I think that's what the conclusion was that they were drawing, that numbers are preferable to non-numbers, meaning the verbal labels.

Then I think your second question was comparing what I would call two different sources of numeric information, looking at numbers, what you have on the left there, compared to visuals. There you didn't draw a conclusion, I believe.

DR. MCCORMACK: That's correct.

DR. COL: But, Ellen, some visuals don't include numbers. Some of the pictographs -- you would have to actually count up the -- some of them, when they have them randomly dispersed -- some of them are visual and don't have numbers, and some of them are visual that actually have numbers in them. So I think that even within the visual, there are differences. It's worth understanding whether adding the number there -- how that affects the interpretation.

DR. PETERS: I would claim that from the visuals, you get a sense or a gist, in Valerie's words, of what the magnitude of the differences is, what the magnitude of a number is. But maybe your question, then, is, do precise numbers on top of those visuals make a difference? Is that

the question?

DR. COL: Some people actually combine the two and they actually have the pie chart with the number embedded. It's hard to tease out whether they are looking at the number or the pie chart. They often are combined.

DR. PETERS: Do you guys know anything from your review about Nan's question?

DR. MCCORMACK: I agree that some of the visuals do embed numbers in them. One of my early comments -- I hope I remembered to mention this -- was that few studies looked at the combined effect of both having the numbers and some qualitative information. That is a gap. Few studies out of the 52 looked at that combination. That would be an area ripe for future research.

DR. PETERS: Thank you.

Noel and then Moshe.

DR. BREWER: I have a different comment, but just to follow up on this, I think it's worth considering omitting the non-numeric box from the narrative and also from this picture. It doesn't seem to offer anything conceptually, and it doesn't cut at the joints of how you have done your analysis. Essentially you are comparing numeric, descriptive, and visual. Those are meaningful categories. "Non-numeric" does not seem to be a conceptually meaningful category.

It's something for you to discuss. I think we have already discussed it at length.

But my main point -- and then I have a couple of smaller things related to that -- is that you comment somewhere near the end that there's a need for more theoretical work in this area, that these are largely atheoretical studies. It's a bit of a glass-house problem here. The report is not so theoretical either. I think you know that. I think it's fair that you have counted things up and you have done work within a very constrained situation -- and I think done high-quality work. But at the same time, I think it's worth thinking about what the opportunities are. For example, is there an opportunity for your organization or for people outside of the organization to take what you have learned and do a higher-level synthesis that starts pointing out some of the conceptual strengths and weaknesses of these approaches or laying out three or four conceptual approaches that would bring you toward understanding some more general principles that might be at hand here?

Let me just throw out a couple that come to mind. This is a way of picking off a couple of other points without having to go into all of them in detail.

One of them Valerie raised, which is this distinction between how people understand a number versus

understand a verbal phrase. There just isn't correspondence. One of you alluded to that in your presentation. But the lack of correspondence between the two starts to suggest that perhaps you need to have both of them.

A second, related point is that accuracy does not reflect deeper understanding. If you give people a number and then test people using numbers as a test of accuracy, of course they'll do better, but it's a shallow test. It's also, in many ways, a shallow way of analyzing the problem. Trying to get at what the meaning is that people carry is really, really hard. It's sort of a fundamental problem in this area. It would be nice to see more of that considered in some way.

Let me throw out a final consideration, again a conceptual distinction to make, which is these between-subject studies and within-subject studies. If a person sees only one risk format and then considers that risk format for giving responses, they may have one response toward it or one ability to understand it. That's different than if they see three or four or five or 10 different formats. The way they think about those formats, the way they respond to them may be fundamentally different. Chris Hsee, H-s-e-e, has done some work on evaluability that lays some of the conceptual foundations

for how one could think about the difference between these between and within designs. Those are some of the conceptual distinctions that may not go into full-blown theory in the sense of, say, some of these grand theories that you all had in your introduction that Valerie also referred to, but some of the conceptual distinctions, I think, could be really important and would inform your literature review, although they aren't necessarily the crux of the data that you're talking about.

DR. MCCORMACK: Noel, thank you for those great points. The short answer is that, yes, there is a lot that could be done as a next step to this. We hope we have achieved what we were contracted to do, which was to review a certain number of studies, to set the foundation and create ideas for going forward for future research and identifying some of those gaps. You might hear a lot about gaps, but what that means is that there's a lot more multidisciplinary work that can be done. Hopefully we have created a foundation, a jumping-off point, for where to go from here.

DR. PETERS: I think that's terrific. I did want to just reemphasize the two points that I heard Noel saying. This idea that meaning is critical -- it's not just about understanding of a specific, precise number necessarily; it's also understanding the meaning of that

number. That's something that Valerie is going to go into a bit tomorrow as well, and as well, another guest speaker, Brian Zikmund-Fisher.

Second, I thought the other point that Noel made actually was important, this idea of joint versus separate evaluation that comes out of Christopher Hsee's work. In part, it's important, perhaps, for the review because I wasn't sure all the time in the studies that you were presenting whether there was a comparison number, so that there was a joint evaluation possible, or whether it was a separate evaluation, so they had just a single number to review. That might be a point to bring out in the review. I think that's actually a very important theoretical distinction, but also a practical, pragmatic, important distinction.

Valerie, I think you had one more thing to say. Then we're going to go to Moshe and transition. I think Moshe is actually going to help us to transition.

DR. REYNA: Excellent. On pages 10 through 11, I just wanted to raise some questions about the definition of decision making as a volitional process, as a conscious, volitional, multistep, deliberative process. I think there's probably a lot of research now showing that decision making is mainly not that. I think it's something that maybe we thought it once was, and certainly is a view,

a philosophical view, that has been very influential. But recent research questions that. I would want to maybe talk with you about how to amend that in some way.

DR. PETERS: Thank you, Vale.

Moshe, please.

DR. ENGELBERG: Two questions, one a quick gap question. It seems that all the studies reviewed were what I would call effects studies. I wonder if there's anything in the literature about the precursors to comprehension, knowledge, and so on, and that is exposure, selective exposure and attention. Will the presence of numbers versus words versus pictures differentially get people to tune in and look further, so that knowledge, comprehension, and so on can happen?

DR. MCCORMACK: The precursor of exposure -- because many of these studies were kind of forced exposure in laboratory settings, people either could look at them or get up and leave. That was less often manipulated because it was part of the experimental design -- so less that we're able to say with respect to that, although I acknowledge that exposure -- its duration, for example -- would be an important variable also to control for.

DR. ENGELBERG: The reason I bring that up is that it seems like different forms of information can have a very different impact on getting people to pick up

something and look at it, so it changes what the dependent variables are.

I have a second question that is not for you so much, but as a newbie here. What keeps going through my mind is what we're aiming to do with this exercise. What I mean by that is, what's our bottom-line purpose? Is it to review and critique the study that's done, so that, even though it's finished, it can be improved or written up differently? Is it just to critique and talk and make suggestions? I'm not sure, fundamentally, what we're aiming for with this particular exercise. I do understand what Dr. Abrams set as context with the ACA bill, and I understand our general purpose in being a panel. But I'm not sure what we are fundamentally doing with this kind of exercise.

DR. PETERS: I think it's a great question, and I'm really glad that, as a new member, you felt comfortable enough also to bring up the question. We have three new members -- I guess I'm the fourth new member -- on the committee today. We also have a couple of visitors as well.

In general, critiquing the study is what we have been doing. We have been looking at just clarifying questions. I think that's very important, because we have to understand the evidence basis by which, ultimately, we

hopefully are going to be able to give some advice or at least some pointers for FDA to consider while they start to make some really important regulatory decisions.

Critiquing the study and understanding it better is what we've been doing.

The next thing we need to turn to -- and we really have to turn to this now -- is the questions that have been brought up by CDER for us that go beyond this literature review, that are very specifically not answered in the literature review.

The third thing I would say that we do, because we're allowed to, is provide general advice on these issues in general. As we start to consider the questions that are posed to us -- and if everybody could start to think about getting out those questions at this point, and what comments you might have -- as we start to consider those questions, we might also want to think more broadly -- and I think this committee is very good at thinking broadly -- about what kind of advice we would give to FDA that perhaps even goes beyond their questions, if we want to.

Does anybody else want to add to that?

(No response)

At this point, what I would like to do is turn to the questions that CDER presented to us. I want to point out something that they actually pointed out at the top of

the questions. What we're discussing today has to do with promotional labeling and print advertising specifically. It doesn't have to do with patient medication information that's being discussed and considered and worked on within FDA. That's separate from this conversation. They are actively addressing those issues, but that's going to fall outside the scope of this meeting. What we're thinking about is promotional labeling and print advertising.

I actually don't know what the usual procedure is within this committee. I assume you guys have read the questions and considered them. I can go ahead and read the questions into the record. I'm not sure if that's something that we do.

DR. ZWANZIGER: Sometimes we do, sometimes we don't.

DR. PETERS: Why don't I at least read the first question? I think it's actually an important piece of this.

Many relevant studies, like the ones that we have seen in this literature review, are designed to test simple examples, whereas FDA faces a more complex world. For example, a study might test the effectiveness of pictographs by communicating information about one side effect, whereas a real-life drug may have 10 side effects. Given this discrepancy, what gaps, if any, exist in the

literature that need to be addressed before we can determine whether a standardized format, such as a table or drug facts box, and what kind of standardized format is appropriate within the context that we're considering, and that's the promotional labeling or print advertising.

Of course, what ultimately we're trying to do is to improve health-care decision making by clinicians, patients, and consumers.

Craig?

DR. ANDREWS: I was just wondering if we could put them up. If everybody has them -- I don't know if the audience does.

DR. PETERS: That's actually a very good suggestion. Let's see if we can do that.

Noel?

DR. BREWER: There are a couple of things that come to mind. One is this issue of what kinds of side effects are compensatory and what are non-compensatory. This is a distinction that Baruch (phonetic) would sometimes make. The idea is that there are some -- like buying car. Maybe you would be willing to have a sunroof if you couldn't have leather seats. You really want to have the seats that warm up. For that, you're willing to give up the fancy trim package. I don't know what those things would be, but you're willing to give up one thing to

have another.

But there are other things for which it's just a nonstarter -- if this is present, I'm not interested. It comes to mind because during one of the open-comment sessions a woman came and told a very powerful story about her son, who had died from taking an anti-allergy medication. She was unaware that one of the side effects was suicide ideation. She came home one day and her son had hanged himself in the family closet.

That, for her, was non-compensatory. This death, given this kind of drug, was completely not an acceptable side effect. If she had known that, she says she would not have allowed her son to use the drug.

I think understanding what people see as compensatory and what they see as non-compensatory is probably not well understood. There are current regulations that require certain kinds of labeling, where all side effects are treated as being the same, and furthermore, all side effects are treated the same, regardless of the severity of the thing they are addressing. Those are two slightly different distinctions.

So I think that's one thing I would like to see more of.

A second thing might have a little to do with the report, or just maybe a more general point. We could use

some better principles on how to communicate complex information. I agree with the summary here that we have stated very clearly what you do when you have one kind of a risk. But I think there are some general principles that one can derive from the literature, if not from these specific studies, and there's an opportunity, either through this review or through other comment processes, to describe what some of those alternative approaches would be. For example, if it's important to reduce the cognitive load or the difficulty with which certain kinds of information is understood, it may be that some of these simpler formats will do better when there are multiples of people reviewing -- for example, in my own research, we use horizontal bar charts a lot. We find that when there are complex presentations, those horizontal bar charts actually become very easy to use. The learning that you do on the first chart you pass along to all the later ones. Some other formats may actually not make them easier to understand.

DR. PETERS: Actually, I just have a quick question about your research. Are you using horizontal stacked bar charts or just horizontal bar charts?

DR. BREWER: We were just using horizontal bar charts. This was for test results, so it's a slightly different deal. For us, we were looking at whether you

have normal, abnormal, or borderline results. Of course, sometimes you have many medical test results. Some of our formats presented 12 medical test results. What we found was that the bar charts helped in any number of ways -- not always accuracy, but particularly with viewing time. That's something that the report didn't address -- how long people had to spend to try to get the story out of it, and also just how easy they found them to use. When you start talking about lots of different results, there are certain formats that are going to be harder -- people feel that they are harder to use.

DR. PETERS: Kala, Craig, and then Sandy.

DR. PAUL: In terms of presenting the data, one of the things that occurs to me, even though this is promotional labeling and advertising, is that it still has to do with patient medical information, because we still have to talk about benefits and risks. We are talking about quantitative. We have to look at how we get people to understand a little bit better how much benefit they might get. Do they even understand the term "on average"? How are they going to use that to determine whether what they could get is worth what they might get from a side effect?

I think, Noel, when you were saying that, the issue with antidepressants and teenage suicide is that

there are going to be teenagers who commit suicide and are depressed, and so there's a background incidence of certain types of adverse experiences. You have a multilevel, complex piece of information, which is benefit to be gained and the potential of averting a bad outcome, when that bad outcome is then attributed as a drug's side effect.

What I'm trying to get at is the layers of information that people would need to be able to decide the risk -- not just the probability, not just the chance, but the risk, the outcome -- is worth taking the drug for. I think flu shots are a good example. I overheard someone say, "I'm not going to take that. I could get sick for a week." But the fact that this person could get the flu and be out of work for a month or a week or whatever was never taken into consideration. So that balance of risk and benefit is missing from some of the information that we have been discussing. I think that's a critical piece when looking to try to help people make an informed decision.

DR. PETERS: If I understand what you're saying, you are talking about, not just the quantitative perspective that we are talking about today, but there's also the experience of the side effect for the individual. Is that sort of where you are headed there?

DR. PAUL: It's more the scope of quantitative information that is presented. For instance, you have a

background history. I'll just use the suicide. That may be an easy one because there is a background suicide rate in untreated depression. It's the actual risk of treating versus the risk of not treating that we really aren't addressing -- okay, an allergy medication. I have never had allergies quite that bad that I would be willing to -- but if this is a teenager, obviously you have to look at it that way. The fact that the medication -- if the medication actually caused a suicide, if there was a real relationship between the medication for allergy and suicide, that seems to be a kind of risk that would -- I'm getting into policy, but it seems that it wouldn't be something that would be easily available. But I'm not going to go there. I thought you said depression. I apologize.

DR. PETERS: Craig, Sandy, Gavin, and then Nan.

DR. ANDREWS: I just want to point out two major gaps, I think, on question number 1. One that is critical, already mentioned, is on external validity of these in realistic settings, especially commercials, the print DTC stuff and the brief summaries, so it's not swamped. The information overload issue is going to be very important.

There is also media placement and all that, but I'm not going to get into that.

The second one I want to introduce is new. Noel

said something there on comparing compensatory and non-compensatory models. I know tomorrow we're going to get into discussions of gist and affect. But I think that's an enormous gap in this area. If you bring together a lot of different literatures, people bring all sorts of biases with them. They may be under fear, under different emotions. How are they going to process this? There is a lot of baggage and biases. We see terms -- I know Ellen has done research on mood effects with numeracy folks and how that enters in, gist experiential analyses. We have holistic processing, magic bullet effects, positivity biases, peripheral processing. There are all these sorts of things where maybe if you have samples there that struggle with numerical information, even when there's numerical information with a context, with evaluative information, they may go back with these biases in how they process things, more affect.

So I think that's an enormous gap. Certainly in sampling different low-literacy, low-numeracy populations, you might be able to tease out how they understand and how they deal with some of this information.

DR. PETERS: A quick clarifying comment from Val.

DR. REYNA: I think what you point out is to separate two things in this question. On the one hand, there is what's presented. Is it even possible to get a

script for a standardized presentation? Then let's just say we could find that holy grail. I think a lot of work has to be done on that. But then what you're talking about is different than that. It says, given even an excellent presentation of the facts, a well-organized one, what are the individual differences that might change how that's understood.

So I want to separate those two things so they are not conflated.

DR. ANDREWS: So more subjective processing, all of the baggage that comes in, a little bit of self-efficacy, but all of the emotional things that are brought to bear. These other things are just as important.

DR. PETERS: Thank you for that clarification.

Sandy, Gavin, and then Nan.

DR. MILLIGAN: I don't have any answers. I just have a question. Again, I'm the industry representative, so it's an industry point of view. In thinking about advertising, it could be the patient's first encounter with a prescription or an advertised drug or it could be that they are on the medication and they are getting some sort of reinforcing message. What's interesting, I think, in the prescription drug realm is, of course, that there is another intermediary involved. Certainly one of the things that I would be interested to know -- and I'm sure there

isn't any readily available research right now -- patients will have a decision or an impression that they came away from a print ad or an advertisement around the risks and benefits. I'm curious how that perception of risk and benefit is then modified with their interaction with the health-care provider. You can only get prescription drugs by interacting with your health-care provider.

So I think there's a third party that we often don't think about when we are thinking about what the effect is of print or DTC advertising to the consumer.

DR. PETERS: I think that's a very great comment.

There's also another variable that we're not considering here that is sort of a third party. It's practice and time. All of this testing has been done within the context of people who have never seen this kind of thing before. What FDA, I believe, is hoping to consider is the idea of a standardized format that patients would then get practice with, that patients would interact with, with the other intermediaries, whether it's a pharmacist or a physician, and that over time, in my view at least, this kind of standardized format would become more familiar, would become better able to understand and use, if done well, and may actually even lead to greater trust in FDA as a source of this kind of information.

Any other comments on that?

DR. ENGELBERG: To Sandy's point, in addition to the health-care provider, there's the pharmacist, there is the Internet, and all kinds of things that are outside the message, being the unit of analysis that I think FDA has to grapple with that may have far more influence on people's risk perceptions and decisions than the content of the message, whatever it is. So I think, from an external validity point of view, that maybe even tougher set of questions needs to be addressed.

DR. PETERS: What do you see as the tougher set of questions, though, in terms of --

DR. ENGELBERG: The influences outside the message.

DR. PETERS: Just generally, okay.

Nan?

DR. COL: I actually just recently reviewed the literature on the impact of physician's opinion as compared to family, Internet, other kinds of things. It's fairly consistent that the physician's opinion trumps all other sources. Even if the patient knows something is a bad decision, if the physician recommends it, their common sense goes down the drain. So I think it's really, really important to look at the moderating effect of the physician.

DR. PETERS: Shonna, do you have something on

point?

DR. YIN: Yes. I wanted to make a comment about what you were saying about having a standardized system where patients can learn and then be able to feel comfortable and use and understand the format. I think that it's important for us to use a standardized format here, and also even -- I know we're not talking about patient medication information, but across the board, this information here applies to so many other places. If we have a consistent way of presenting this kind of information that we have decided upon using evidence, I think it behooves everybody to try to be consistent in that, for our patients, for the doctors, and everybody.

DR. PETERS: Bill.

DR. HALLMAN: To follow up on that, I think one of the great advantages, if we could come up with some sort of magic standard format, is the ability, not just with the practice effect, but to be able to compare drugs directly. If there is a drug that treats allergies, one of which has a side effect of potential suicide and one that doesn't, you would be able to kind of pick that out if you could put the two things side by side.

The other is this issue of the physician as an intermediary. I note that many television advertisements for drugs end with a kind of tagline: Ask your physician

if this drug is right for you, which, to me, has always suggested -- so we have just give you a whole long list of side effects. Don't worry about those. Go talk to your doctor. It's almost, in a way, a distracter. I don't know that anyone has actually looked at that -- sort of discounting what we have just told you because there is an expert who knows all of this.

DR. PETERS: You are bringing up sort of a broader possible issue with direct-to-consumer ads.

DR. HALLMAN: It's a question of actually what's being communicated by that listing of side effects. Is the expectation that we are actually communicating with consumers or are we just sort of going through the legal requirement and then ending with "but ask an expert"?

DR. PETERS: Thank you.

Gavin, Nan, and then Kala.

DR. HUNTLEY-FENNER: The things I was going to comment on are, I think, anticipated by some of the more recent comments. I just want to say a couple of things in regard to Bill's comment, which I think is important. Having a standard would allow you to make certain kinds of comparisons. But I think therein lies the problem, as it were, because implicit in that is that individual differences aren't important for the occurrence of side effects. You don't want to sort of minimize the importance

of having that conversation with your doctor, your pharmacist, or whomever.

Similarly, with a standardized format, the idea is that it could be more transparent, easier to identify critical information. But in becoming transparent -- for example, by putting hard numbers on paper in a black box -- you immediately turn off the reader who is maybe not less numerate who looks at it and says, "Well, that's not relevant to me."

So I think there are certain tradeoffs. The goal of standardization in and of itself may not resolve the issue that we are trying to go after.

This is the comment that I have regarding question 1. Here I'm thinking in particular of the second part of question 1, which is, what kind of standardized format is appropriate? I'm thinking, what would be the purpose of the standardized format? We talked about transparency and ability to compare. There are some problems, as we know, with trying to achieve that, even if you were successful in achieving that goal. But it seems to me that one of the purposes can't be -- and you can challenge me on this -- that it provides the individual with enough information to know whether this medication is right for him. The reason that can't be the purpose is that you don't ever want a person to feel comfortable

making that decision without having a conversation with a professional medical expert who knows them -- their doctor or their pharmacist or what have you. If you put that out there as the goal of a standardized format, I think you really have to grapple with that issue.

On the other hand, there are certain things that a standardized format probably could and should aspire to. One of them is teeing up the right -- first of all, demonstrating that there is a risk, that it's not just all benefit, that there are risks associated with a medication or a device that you should be aware of; two, teeing up a conversation with a health-care provider. If you think that this advertisement is relevant to you or your condition, what are the kinds of questions that you should be asking? The standardized format should drive the person to be thinking along the lines of questions.

A third purpose might be to identify potential adverse events. If you are on this medication or using this device, what are the kinds of things that you should be aware of or mindful of from a reporting perspective, and how, where, when, and why should you go ahead and make those reports?

I'm just throwing those out there. That's my impression. I know it sort of edges into probably the policy arena. But my perspective on it is that we need to

answer the question of what we should reasonably expect a standard format to accomplish, before we can say what the standard format should look like.

DR. PETERS: I think that's an excellent sort of list of purposes and an excellent question. I would add one more to it myself -- but again, I'm not a policymaker -- just to help people understand the magnitude of the benefits and the risks that may or may not be in line with what their expectations are for the benefits and the risks.

I wonder if Mr. Abrams might like to make a comment about what FDA perceives as the purpose of a possible standardized format.

MR. ABRAMS: We're looking very closely at this suggestion. Our purpose is to get good information to patients and health-care professionals to have good decision making. What is the best information that could be provided to patients and to health-care professionals to have them more informed when making that decision?

We are looking at this, but we have a lot of other initiatives, guidance development and rulemaking. This is one segment of that. I just want to remind the committee about that.

One thing I would like to point out is that we are talking about information being conveyed to the

patient. This provision in the bill is for all promotional labeling and print advertising. We need to consider what should go to the health-care professional, too, what information he or she needs to make the best judgment for the patient.

One question I would like to bring up is, how do you do that when you have such a range of patients? You can't have one set number for all patients. That's something that I think the committee really needs to look at closely, too. You can't just box things so nicely. Patients are very, very different.

DR. PETERS: I think what you are doing is guiding us into question number 2. But if I could stop for a moment and ask you, what's an example of "patients are different"? Are you thinking about that in terms of the example looking at -- there are some patients who are considering a medication for preventive care, for example, as opposed to having the disease already.

MR. ABRAMS: I think there are many differences. First, what stage of decision making is the patient in? In addition to that, you have younger patients, older patients. You have patients with difference severity of the disease. You also have patients who are going to have more aversion to risk.

We were talking before about the risk/benefit

ratio. It's going to be different for each patient.

You also will have different uses of drugs. We are talking about advertising a prescription drug, but a lot of prescription drugs have multiple indications. Obviously, information that you want to convey about use of a drug for hypertension would be different than the use for congestive heart failure.

DR. PETERS: Thank you for that clarification. And you're definitely going into question number 2. Some of those are things where perhaps different numbers are involved. You have different usages of the drug, and so there may be different data involved. Some of it is characteristics of the patient, like aversion to risk. Whether you would really have a different standard format for people who would differ in aversion to risk I'm not sure.

But thank you for the clarification. I appreciate that. We'll be going more into that in a moment.

I think we have a couple of responses still on number 1. I have Nan, Kala, Michael, and then Moshe.

DR. COL: I'll leave mine until the next section.

DR. PETERS: Kala and then Michael.

DR. PAUL: I had a number of thoughts that kind of connected people's thoughts when I was listening. From

my own experience, I have to say Sandy is right. People look at the risks whether you present them quantitatively or qualitatively when you are talking about patients, looking at patient literature. They say, "My doctor told me to take it. I'll take it."

They also like the FDA, surprisingly. They trust the FDA. They say, "If it's out on the market, it has to be mostly safe, and if my doctor told me to take it, I'll take it."

So they abrogate the responsibility to make the decision for themselves, other than the decision they made to trust their learned intermediary.

Some of the things that Gavin said are really important. When you are talking about people making a decision or thinking about using a product that they have heard about in an advertisement, the idea is to make them ask their doctor about the medication. One of the things that they should -- if they are not going to make the decision based on the risks, if you really don't quantitate the risks -- and I'm not sure that we can actually come up with a single format that would help them understand the quantitated risk -- is to have them understand that there is information that should be conveyed to the doctor that they should be asking about, as in the ED products: Are you healthy enough for sex? Of course, there are other

things that they have to ask -- make sure you tell your doctor about any problems you have with your liver, if you know what that is.

One of the questions that Dr. Abrams raised is, how do physicians make decisions on using products? You are talking about -- and I think this goes back to some of the information that came from one of the presentations that Woloshin and Schwartz made on the amount of benefit a product can provide versus the risk profile. What are the things that a physician uses? You are talking about, in a promotional ad, what kind of information -- if you are going to make quantitative standard information available, what are the things that would influence, appropriately or inappropriately, someone making the decision to try a product on a patient? I'm sure there's a tremendous amount of literature on that. I unfortunately don't know the literature.

But when you brought the whole idea up of our standardizing information in promotional ads for the medical professionals, that's a whole different ball of wax from talking about patients, because literacy, numeracy shouldn't be as great a problem there, although it may be greater than we think -- numeracy. I was just very surprising in hearing that, because it wasn't something that was in my consciousness in terms of all this

discussion. We have been so focused on patients that I don't think we have considered making a standardized presentation of information outside the package insert for physicians to go along with the advertising. That's something that I think we need to put back on the table.

MR. ABRAMS: I thank you for that comment. The law directs us to consider all promotional labeling, so we have that directive. Even though often the discussion about prescription drug promotion is so much about patients and consumers, most of the promotion that occurs is directed to health-care professionals. About 75 percent of the promotion is directed to health-care professionals. So I think it's an area that I appreciate that the committee is willing to consider, too, to advise us on that.

DR. PETERS: Thank you.

Michael and then Moshe.

DR. WOLF: I was going to make just a couple of quick comments to Nan's point earlier about the fact that the physician is still the most trusted source and often the most utilized source of health information, especially on medication use. That's a big issue. Getting to the comment there about who is going to be the target audience and would there be a value to a standard format, that was the first thing I was thinking, because it will be increasingly easy to get this information out and shift

from pharmaceutical detailing to academic detailing by standardizing content and how you summarize a lot of that information. There are studies that show that physicians, just like patients, need help summarizing this content very quickly.

One quick comment that might be leading into question number 2, where you start seeing a lot of these hypothetical scenarios -- to me, it seems like kind of a no-brainer that providing a standardized format would be a good thing that would be of great value to a small number of patients and that may at times be utilized by a slightly larger number of patients, more likely for physicians. I think more people -- I mean, I can disregard this information. They will continue to do so. That would not make me not want to still go forward with it.

But I do have a question about how this information is synthesized, how this information would be enforced. Who would be responsible for it, industry versus FDA? I'm assuming industry. How do you make sure this information is accurate, constantly upgraded?

It's a big-picture question. I still would want to go forward with a standard format. It doesn't seem like there's enough evidence to say what it would look like, even though the Woloshin and Schwartz model seems to be the best out there. There are still some testing suggestions

for it. Going into it, if there's a way that we think about enforcement of this information and making sure that it's accurate, and not let it be like the med guides program, as an example that has kind of gone by the wayside, that would be what I would be pushing for.

DR. PETERS: Moshe.

DR. ENGELBERG: A few points. One is, building on Gavin's point about objectives, essentially, for a standardized format, I feel that as a committee should recommend -- this is something we do on every communication research project we're involved in -- establish very clear, in plain language, think-feel-do objectives. The FDA wants this standardized way of presenting risk information. When people look at that, what do you want them to think? What do you want them to feel? What do you want them to do? I believe all those are precursors -- at least the think and the feel -- to decision making. I would like to put that on the table as a suggestion for a recommendation that forces accountability, as well as clarity for how this is supposed to work. Then there are benchmarks with which it can be evaluated in consumer research.

So that's point one.

DR. PETERS: Just to clarify real quickly, you are suggesting this as a recommendation for the committee to ponder or as a recommendation to put towards FDA to

figure out, within the context that you just mentioned -- the think-feel-do -- what FDA should be thinking about in terms of what the standardized format should do? Are we considering the goals or is FDA considering the goals in your recommendation?

DR. ENGELBERG: Being new to the committee, I'm not quite clear on how things work. I would say whatever will make it happen. I'm not sure which mechanism that is.

The second point is -- I'm thinking pragmatically. This gets at, Nan, what you mentioned about how the doctor trumps everything. It seems to me, particularly for prescription drugs, that patients are so predisposed -- they are not starting with a blank slate -- they are so predisposed to get the med because their doctor said so, and by the time they get whatever the information is, I believe they will have already purchased the medication. No?

DR. PETERS: This is advertising.

DR. ENGELBERG: Okay. I was thinking that part of it is what comes with the medication.

DR. HUNTLEY-FENNER: Some patients might be using the medication, and this would be useful information from that perspective.

DR. ENGELBERG: Then I'll only say the relevant part of my point. I wonder if it would be useful to

consider having physicians give out risk/benefit information along with the prescription, because then it could be evaluated by the patient in real time with the physician rather than in the context of a TV ad or a standalone interaction between the consumer and the message.

DR. PETERS: I think what you're bringing up is a broader issue than what we are considering here, but I think it's in line with one of, I believe, Shonna's suggestions about having a consistency across not just the promotions and advertisements, but also going into the patient medication information guides. What you are suggesting is to have that even at the point of contact with the health-care professional. Maybe it is the PMI that's there at the point of contact. That kind of consistency would aid in the learning that patients go through, since they are going to be learning about this over time, but it's also going to affect their learning in the moment of what is really going on with the medication -- should I take it or not take it? -- this joint decision that I'm making with my physician.

DR. ENGELBERG: Right. It's probably the most teachable moment, I would contend.

My final point is, it seems to me, as I look at the question, that implicit in it is either/or. We are

saying, what works best? Is it A or B? For example, one of the studies that Suzanne presented showed multiple forms of qualitative and quantitative. I'm wondering if we are being overly narrow, if the either/or thinking is, in fact, driving our thinking, and if it should, rather than a standardized message that might include multiple pieces.

DR. PETERS: Multiple pieces meaning not just numeric information versus labels, but perhaps a combination of the two?

DR. ENGELBERG: Right, or different kinds of numeric information.

DR. PETERS: Or different kinds of numeric information or possibly pictographs. I think that was part of the target of the literature review. One of their final -- I think "recommendation" might be too strong a word -- one of their final comments was that, although perhaps there's not quite enough data for this, it looks as if a combination of numbers and verbal labels might be helpful. I think that's in line with what you're saying.

DR. ENGELBERG: Yes.

DR. PETERS: Are people interested in seeing a version of the drug facts box put up on the screen? The drug facts box that Schwartz and Woloshin came up with actually does include verbal information, as well as two numbers that allow for number comparison. It might be

useful, Lee, if that's possible to do.

DR. REYNA: It was displayed during the presentation as a blow-up.

DR. PETERS: Personally, it's either my glasses or the size of the font. It was hard to see. I'm not sure if it's going to be a lot easier to see here.

How well can people see it?

In general, if I can sort of describe this -- and anyone else who knows more of these details -- up at the top are some indications about what the drug is for, who might consider taking it, some information about the drug itself and whether you should use it and how to use it. Then the table has a couple of elements. In the very top row it includes the number of people tested within a particular study. This is really geared towards a single study. This is going to be towards some of the questions that are going to come up in question 2. This facts box is geared towards a single study, as I understand it.

In the non-colored columns over to the right, you have what happens with women given a sugar pill versus women given the drug. In this case it happens to be tamoxifen. Then in green, although we can't see them, it details out what the benefits are on the top, I believe, and then what the risks are underneath that. Tied to any one of the number pairs that are there, there is actually a

verbal comment that says to what extent the drug does -- whether there are more or fewer side effects or more or less benefit for the drug compared to the sugar pill.

Do I have this about right, Kala?

DR. PAUL: This particular one -- I don't know if this is the time to say -- this, to me, is a hybrid that doesn't do either of the things it's supposed to do. It's neither technical enough for physicians and it's way too much information for patients, the way it's formulated. If we're just talking format and concept, I can go with it. If we were to use this as a closer approximation of information patients could use, I would have a real difficult time supporting that. It's not as easy for patients to interpret this as we might think just because there are fewer words.

This kind of thing might be something -- if it were higher-level reading -- that a physician might be able to use, because you would want to see some of these data just put down like that. But I don't think a patient is able to make the assessments.

I will just register this. I particularly object to the term "sugar pill," because everyone I have ever used this with in testing has said, "I don't have diabetes." "Placebo" is actually better known than "sugar pill," in my experience.

DR. PETERS: Craig.

DR. ANDREWS: Let me get to, again on the evaluative portion -- you are talking about the description of benefits and risks specifically on different attributes, as opposed to an evaluative, good/bad sort of -- is that what you're talking about?

DR. PETERS: Yes, that's correct. In fact, let me just read one of them. For example, one of the possible side effects is stroke. Where the stroke numbers appear, over to the left in green it says -- the comparison is among the women who took tamoxifen -- it says more women had a stroke. So that's the comparison of tamoxifen to the placebo or sugar pill.

DR. ANDREWS: The reason I bring this up -- I also saw in the presentation that they had absolute numbers and relative -- the percentages. So you have absolute numbers, relative, descriptive. That might be about attributes. Then I thought back to the nutrition facts panel. There's a lot of history here with that. They went with absolute and relative information on the daily values, not with -- they tested adjectival, evaluative sorts of things, like the gist issues, but didn't go with that.

There are some decisions up here as far as the right approach -- absolute information, relative, descriptors, evaluative. How far do you go? I think these

are all major questions.

DR. PETERS: I agree. Is there some data that you wanted to add with respect to that interesting question you brought up?

DR. ANDREWS: This goes way back. Actually, the FDA has data, I know, on the nutrition facts panel and testing adjectival formats versus numerical. There were articles on it years ago.

DR. PETERS: Nan.

DR. COL: I love the concept of this. Having tried to translate this for some other cases, I have some real problems with absolute risk. I know the mantra is that absolute risk is better than relative risk, but from a physician's perspective, absolute risk takes into account the person's baseline risk, and if you are talking about a scenario where everybody's risk is the same or they are basically the same as people who are in the trial and there's no significant difference in baseline, then presenting absolute risk is giving good information. If, in fact, baseline risks are wildly variable and the person's absolute risk -- again, after you factor in the baseline risk -- ends up being quite different when you factor that in, you can give people wildly inaccurate information. For example, in this particular trial -- I'm guessing this is from the P1 trial -- these were pretty

healthy women, who were actually not at particularly high risk for breast cancer. Most of them were just barely over the threshold for making the criteria. If you are trying to apply these numbers to a woman who, say, is older, at much higher risk for breast cancer, and who is obese, has other risk factors for heart disease and stroke, the benefits from tamoxifen could be multiple-fold higher, and also her specific risk for some of these conditions could be orders of magnitude higher. This is based on a very healthy, selected population.

When you give absolute risks, it's imperative that they actually pertain to the population. We know that these are from randomized trials that are not reflective of most women who are going to be considering this treatment. So I'm concerned about misinformation. How we present it is one thing, but this is really potentially dangerous if it doesn't reflect the risk of the people involved.

DR. PETERS: I think this is actually a point that Dr. Abrams brought up earlier, that patients might differ quite a bit. I think it probably was geared toward their background risk. People who are older and sicker may have greater background risk, and these data would not represent them.

DR. COL: I'm not talking about -- I think that most people -- my guess is that most of the people who are

going to be considering this are not relative -- I think it's the issue of the majority or the minority. The data that we have, that would go into this really reflect a very, very small minority of the population. When you start looking at the kinds of patients who come into primary care who are considering treatment for these conditions, these risks are wildly off-base for how you would counsel. They could be adjusted, but you would have to adjust for multiple comorbidities, age, other risk factors -- the exact criteria that kicked them out of that trial to begin with.

DR. PETERS: So one of the questions, I guess, that we need to think about is, recognizing that as an important problem, recognizing also that these are presumably going to show up in promotional advertising, where -- to Shonna's point -- people then go and see a physician and the physician acts as an intermediary, is the problem that you bring up something that -- in your opinion, let's say -- would mean that we really shouldn't provide any kind of a standardized format?

DR. COL: I think each of these risks would have to be -- I think we need more rationale and objective criteria for which kinds of risk are amenable to this. There are some risks that are completely random, where we can't predict whether the risk is higher for you than for

somebody else. I think for those, this format is great -- how often are some of these effects going to happen? But for risks where we know baseline risk is absolutely critical and where we know that there is actually critical variation in our population, such as risk for heart disease/stroke -- endometrial cancer depends on whether a woman has a uterus or not. Thirty percent don't. There are a lot of these risks that this would work for, and there are also some that it doesn't work for.

How do we decide what gets in the box and what doesn't get in the box? There might be some critical risk that -- are we looking at things according to severity, the difference in the treatment versus control, the magnitude of the difference? Are we looking at statistical significance, the strength of the effect, the certainty, how strong the signal is, the duration of the effect, whether it's reversible or not, getting at some of those issues, things that you wouldn't want to go? How do you decide which factors go in that box? That's huge.

DR. PETERS: Certainly deciding what factors go into the box is medication-dependent. You need experts within the disease to be -- which is not at our particular table, although you may actually have some of this expertise yourself.

But I think you're bringing up some interesting

questions that FDA, of course, needs to consider -- and I'm sure they are -- around what would get included. The kinds of questions that we can deal with are the second part of what you were saying, which is, how does it get formatted? Is it ordered by severity, for example, just to pick one of your examples?

You brought up an earlier point, and I want to make sure I captured it correctly. You said that if for a particular side effect we know how it varies -- let's say older adults are different from younger adults -- I think what you are implicitly suggesting is that we either shouldn't have a standardized format or for those kinds of risks, there should be a standardized format that differs for the different populations. It's more that second one?

DR. COL: Exactly.

DR. PETERS: So that there is perhaps a more complex way that FDA might need to think about a standardized format.

DR. COL: Exactly, because I think, if you don't, if you, in fact, know that most of the patients considering this are 10 or 15 years older and are at a much higher baseline risk for stroke and blood clots -- if you're presenting this very small risk, people are actually going to be making decisions based on a risk that's -- they are going to be grossly underestimating their risk for that

complication and making bad decisions.

DR. PAUL: I'm just trying to think back about what this information is supposed to be. It's limited by the PI. If we don't have that data in the PI, there's no way you are going to put it in a standard risk presentation. You could put a caveat: Know that patients who are older may have -- or that the risks may vary with different patient populations. But if you don't have the data that supports the statements that, Nan, you were trying to make, there's no way it's going to go into a piece of information in a company's promotional ad.

In addition to that, one of the things that I'm concerned about with something like this is that we are talking about informational overload. You are talking about a physician 75 percent of the time who is being told that a product does X for a patient with XYZ condition under certain circumstances. The idea, as I understand it, behind this box is to give the physician some idea of the magnitude of that benefit, at least on average, as much as the data we have to support it, and the types of things that they would need to consider as either adverse outcomes or things that they should consider to find out about before they give the drug in making the decision to treat.

So it seems to me, unless I'm missing the point of this going along with promotional advertising, that you

are trying to give the physician a snapshot of how to decide the critical pieces to decide when thinking about using that drug. This is, in some respects, as I'm thinking about it -- please correct me if I'm wrong -- a condensed and focused version of the highlights in the PI. You need this information in order to be able to decide if you're going to even further consider this, against what the advertisement is saying this drug can do or should do for your patient population. That's, I think, where we have been with a lot of this information for patients and physicians all along.

We have this concept that benefits are being touted, in an unquantitated manner, far beyond the risks, and we are trying to offer that balanced information in a capsule to assist decision making, but also in the context of that advertising piece.

So that's what I'm worried about. Yes, I would say all the things you brought up, Nan, are absolutely correct, but I'm not sure that there is data around to say those things in this particular standardized format.

DR. COL: A great point, and it just forced me to think a little bit further. I think the data are there. The data are the relative risks. I guess my issue here is that when you translate relative risks into absolute risk, that's when you are locked into a baseline risk for a

population. The relative risks for most of these studies are usually constant across various risk groups. The absolute risk varies according to the person's baseline risk. In fact, we do have the data. The data that we have that this is all based on are the relative risk.

So perhaps -- again, this is violating some deep rule of risk communication -- I think in situations where we can predict risk -- and risk varies tremendously -- I think actually reporting the relative risk and then perhaps give an example -- in a healthy, selected population, here's what it looks like, but here's the relative risk -- so if you have somebody who you know is at high risk for this or at very low risk for something else, they can do the translation. Once it's already translated into an absolute risk, I can't figure out how to go back and infer how I would adjust that risk for somebody who is at much higher or lower baseline risk.

I think we have the relative risk. We need some compromise for how we present that.

DR. PETERS: Noel, and if we have time before lunch, Gavin and then Michael.

DR. BREWER: I'm sitting here enjoying the conversation greatly. It's very concrete, and I think, in many ways, we're benefiting from being able to respond and speak in the context of the systematic review that was

done. So this has been a particularly productive conversation, I think.

I want to pick up on a comment that Moshe made, talking about this idea of either/or or both. I agree very much. In my own research, we have focused on most commonly combining those ideas, although occasionally we have separated them. I'm not sure our strongest research has been where we have separated them.

The gist of it is something like this: You ask patients if they would like to see information on the risk presented in solely verbal terms -- the risk is low -- or they would like to know in percentage terms -- the risk is 6 percent -- or some combination -- 6 percent, which is a low risk. They certainly prefer, in the study that I'm thinking of, that combined format.

What I think is important, to pick up again on some of the earlier conversation with Valerie and with others here about how people interpret these two different ideas -- 6 percent and low -- people assign different meanings to them. But the one I want to focus on is the percentage scale. A percentage scale is not inherently meaningful. It has an objective meaning in the sense of the frequency with which something will occur, but it does not have an inherent meaning of good or bad or high or low. A 3 percent risk for breast cancer recurrence -- that is

low. If that's your recurrence risk, you're in good shape. However, if you're using hair dye that has a 3 percent chance of causing breast cancer, that's awful. That's very high.

So as experts and, to some extent, as lay people, we automatically interpret what the percentage means, or we have some ability to, but I don't think we can take as a given that consumers will be able to follow us into our varying worlds where 3 percent means one thing in one world and 3 percent means something else in another world. So I think the use of those two things together is deeply important, for conceptual reasons and for practical reasons.

DR. PETERS: I think that also goes back to a point that Craig was making earlier about evaluative adjectives. What Noel is saying, I believe, is that for consumers to really be able to use this information, they have to understand that evaluative meaning.

DR. BREWER: And I have really not acknowledged Valerie in all of this. This is the core of her theory, the verbatim number that you are giving versus the gist that people walk away with. That verbal descriptor may or may not be the gist, but it's the meaning that underlies it that they walk away with. So thank you, Valerie, for influencing my thinking over the years.

DR. REYNA: You're welcome.

DR. PETERS: Gavin and then Michael.

DR. HUNTLEY-FENNER: The discussion between Kala and Nan has certainly distilled my thinking on this, so thank you.

It seems to me that ideally you want something to tee up a conversation with a physician. The questions that one should ask if you are not a perfectly healthy individual don't sort of pop out of a structure like this. I think that's something we ought to be thinking about as we are considering recommendations for a standardized format. What are the kinds of things you should ask if you are obese or you have some other kinds of issues that might be important?

DR. PETERS: Thank you. Michael.

DR. WOLF: I'm asking more questions than anything. I may definitely have some concerns, but I appreciate the general directions and the combination of information. In thinking about a standardized format, do we, one, have to consider all medicines in this context -- that we would be making recommendations for this presentation style to be going direct to consumers for all medicines -- versus some medicines where it makes sense?

Another one, I guess -- and I think Noel answered this very directly, especially in this particular format --

is presenting this information to a general population, even if you could get accurate information, for instance -- so there was no learned intermediary and there was a patient in the act of making a decision about using this medicine. Would it do harm in the sense that they would be misinterpreting the information in a way that they might choose a medicine or seek out a medicine or choose to shy away from a medicine because of this information? It seems like all of that kind of factors into whether or not we want a standardized format, to some degree. It seems like some people are saying, especially, what we do know -- there is evidence to say that they could look at this and greatly walk away with the wrong impression about the medicine, which would kind of set us apart.

I guess the first question I was looking at was, could we consider a standardized format only for medicines with black-box warnings or a certain type of risk?

DR. PETERS: Tom, do you have a comment?

MR. ABRAMS: Not at this time.

DR. PETERS: Kala, do you have another point?

DR. PAUL: Yes, just quickly. Michael, you brought that up. We use the terms "common" and "not common." But, really, most of the issues that we run into that you are alluding to -- if you look at the list of common side effects -- headache, diarrhea, constipation,

and maybe stomach problems -- you see them over and over again. People are not particularly concerned with them. We talk again about risk and probability. Most of those, whether they -- they could even be high-probability, but they are low-risk. So we really are looking at the serious side effects, the things that people are worried about. Maybe by looking at a standard format, where it's important that you tell your doctor if you have X is not because you might get a headache, but because you might die or you might have hepatorenal failure or whatnot -- one of the things to consider in talking about a standard presentation -- are we obliged to tell patients about the, quote/unquote, common risks, whether it's 1 in 10 or 1 in 6 or whatever, or are we obliged mostly to tell physicians and patients about those things which have a real impact on whether or not you take the medication, those that are high-risk, whether they are low-frequency or not?

DR. WOLF: I think some of us remember one of our old committee members who brought up -- and nearly gave Nancy Ostrove, I think, a cause for pause -- maybe we should just disregard all the very rare and low-event side effects or adverse events, regardless of how harmful they may be.

DR. PETERS: Bill and then Moshe.

DR. HALLMAN: I want to go back to the issue of

severity, to key in on this point. It also occurs to me that when we're talking about side effects, there are certainly differences between conditions or diseases that may be promoted by taking a particular medicine, like for cancer, and simply symptoms. In a way, there may be two kinds of probabilities that one would want to know about. There's the probability or the likelihood that you would end up with diarrhea, for example, but then there's a severity attached to that. The probability of it being severe is -- there is also a quantifiable probability of it being severe or mild or whatever. This kind of thing only captures a kind of categorical outcome. You either have diarrhea or not, you have cancer or not, without any of that second kind of probability being communicated.

Does that make sense?

DR. PETERS: It does, although I think it does depend on how in the end FDA decides to operationalize that side effect. It could be done in a different way. It could have been done as a proportion of people who had particularly severe diarrhea, for example. So I think how you operationalize it makes a difference there.

DR. HALLMAN: I think that's sort of the point.

DR. PETERS: Yes. But I think it's an important point. I like the general point. What data actually go into it -- those are going to be things that FDA is

ultimately going to have to make some decisions about.

I think we have one more comment, from Moshe. Then we'll break for lunch right after that.

DR. ENGELBERG: Building on what Noel said, are we at a point where as a committee we can conclude that numbers alone are not sufficient, that, for example, we need to attach a contextual judgment, like 3 percent is low or 3 percent is high, depending on the context -- minimally, attach a contextual judgment, to Bill's point, maybe attach a severity thing? There could also be a seriousness piece that says, "I have a risk of pancreatitis. I don't know what that is. Is that a bad thing?"

I'm wondering if minimally we can conclude that numbers are not enough, and adding to that, maybe say the next piece to that is a judgment of low, moderate, high -- some scale like that -- and then possibly severity and seriousness of the side effect.

I mean that as a question, if we are ready to come to a conclusion.

DR. PETERS: Go ahead, Valerie.

DR. REYNA: Briefly, I would agree with you, but we do need some research about the nature of what low is. I think that is, in part, an "ought to" question, but it's also a descriptive question. It has to do with exactly --

I think the data strongly support that it's contextual. You, in fact, are presaging some of the things I'm going to say tomorrow as well.

DR. PETERS: Thank you.

We're going to break for lunch. I have a couple of comments very quickly first.

One is, as we start to ponder what kinds of recommendations, if any, we want to give as a committee, one thing that we haven't been mentioning is how a standardized format compares to what's being done right now. Is it better? Is it worse? That's something we haven't really been discussing as we go along. We have been talking about some of the intricacies of how a standardized format could be done. People have been bringing up a lot of potential problems with it. But I do think that in the spirit of comparison and joint evaluability, we also want to think about our recommendations in comparison to how it currently exists.

We haven't covered all of the questions that CDER has posed, although we started to tap into some of this complexity that FDA is going to have to face if they are going to come up with a standardized drug format. If over lunch people could take a look at question number 2 and the various scenarios -- we have hit on some of those scenarios already, but not all of them -- take a look and see if you

have any thoughts on the various scenarios.

At 1:00, I believe we have an open public hearing. If anybody wants to say something during that open public hearing, please see Lee during the lunch break. We'll go ahead and convene at 1:00. Thank you -- oh, I'm sorry, Lee has one more thing to say.

DR. ZWANZIGER: Just briefly, again, while you're looking at your discussion topics over lunch, please try to remember that we need to capture the discussion in the open meeting. So just think quietly to yourselves.

The other thing is, out at the sign-in table, where you might have picked up some handouts, a couple of my colleagues are there and will help point you toward lunch.

DR. PETERS: Thank you. See you at 1:00.

(Recess for lunch)

AFTERNOON SESSION

DR. PETERS: This is the time for the open public hearing. We do not have any speakers signed up for today. I will open and then officially close the session.

What we're going to do instead, given that there are no public speakers today, is continue our discussion from this morning.

This morning, it seemed to me as if there was perhaps starting to emerge a general consensus that providing quantitative information seems like a good idea, but exactly what form is not clear. What I thought I would do is read into the record the original recommendation from the Risk Communication Advisory Committee from, I think, 2009, if I recall. This is number 3 in terms of the recommendations that had been made by the committee that day.

What the committee said at that time was that FDA should adopt the drug facts box format as its standard. It should engage in a process for creating a standard for elaborating information. This adoption should be supported by a rigorous evaluation process, building on existing research.

I did also, though, want to note some of the discussion that happened and how the committee meant the spirit of that recommendation. After several comments

indicating that at present it's not clear how a drug facts box format might best be integrated with tiered information, how it might affect subsequent consumer decision making, and what further development might be needed, Dr. Fischhoff specified that the recommendation should be read in the spirit of a drug facts box being a conceptual standard, that further work should address how to provide more detailed information, and that any adoption should be supported by rigorous evaluation, building on existing research. With that the members agreed unanimously.

So I just wanted to read into the record exactly what had gone on -- or at least at that level, a summary of what had gone on -- with the committee at that point in time. I had a number of people ask me whether that drug facts format that was put up on the screen was explicitly recommended. No, it was the spirit of that. I just wanted to be clear about that.

We have started to talk about some of the complexity that was also discussed in the Risk Communication Advisory Committee back in 2009. But now we have some more specific questions and some more specific examples from the Center for Drug Evaluation and Research, in terms of some other sources of complexity that the committee hadn't been considering at the time.

One of the things that I do ask people to keep in mind -- actually, two things. One is the comparison to what we have right now. Is half a loaf better than a full loaf, to paraphrase or perhaps just steal from Kala? The second thing is the health provider, whether it's a physician, a pharmacist -- the health-care provider as an important intermediary.

With that, what I thought we would do is go ahead and take a look at the further questions that CDER is asking.

Question number 2 asks, are there any data that would shed light on how to select and present information that would be most useful for improving health-care decision making by clinicians, patients, and consumers -- for example, and then they provide a number of different examples.

I thought we would go through the examples one by one. I know CDER is very interested in getting some feedback from us on each of the cases. If it's okay with everybody, I'll just go ahead and go through these one by one:

A: The clinical trial data available about a product comes not from just one study, but many studies that may differ in quality, methodology, and results.

The question is, what do we as a committee, as

the Risk Communication Committee, have to add to that particular example and the question that they have?

Noel?

DR. BREWER: I think one place to start is to distinguish between efficacy data and side effects data, because they are probably really different things. Pooling side effects data is, I think, a trivial matter. I think that just doesn't take much to do. To treat it as some kind of an unweighted meta-analysis, I think you would just use the raw data and just combine it and take the percentages.

I think the harder thing to do is to decide whether it's appropriate to combine the effect sizes and yield some sort of a combined effect size. I don't actually have enough in my mind yet to say what I think about that. Maybe I don't talk for a few minutes, I'll actually have an opinion.

DR. PETERS: Kala.

DR. PAUL: In light of this question, I'm asking, are we as a committee being asked to look beyond the label or simply take what's in the label? A lot of that is done in terms of the efficacy and -- the final statement of safety and efficacy is in the label, in a manner. I don't know whether we are being asked to think about other ways to present that data or to look beyond the label in

presenting it.

MR. ABRAMS: We would not want to limit the discussion to just the approved product labeling, but I think that would be a good place to start. I still think it poses the same complexity. You can have three clinical studies with different durations, patient populations, with different data sets. I think that as a starting point for the discussion would be very helpful for FDA.

DR. PETERS: Moshe.

DR. ENGELBERG: Is it fair to assume as a premise that it is not reasonable to expect patients or the public to understand and discern results from multiple studies?

DR. PETERS: Is that a fair question? What I can say from the literature is that when you provide more information and when you provide conflicting information, people understand less of it. By providing a more precise point estimate -- it's basically the idea that less can be more. It's particularly true for people who are lower in numeracy, lower in education.

If I could add something here, I wonder to what extent FDA has been in contact with some other groups who do this or who do similar tasks to this at least. For example, AHRQ's Eisenberg Center for Communication -- I'm probably missing one word in there, maybe a couple of words -- the Eisenberg Center was charged with coming up

with effective communications that did go across multiple studies that ranged in quality and exactly what the efficacy was, exactly what the side effects were in terms of likelihood. I wonder to what extent FDA has spoken with these other groups that have gone through this process already.

MR. ABRAMS: My knowledge is limited, because that would be under the Office of New Drugs in CDER. However, I know there has been a lot of thought given to this topic and discussion in FDA and, I believe, outside of FDA. From the discussions which I have heard, it's a very difficult situation. To try to come up with a single number to represent what's known about the drug could be quite uninformative or misleading, because you're not accounting for different populations, different duration, different dosing regimens, the severity of the disease. It's a complex situation, and it could be actually a very uninformative or misleading situation to try to force things together that are apples and oranges -- different study designs and methodology.

DR. PETERS: If I could just poke at that a little bit further, I actually worked with the Eisenberg Center back some number of years ago, in the first iteration of it. My question for you is, is what you're saying -- I understand that there is a lot complexity in

these processes. I remember in working with the Eisenberg Center that the people who were charged with that particular task had a very difficult time with it. Most of the time, they did, in fact, in the end come up with a precise point estimate. Sometimes they didn't, and we didn't include it, as a result, in the patient information, and even possibly in the physician information pamphlets that we came up with.

So I guess my question for you is, in terms of what you were just saying, do you think that that's true for every drug that FDA regulates, a small proportion of the drugs, most of the drugs? Can you give us some idea of sort of the scale of the problem?

MR. ABRAMS: It's a good question. Obviously, certain drugs are more complex. When you have an oncolytic drug with many different subset populations, that gets more difficult, I think, to try to define than an asthma drug. I don't know the answer to that. Once again, I'm not in the Office of New Drugs, but I do have a lot of discussion with medical officers and medical experts. They are very good at making hard decisions -- approving drugs, looking at the data, analyzing. They're smart people. I'm not talking about myself here. They are very smart people, and they do make good decisions. From my discussions with these folks, they do not see -- and I can't say for every

drug -- an easy way of having a single number, without it being relied on in an uninformed and possibly negative manner.

DR. PETERS: Valerie.

DR. REYNA: I think other people have attempted to -- how do you synthesize studies, especially, as the question says, when they differ in quality and rigor and so on? You don't just add them together, of course. In the efficacy domain, there has been a lot of prior work on this that we can draw on, obviously, in the Cochrane Group, the Campbell Collaboration for the Social Sciences, the What Works Clearinghouse, and so on. If the question is what's effective, how to combine conflicting studies versus an absence of studies, so on and so forth, different indications for different subgroups of users -- the Cochrane Group, for example, is a real leader in describing guidelines for how to integrate evidence.

At the end of the day, though, I think there's no substitute -- even though meta-analyses are wonderful and routinizing everything is wonderful -- and to the extent that you can do that, that's great -- at the end of the day, there's really no substitute for in-depth research training and understanding the nature of the quality of the research, rather than just adding it together and hoping it's all uniform. It's not uniform. There really are

insights into the quality of the work that have to be done by experts who are researchers who are well trained. That normally takes years of graduate training.

So I would suggest, for those sorts of things, one can take advantage of expert panels in a number of ways, from the NIH consensus process to the National Academy of Sciences. There are other mechanisms by which you can access the expertise of people with domain-specific expertise, so we don't just add everything together.

Also my thought about this -- unlike Noel, I'm concerned about -- I don't think adding up side effects is trivial. I think all of these things are contextual. I think different users do matter, different classes of users. However, I don't think it's infinite. It's not that there are an infinite number of distinctions that have to be made, but there are major distinctions of classes of patients and classes of indications that probably should not be summarized across because you're averaging in signal with noise.

I think I'll just stop there.

DR. PETERS: One of the things that we talked about a lot in the first couple of years of this particular committee had to do with strategic risk communication. Strategic risk communication around an issue like this might mean pushing some of these decisions back into the

drug review panels. I wonder to what extent pushing these kinds of decisions back into the drug review panels, where you also have experts, perhaps, in judging the quality of studies -- and perhaps they sit there already -- you have people there, perhaps, who are communication experts, who could think about some of these "less is more" sorts of issues. We don't want to provide too much information.

DR. REYNA: I think there are two issues here that are being combined. One of them is content domain knowledge about the actual state of the world. What are the risks and benefits of the medication? In order to understand that, you really have to be a domain expert and you have to understand the quality of the studies.

The other issue, though, is, once there's some consensus, some scientific consensus, how do you present that information? How do you maximize the ability of the human -- the patient or the physician, in some cases -- to understand that information? That's where I think the expertise around the table would be relevant.

But I don't think we need to think about averaging across indications or averaging across major different classes of patients. I think if we separate those, our task might be doable, eventually.

DR. PETERS: Noel?

DR. BREWER: I think there is a meaningful

difference between side effects and effectiveness.

Effectiveness is -- to determine that requires an evaluation study, some part of which answers the question, compared to what? The side effects kind of do and kind of don't. You have these two arms, and you might want to know what it's like in one arm and another arm. It certainly helps to know that in one arm it's 3 percent and in one arm it's 6 percent. But I'm just a lot less concerned about those kinds of comparisons. I think I might be concerned about some epidemiological questions about sampling and, as you are saying, these different populations -- that you could push those numbers around and they could be pushed higher or lower, so that if you're recruiting a largely sick population compared to a largely healthy population in some of these different studies, as you start to combine these things, you could get kind of a peculiar mix. But I'm just less bothered by that, although I appreciate your comment. We may just disagree. It is an empirical question. I think we agree on that.

The effectiveness data, though -- it strikes me that it's a different category. The arguments about effectiveness are very, very complicated, as Valerie was saying. I just don't think that most lay people can make a very careful decision when you have two or three studies that vary on quality and a couple of other dimensions. I

think it may be more than is really helpful. I guess I might think of two artificial classes of situations, one where there's a single number that we can point to with confidence, in which case we should give that single number or the pairs of numbers in the intervention and control arms. But let's take the other situation, where there is substantially conflicting data, where you have some kind of a cohort study, another one that's a randomized, controlled trial, but it's small, and then the dosing regimen was sort of screwed up along the way, so that there wasn't really the right kind of dosing that maybe would have given the full story. You can come up with these sorts of peculiarities among studies.

I agree that it would take an expert to really yield an opinion about these, and I think some digested form that would be a sentence or two -- maybe each study would be described in a sentence, a narrative sentence -- would probably be substantially more helpful than one of these enumerations of all these numbers without some kind of context to understand them.

So I guess I sort of lean towards, when there's something that we can say with confidence, the number makes sense to me, but when there's a great deal of uncertainty around it, having a narrative description instead of the number would be far preferable. Of course, that then

starts to raise the question -- you have this ideal situation of A and B, these two polar extremes. Where do you draw the line? When have you crossed that point into being uncertain about being able to combine it into a single point estimate?

DR. PETERS: Kala and then Nan.

DR. PAUL: Listening to Noel and some of the statements you were making about describing the studies, I'm brought back to a question, which is, what do we expect the patients to do with this? Where is it going to be? If it's going to be in a television ad, going to be in the back of a print ad, this type of information, this depth of information, is almost, in my book, impossible to deliver with any degree of quality that it's going to be understood, taken in. Then the question is, how used?

I'm wondering in what context -- just to bring us back to the context of putting this information out there, where somebody is going to have to see it and potentially, like on a television ad, digest it quickly or look at it as they are flipping through a magazine, but you are space-limited. All of these subtleties kind of fall by the wayside when you are limited in either time or space to convey this kind of information, unless you're going to give something else up.

I want to put this discussion back in the context

of the place and time in which we are applying this -- unless I'm wrong, Tom. Maybe you can address my comment.

MR. ABRAMS: The first thing is, we want good information out there. We are involved in a number of initiatives -- the agency as a whole, prescription drug promotion as a subset of that. There are a lot of initiatives as far as guidance development and rulemaking to get good information out. We want to have the right drug to the right person at the right time.

But we don't want to delude ourselves by saying, oh, let's come out with this information, if it's not going to be useful to serve the public health, having better decision making in health-care decisions. That's why we are posing these questions to the panel.

One thing we need to keep in mind as a group is that this is prescription drug promotion, and it's limited, as you said, in space. It's to sell a drug. It's not a medical textbook or a summary of data. I love reading data of different clinical studies and kind of drawing conclusions. That takes a long time. That's not what we're talking about here. We're talking about prescription drug advertising and promotion. That's the area of the bill.

I think you raise a real good point as far as space limitation and what the intent of this is.

DR. PETERS: We have Nan, Moshe, Michael, and then Craig.

DR. COL: Excellent point. When we look at what's most important, where the action is, I disagree with Noel, for possibly the first time. The clinical decision that most patients are making is not between a drug that works much better than the others. Most of the drugs we have for an indication work kind of so-so, and they all kind of work about the same. At least in primary care, most of the decisions are around a whole bunch of me-too drugs that all work about the same, for lipid lowering, hypertension, osteoporosis prevention. There are a whole bunch that are almost nearly indistinguishable. That's usually the result from the systematic reviews, that there are 10, 15 drugs that all work with about the same efficacy. The real difficult choices are, how do you choose between side effect profiles?

Again, I differ with you as well, because pooling the side effects I think is extraordinarily challenging. If, in fact, the trials were ascertaining side effects in a uniform manner, you could just do what you're saying. But the problem is, the trials are designed so they are tracking the efficacy as the main outcome. They probably have a couple secondary and tertiary outcomes. But by the time you get down to whether it causes pancreatitis,

whether it causes jaw necrosis -- these are things that are haphazardly collected, at best, often in the other category. A great example is hormone therapy. For years and years, there was no indication of -- no, I think it was tamoxifen. There was no indication that it caused endometrial cancer until all of a sudden somebody in some case report reported, oh, endometrial cancer was there. Then they started tracking it. Only when they started systematically tracking it did they discover it's a tenfold risk.

If you don't look for something, you are not going to find it. That's a problem with the adverse events. We don't have a way of finding it. If it's not on your list already knowing about it, you are going to have remarkably non-uniform ascertainment. You will have some trials where it appears it's not there, and it's not there -- you don't know whether it's not there because it was looked for and it wasn't there or it just never got on the list.

So I think it's hugely complicated and important.

DR. BREWER: Can I ask a clarifying question? I appreciate the complexity of what you described. It's exactly how I would think about it as a scientist. We're completely in agreement there. How do you take that complexity and map it over to what consumers need in a

brief, focused amount of space? In particular, let's say it's endometriosis. Do we have 20 things we talk about, or 50 or 100 or 1,000 possibilities? Do we talk about the absence of all those?

DR. COL: I think, actually, the drug facts box and the food labeling things can actually be very informative. I think there are ways to simplify this complexity. If we just rely upon the way that trials haphazardly decide they are going to collect side effects, and also pooling them -- some of them may look at very specific upper GI stuff, lower GI stuff, some may be all GI stuff -- if we could come up with a way of saying, here we have minor, transient things, such as nausea, headaches, whatever, that are not very severe, and then we had a separate thing, where we said, here are some serious things -- and I think you could get a reasonable group of people to come up with a reasonable definition of what serious things are. Those serious things you could put in terms of cardiovascular areas, GI, cancer, and death. I think there are a couple of areas where you could reduce it to a couple of the main concerns. Then you could have sort of an "other," where you put -- but I think that we could have something that is comparable to what happens in food, where we talk about calories, protein, calcium.

Right now we kind of do that, but we do it

haphazardly. We don't have a common definition of how we talk about heart disease. Maybe it's vascular disease. We separate out these things. Sometimes things look good because they have parsed the disease into so many, so it looks like they only have two events here and zero here, one here and zero there. If you pooled them all, it actually looks pretty big.

So I think that having a uniform way of aggregating side effects would not -- I don't think it's trivial. I don't think it's that hard to do, and I'm sure that people have done that. We just have to come to an agreement on how we want to do that.

DR. PETERS: I think what you are saying is that one of the things that perhaps we can make as a recommendation is that side effects should be grouped. They should be grouped by level of severity -- I think that was your primary recommendation -- and then perhaps, within severity levels, group them by what kind of risk it is.

DR. COL: What kind of risk, but also you could have sort of like sub-trees of what things fall within that. You couldn't parse things in a way that would do away -- for example, some of the class of the osteoporosis drugs that tend to cause some GI effects -- if you look at some of the studies, it's very hard to compare one study to the other because of the way they parse things. If you

separate out pancreatitis from other GI effects -- if you have one where you have all the five different components and you parse them out into various -- you get very small numbers, and each one of them looks non-important, whereas if you pool them all together, you can actually have a meaningful result. It's just consistent ways of how we define groups and what goes in them, how we report it, so we have the same level of aggregation going across.

DR. PETERS: That doesn't happen in the trials and it doesn't happen in the systematic reports, systematic reviews -- going beyond a topic area, actually packing things together within cardiovascular risk or gastrointestinal risk, rather than having each of the little subcomponents.

DR. COL: Exactly. Have a defined sub-tree so that you could actually combine things at similar levels across different studies.

DR. PETERS: Thank you. Moshe, Michael, Craig, Shonna, Kala, and then Bill.

DR. ENGELBERG: As I look at the question, which is about data to shed light on how to select and present information, I keep coming to the point that I think we're too far apart -- we're making it very difficult to answer the question. In a sense, the independent variables are all about sleeting and presenting information, and the

dependent variable is about decision making. I believe that that's too far apart in order to answer the question for the A, B, C, D, and so on. The gap, I feel, needs to be answered by determining where FDA is putting a stake in the ground in terms of what their job is. What I mean by that is, is FDA's job to provide the facts, which would be data -- provide data points? Is it FDA's job to go beyond the facts and provide meaning, what the fact means? Is it FDA's job to go beyond the data and the meaning to make a recommendation -- here's when you should take this drug?

Until we know that, it seems to me, it's really hard to figure out what data is available to solve this.

DR. PETERS: I think, to some extent, we have had some discussion that maybe the facts alone aren't enough. Maybe we need to pack together some facts in order to be able to do comparisons. Some of these questions, like the packing together, are not questions -- how to do it for a particular drug is not a question for this committee. But the suggestion of packing things together could be a suggestion that comes out of this committee.

We have heard that just the facts might be enough because people need some additional meaning. I don't know how the FDA would perceive that part of the job. Whether the FDA would also want to take on the job of "you should take that drug" -- I could fairly comfortably say they

don't want that job.

But perhaps Dr. Abrams could comment.

MR. ABRAMS: Let me just say it's my personal opinion. I think that's a practice-of-medicine issue, not FDA's.

DR. PETERS: For which one?

MR. ABRAMS: I think drug selection should be the practice of medicine by the prescribing physician.

DR. PETERS: Absolutely.

MR. ABRAMS: If you start making recommendations that you should use this drug, I think the individual physician has to look at the individual patient -- not an easy thing to do -- and weigh the risks and benefits for that individual patient, in consultation with the individual patient.

DR. PETERS: I think that's, in my view at least, certainly appropriate.

I think there was a more intermediary step that Moshe was suggesting, though, which is around whether it's FDA's job to provide meaning to the facts, to say whether a risk, for example, is low or high, good or bad.

MR. ABRAMS: I think FDA's job is to review the data submitted with the new drug application and make the difficult decision sometimes about whether the drug's benefits overall outweigh the risks. I think that's a huge

task.

DR. REYNA: Distinctions: If the goal is informed patient decision making, I think we are already beyond just listing facts, because nobody is going to be informed. I think we can probably have pretty good consensus on that. You were saying that earlier, Moshe. The quantitative information might be essential, but it's not enough. So if the goal is to inform the patient -- and we are in the era of shared patient decision making. It would be nice if we could leave it up to people that only had advanced degrees, I suppose, but that would infringe on patients' rights to make these decisions. They are going to be part of the process.

It isn't necessarily providing the meaning for the patient either. It's presenting information in such a way that the patient can derive the meaning. That's the distinction I would make.

DR. PETERS: Michael, Craig, and then Shonna.

DR. WOLF: These comments kind of keep changing what I want to say. But there's something very odd here. I think Dr. Abrams made a good point earlier that what I wasn't really doing is keeping myself contextualized to direct-to-consumer advertising, where there's limited space and there's enough to actually -- what you can actually convey versus the very fact that for A up here, we should

be doing this. We are doing this supposedly in a prescriber insert, summarizing the clinical trials. But how does a clinician actually pull that information together, beyond getting academic or pharmaceutical detailing or some information or guidance from their professional societies. Somehow or other, this is happening. We just don't know how to actually get it and put it in a way that can be meaningful for patients. It may never be able to be possible. But if we really believe in limiting information that that one out of 100 patients that does understand, want to understand how their physician makes a decision -- because, again, a lot of what we're talking about is, except for the very, very odd loopholes of mail-order pharmacy, these are patients that are not making informed decisions on their own. There is a learned intermediary that is responsible and required to actually make a prescription for the medication.

Whether or not you can do this -- I don't even know how we can get into the trees here without even talking about types of quality format, how we present risks and side effects, when we don't even know if we can get this information into a 2.5-by-2.5-inch box on a magazine ad or how it could be quickly relegated into a TV ad for some of this information. But somehow or other, we have to get this content out there so we can expose the decision-

making process, from a clinician's perspective, of how they chose this drug versus another drug or treatment.

So I kind of find the conversation is -- I don't know if we're on the right track where the conversation should be going at this point. Maybe going back to what you said, Ellen, at the very beginning, is looking at how we currently do things. How is this information, one, presented, and how does the industry actually pull together on the prescriber insert with guides from the FDA, the summary of clinical trials, to show that most drugs do have more than one set of information, of studies to have to kind of culminate together to make these decisions? How is it being used? We do have studies. I know out at -- is it Brigham or Mass General? -- there was a big study, that black-box warnings, these contents -- the information about the use of medications goes unutilized.

Again, I'm sorry if I just made comments being completely confused. But now I'm feeling very, very pessimistic, even though I feel like there's an obligation, that we should find some way, maybe outside of this context of direct-to-consumer advertising, to offer patients this information, or even clinicians this information, in a better format.

DR. PETERS: Craig, Shonna, Kala, and then Bill.

DR. ANDREWS: This discussion is fascinating, on

a policy level, an operational level. I really enjoy it. There's always some history here. I think back to the nutrition facts panels, where they decided more on giving folks the facts and didn't quite go on to meaning. Now we're seeing front-of-package symbols and other sorts of things -- in fact, we have been involved in some of the research on that -- to provide additional meaning.

Again, this is very important. Other agencies may just have folks giving the folks the facts. But I don't know. Here there are public health mission issues. As Val said, it's really their perceived meaning as well, from the patient side.

On the operational issue, this is like musical chairs. I was thinking of leaks in a dike and putting a finger in, in different places. You have to pick your poison here. It's a very difficult situation. We have different populations, different duration issues, different types of risks, and different severity. How do you deal with that? Do you include a drug facts box with bold disclosures talking about different populations and duration issues? Or do you deal with the population and duration issues with line graphs? Some of you might have seen that for multiple ones, for different types of risks. Yet you are running out of space in the brief summary. And don't even think about that with the commercials.

So it's a difficult issue. You probably have to pick one area, because you're going to have loose ends on the other ones.

DR. PETERS: Thank you.

As Craig did, by the way, let's go ahead and open up comments to any of the other examples that CDER has brought up. I think it's a great idea, because we are only at this point hitting on issues with A, I believe -- although a lot of the discussion is relevant to many of the other examples, too. So please feel free to pick from some of the other examples as well.

At this point, I have Shonna, Kala, Bill, and then Gavin.

DR. YIN: I want to comment on something similar to what Craig just said. It's kind of overwhelming to think about all the complexity of different populations, different severities, and things like that. I think we really need to try to think about prioritizing which ones are the most important. I know that there are a lot of different populations that might react differently to different medications. But maybe we should just focus on the typical patient that this particular drug is targeting and then have a little stipulation that if you fall into a particular higher-risk category, for whatever the reason is, you need to find out more information. The kind of

information we are trying to have on the advertising -- and we only have very limited space -- we just have to think about it as a conversation starter, and not as an end-all/be-all and give everybody all the information that we have. But this is a first start, the beginning of a conversation which is going to continue with the doctor, with the pharmacist, and other health professionals.

DR. PETERS: I like that phrase, this kind of information as a conversation starter. I think that's very nice.

Kala, Bill, Gavin, and then Noel.

DR. PAUL: My organizational little heart wants to clarify some terminology, from the standpoint of drug development. Nan, it's not a haphazard process, I don't think, in the drug development. These are treatment-emerging adverse experiences that are reported. Those that are low-incidence may or may not be caught in trials. They do fit into system-organ classifications. There is a classification that is already existing that's being used for international reporting of adverse experiences, and adverse experiences in the United States.

Also, terminology: If we are going to suggest something like "serious adverse experiences," the term "serious" is a regulatory term and the term "severe" is not what we're talking about. You can have a severe headache,

and it's not reportable under the issue of serious.

"Serious" means it has a very distinct regulatory definition of certain types of adverse experiences, those that have hospitalizations or are congenital defects and so forth. I won't go into that. But if we are going to be talking about serious adverse experiences, we are talking about something slightly different from a severe adverse experience, as opposed to the severity of the disease state, which is something that is mentioned in F, which may affect how the data is interpreted.

Given all that, and the fact that Shonna mentioned about a conversation starter -- and I think Gavin also talked about this -- in the short time that you would have in an ad or in the short time that you might have somebody's attention in a print ad, isn't that what you want to do? You want to say, look, these are -- even if you use system-organ class as well -- there's a cardiac event or these things might be expected. Those are risk factors. Talk to your doctor if you think you have these risk factors or if you're interested in this drug. I'm just using those as examples, where we may or may not even need to be looking at quantitative information, but looking at the kind of information that would let the patient know that there is more to be learned than just what was presented in the ad.

But then, given that, I'm wondering, is that going to be any better or worse than the current things that are on the backs of print ads, like the patient package inserts or the brief summaries, which actually distill the package insert in a theoretically patient-friendly manner?

DR. PETERS: Bill, Gavin, and then Noel.

DR. HALLMAN: I think I want to echo the last two comments. I was struck by Dr. Abrams telling us that about 75 percent of the promotional advertisements are actually targeted to physicians. We need to be thinking about what we're doing for consumers and what we're doing for physicians separately. I don't think we are creating something for both audiences.

I agree that what we should be doing for consumers is a kind of agenda setting. When you have your discussion with your physician, here are the kinds of things that you should be talking about. There are GI side effects. There are these other kinds of endpoints that you will want to discuss with your physician, especially if you fall into these particular risk categories. That may, in fact, be enough for the consumer to start that conversation.

I think then what we really want to focus on is what's usable to a very educated consumer or to the

physicians themselves and creating some sort of a standard format for these kinds of things to be reported in which they should be reported. What I would envision is a Web site, for example, where the information is reported. We're not talking about a package insert, that level of information. We're talking about something in between the package insert and what we currently have now in terms of consumer advertising. So there would be a cue to both the physician and the consumer that these are the areas that they should be looking at.

I really do see this as sort of an agenda-setting exercise.

DR. PETERS: I want to make sure I understand the first part of what you were talking about. If I understood correctly, I think you were saying that the idea of a drug facts box maybe should be pushed onto a Web site rather than having it in direct-to-consumer ads.

DR. HALLMAN: It depends on what you define as that box or what's in that box. I can certainly see some sort of a standard format for a label for consumers in a magazine, print ad, on television that is that agenda-setting piece -- talk to your physician about these things, especially if you are in these categories. That's very limited information. But that then has a parallel in the Web universe or in more lengthy materials. Yes, I need to

talk to my doctor about potential GI effects. There needs to be a companion to that that says, here are the GI effects and here's what we know and here are the particular risk factors, just as Nan was saying. Here are the potential cardiac outcomes. Here are the things that you need to know.

If we do that in the same order and pretty much the same way, then you can actually get these kinds of practice effects that we were talking about earlier.

Does that make sense?

DR. PETERS: It does, yes. But where, if anywhere, is quantitative information?

DR. HALLMAN: I would see the quantitative information being in the second piece.

DR. PETERS: That's what I thought.

DR. HALLMAN: There could be some qualitative information in deciding what goes in that agenda-setting box -- here are the very serious things you should talk about, but then there are also these other kinds of things. We can probably talk about that. But I see the quantitative stuff being in this companion -- and I could even see the companion Web site or whatever it is allowing you, as an advanced consumer or as a health-care provider, to manipulate -- can I see it in percentages? Can I see it in a graph form? Can I see it in a comparison form? It

wouldn't be difficult to program something like that, so long as the information was put together in a very consistent way.

DR. PETERS: Gavin, Noel, and then Nan.

DR. HUNTLEY-FENNER: I think we have had a bit of a wave building here. I just want to echo some of the comments that I have heard so far. In particular, this issue of a conversation starter I think is a very nice way of framing the problem.

One possibility is that you could do away with quantitative information and present information in a way that's immediately recognizable by particular classes of individuals. Let's suppose you notice that there is a set of side effects that are going to be relevant for persons with heart disease or potentially relevant for persons with diabetes or who have acid reflux -- that is, known conditions where you sort of think of yourself as being a part of this class of person. You might then have a simple section that says, ask your doctor about side effects, especially if you, and then you can then list the top two or three issues.

The advantage of that is that the person who is reading that will immediately, potentially, recognize themselves, if they fall within it, and there will be an interest there. It highlights the issue of side effects in

a way that connects with their daily lived experience, and I think makes it far more likely that they will want to go ahead and have that discussion. The nice thing about it is that we're familiar with this way of structuring information. If you look at the nutrition facts label, there's a set of nine or 10 different items in a list and each one has a number next to it. We can look for the number that we are interested in. If we think we're iron-deficient, we may look for iron-rich foods. This is a version of that in the health domain.

The downside, of course, is that I suspect that 90 percent of side effects will probably hit two or three of these major categories. Just about every medication may have those two or three categories represented. You would want to think through that issue.

But I want to put it out there. What do people think about getting rid of the numbers and just highlighting the specific patient categories that will be recognizable to individuals who fall within those categories?

DR. PETERS: I guess my question is, how is this different from what's currently out there? What I heard, I think, was that maybe you wouldn't have the sort of laundry-list approach that's currently used, where people very quickly, down at the bottom or in very small font,

say, here are all the side effects mentioned. In place of that, maybe you would talk about major adverse events that particular classes of people should look out for.

DR. HUNTLEY-FENNER: You miss a number of things. You'll lose the iteration of major adverse events. You'll lose likelihood. You'll lose, depending on how you implement this, maybe severity. What you gain is something that's recognizable to a person who may be in an affected class. You gain the attention of the person who may be put off by a number that is potentially not meaningful. You gain, I think, a conversation that's actually going to lead somewhere with respect to side effects that are specifically relevant to a given individual.

DR. PETERS: Thank you.

I have Noel and then Nan.

DR. BREWER: I'm sensitive to our timing. Can you give us some guidance?

DR. PETERS: Actually, thank you. We're at 2:05 right now. Thank you for the time note.

I think what we're going to do, actually, is stop our conversation at the moment. We're going to go ahead and move on to the next group, because they are scheduled at 2:00, and I hate to keep them waiting. As we are able, we'll return back to this conversation.

I think we have provided a lot of thought, and

good thoughts, to FDA already. It would be nice to continue the conversation if we can. I think that, as a committee, we would probably like to get to a point where we feel as if we have a consensus of some sort. I think we haven't reached that point quite yet maybe.

Why don't we go ahead? We now have a different topic. We're going to switch topics quite a bit. We have a different topic, from the Office of Special Health Issues. We're going to be talking now about MedWatch and some of the issues that they are facing. I believe our first speaker is going to be Heidi Marchand.

Agenda Item: Session II: Office of Special Health Issues

Office of Special Health Issues and Therapeutic Product Safety Communications-MedWatch, Safety Message Uptake, Opportunities for Improvement

DR. MARCHAND: Good afternoon. I appreciate the opportunity to present before the advisory committee today. My name is Heidi Marchand, and I'm currently the assistant commissioner for the Office of Special Health Issues. With me today are two of my colleagues, Captain Beth Fritsch and Dr. Anna Fine. They will also be involved in the presentation today.

For the agenda, we'll be giving you an overview of the Office of Special Health Issues' role for

communicating with patients and the health-care professional audience. We'll talk to you more specifically about the MedWatch process for reporting safety into the Food and Drug Administration. Finally, we'll summarize our activities with regard to the MedWatch safety messages that we disseminate externally and give you some results of surveys that have been conducted over the last year as to the acceptance of those MedWatch safety alert communications and safety labeling changes.

With that, the first thing that I thought would be helpful is to orient you a bit to where our office resides within the Food and Drug Administration. Sometimes it can be daunting to figure out who is coming from which office and in which areas they interact and how they, in fact, internally communicate. So I thought it would be helpful to explain that our office is within the Office of the Commissioner. There are several offices, obviously, within the Office of the Commissioner. We specifically report into the Office of External Affairs. Our associate commissioner is newly appointed Virginia Cox. She joined the Office of External Affairs about three months ago. I am the director of the Office of Special Health Issues, which is one of three offices that report into the Office of External Affairs. The other offices that report in include the Public Affairs Office, the Web staff -- it's

fda.gov's Web staff -- and then also the Office of External Relations.

Our Office of Special Health Issues particularly has a focus for ensuring that we have outreach and communication and network with two distinct groups, one being the health-care professional community and the other being the patient community. With regard to the health-care professional community, we focus on professional organizations that are well recognized, such as the American Medical Association, the American Pharmacists' Association, the Nursing Association. In fact, we have about 600 organizations that we try to communicate with in one form or another. So it's quite expansive. We do develop targeted, identified groups, depending on the topic that we are trying to communicate.

The other group that we interact with is the patient liaison community, in which we have patients that range from individual patients who might be contacting our office to learn about how to access something like an expanded access program for getting access to an investigational agent, to a very well-organized patient advocacy group that might be wanting to engage with the FDA and learn more about FDA processes or, in fact, have an issue that they would like to raise within the FDA.

I thought it would be interesting to show you

this organization, because, as we reside in the Office of the Commissioner, we have the ongoing interactions across a number of the different centers. So while we have the Office of Foods, the Office of Medical Products and Tobacco, and the Office of Global Regulatory Operations and Policy that we interact with, we primarily are helping to engage our stakeholders on topics that are most relevant to the Center for Devices and Radiological Health, the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, and, less so, our newest center, the Center for Tobacco.

Again, we'll maybe have a topic like endocrine metabolism as a focus area that we would like to develop expertise in and recognize the importance to public health, and by virtue of where we are organized, we'll look across the different centers and be able to pull forward points of communication that might in touch in devices or biologics, or perhaps there is a combination with the Center for Drugs, and so forth.

I think it's also worth mentioning that our office originally was put into place in the early 1990s with a focus on patient communication and outreach. It has been more recently that we have actually developed a health-care professional focus. In 2006, we got more specifically organized, and then in 2010, we actually

developed these into two different program areas. The staff is composed of about 20 FTEs that include physicians, lawyers, pharmacists, nurses, as well as economists and other public health specialists.

So that's where we are within the FDA. What our role is I talked a little bit about. I see our office as serving a function of bridging communications across the FDA internally, as well as externally to organizations -- health-care organizations like the American Nursing Association, the American Medical Association, and pharmacist groups, as well as more specific groups under those umbrella organizations, as well as the more focused and developed patient advocacy organizations. We do communicate a number of safety message on human therapeutic products, using the term "human therapeutic products" in that it's not limited to drugs or devices only, but it has the broad reach of many of the human therapeutic products.

One of the roles of our office is to make sure that we are communicating externally to these different organizations, but we are also very much functioning in a role of listening to what those organizations are telling us. This is on an informal basis. There are a number of different mechanisms by which the external public can communicate with the FDA. For example, if there is an organization that is coming to speak at an advisory

committee meeting, we might be in attendance. We also might be asked to give some perspective internally as to what that organization's role is, what topics they have been interested in, how they define the need, to learn a little bit more about the FDA process and so forth. It can be quite a dynamic interaction. We do make ourselves available in small group settings and larger group settings, and help to advise these organizations on how to interact with FDA.

Now I would like to talk a little bit about the tools that we actually have available to us as our area of responsibility for communicating externally. My office is responsible for taking on the role of maintaining several different FDA's Web pages. These may be familiar to you. I think in the background materials there was a link provided to a number of these pages.

One of the first is the FDA health professionals page. That page is available to any health professional or anyone in the public through the www.fda.gov Web page, the opening page for FDA. It's right there on the front page. You can get, if you are a health-care professional, into more information for health-care professionals. We'll highlight different initiatives and so forth.

We also have responsibility for a patient-oriented Web page from our Office of Special Health Issues,

as well as the MedWatch page. The MedWatch page is available through the FDA health professionals page as well. The MedWatch page is very robust and very dynamic. We provide information, basically updated several times a week -- at least once a week and oftentimes three to five times a week -- where we will have information with regard to a MedWatch safety alert.

Then there is also on that MedWatch page the opportunity for input into FDA with regard to safety and/or any kind of difficulty on a human therapeutic product. It's the interactive reporting form, which is an electronic form, as well as being available through paper and so forth. Our office, in addition to the other centers, works on that. You will hear more about that, as both Beth and Anna will describe.

The other Web page that we have responsibility for is the Medscape page that links from our FDA health-care professional page. This is a program that we launched in June of 2011, where we have a memorandum of understanding in place between FDA and Medscape to help further disseminate some of our key messages. We do that through various different tools that Medscape has available, through videos, commentaries. Some of those programs also offer continuing education.

Here's a look at the health professional page. I

just have a screen shot here on the slide. You will see that we have a component that includes videos and commentaries. What we have here for the prevention of surgical fires is one that we have done recently with Medscape. That was something that was raised within the Center for Devices and was a topic where we felt we really needed to get this out to -- all the hospitals or all the health-care practitioners in the country should hear about the challenges and the risks in a hospital setting when there are materials that could potentially be, quite surprisingly, problematic in having a surgical fire. We worked with Medscape in actually having a video and FDA commentators, as well as a health-care professional from a hospital come and talk about the way of best managing this.

We also had a very specific FDA commentary on the unapproved drugs initiative. This initiative has been going on for about the last three years. Over time, there have been various different drugs that have been affected by the unapproved drugs initiative, in which the drug was removed from the market with the expectation that an actual NDA or application for a product would be introduced or submitted to the FDA. There's an explanation, which is rather challenging to get through, from a regulatory perspective, but we have this material available, and Medscape has also disseminated this broadly to health-care

professionals.

The third item listed here, the medical product safety educational resource, is a multimedia that was done under the auspices of the FDA, in which we profiled the value of reporting medication errors and medication problems through MedWatch. This particular video is targeted to the nursing profession.

So here's our health professional page. We do rotate the topics as they are of relevance. Oftentimes these will further communicate messages that FDA may have either with regard to some sort of a press release or other kind of initiative. We can actually get into quite a bit of detail and get additional information to our community.

I want to point out here -- I mentioned that the MedWatch page is also accessible through this health-care professional Web page. In the right column, you will see "Spotlight" and, beneath that, "Recalls and Alerts." The top bullet there is the MedWatch safety alerts for human medical products. Beth will be talking a little bit more about the detail behind that particular link. That is the other page that our office maintains with regard to the MedWatch safety alerts.

This is another page, the patient Web page that we also maintain. I would like to point out here that this will have targeted information for patients. One of the

areas where we do engage with individual patients or small patient groups is access to investigational drugs. You'll see individual links here that will drive patients to further information, whether it be through an expanded access program or through clinicaltrials.gov, where patients can actually learn about products that are under drug development.

The other point is that on this page we'll direct patients to this if they are interested in becoming a patient representative to an advisory committee. There's an actual application process. It's through this particular Web page and this link that patients have information about what an advisory committee is, what the role of a patient representative is on the advisory committee, and so forth. Again, you'll see a bullet point there with a link to our information for health-care professionals page, which takes us back to one of the OSHI-managed Web pages.

The third one that I would like to tell you a bit more about is the Medscape page. As I mentioned, it's one of the pages that we sort of maintain, if you will, the link to. With regard to Medscape, we have from FDA's homepage a link to an external site, Medscape. We have different kinds of mechanisms. There's the expert commentary and interview series. I'll point out here the

one to Dr. Tan, which is the third one down, the changes to the sunscreen labeling. I don't know if any of the committee members had a chance to listen to or be part of that particular communication, changes to the sunscreen labeling. We had quite a rollout in communicating those changes this summer. Dr. Tan is a clinician who is in the OTC division, the over-the-counter division. He gave an explanation as to what the changes were from previous labeling for sunscreen to what the new requirements are for the rule for sunscreen labeling. What we were able to do was to very quickly, on that day when that rule was announced, take Dr. Tan and then make his commentary available through FDA's Web page and also through Medscape. So it was disseminated broadly by Medscape, targeting the physician community. Within FDA, we have another office that deals in outreach to consumer affairs and consumer groups. It was disseminated quite broadly to patient and consumer groups as well. There were a number of different kinds of tools that were used to develop and disseminate the sunscreen rule.

Those are our Web pages. That's sort of a highlight and an overview of the Web pages. There are a number of links, of course, that we have on each of those pages, circulating back into other FDA areas. Those pages themselves are thoughtfully considered within our office as

to new information and the points of dissemination through the Web page.

I didn't point out, but should have probably, that some of those Web pages specifically have RSS feeds, so an organization could get up-to-date information and have it as a site available on their own Web site.

With that, I would like to describe to you some of the activities that we have for the OSHI-managed electronic subscriptions. Our office is very involved in communicating to a range of patients and health-care professionals. We do have newsletters to the health-care professional community every other week, or bimonthly, and similarly, to the patient network. These are subscriptions that the individual, as an individual, needs to subscribe to through the GovDelivery process.

Similarly, we have the drug safety labeling changes, which is a function under our MedWatch program. You will hear us today describe MedWatch as MedWatch-In and MedWatch-Out. The Office of Special Health Issues primarily is focused on the MedWatch-Out process. But with regard to the MedWatch-In, we're responsible for communicating and informing people about the process for being able to communicate into the MedWatch program.

DR. PETERS: Could we interrupt for one moment? Could you clarify a little bit what MedWatch-In is as

opposed to MedWatch-Out?

DR. MARCHAND: I think we're going to get into that level of detail --

DR. REYNA: We don't know what the words mean. Do you mean from the outside to the inside of MedWatch or inside to the outside? Is that all you mean?

DR. MARCHAND: Oh, okay. Thank you for the question. When I use the term "MedWatch-In," what I'm talking about is that the external community outside of the Food and Drug Administration, the public, is reporting into the FDA. Under the umbrella of MedWatch, there is further delineation, where there is a MedWatch report-in by the public, meaning the health-care provider or a patient or a patient's family member or a consumer. That's what we refer to as the voluntary MedWatch reporting-in component.

There's also a sponsor or industry-required reporting into MedWatch. There is actually a separate but very similar form.

So we have to, while we're managing this program internally, be very careful and very specific as to which MedWatch we actually mean. So that's MedWatch-In.

The MedWatch-Out program -- think of it as two products, primarily. It's reporting out from FDA to the external community on safety alerts, which are safety alerts for human therapeutic products, as well as safety

labeling changes, which are specific to drugs only.

We can get into more detail on that. It probably does require almost a map or a chart explaining which is which. We use these umbrella terms sort of amongst ourselves and have a level of confidence that we know what they mean. But I think it's always helpful to make sure that we do know what we mean. There are slight distinctions. So keep me honest on that, please.

The other subscriptions that we have -- we talked about the *Healthcare Professional Update* as a newsletter every other week. The *Patient Network News* is a newsletter every other week that patients and health-care professionals self-subscribe to. The drug safety labeling changes and the MedWatch safety alerts are all information that our office communicates externally to anybody who signs up for this through GovDelivery. As I said, the first two are bimonthly. The next two, the drug safety and MedWatch, occur -- the labeling changes, monthly and the safety alerts, kind of as needed. That can be anywhere from one to as many as five safety alerts per week. Then the HIV/AIDS communication is if there is something of high interest with regard to HIV therapy or new detection or some sort of information for HIV/AIDS, and similarly for the hepatitis. So we are involved in communicating externally through those electronic subscriptions.

The other thing we get involved with -- and this is probably the most interesting, kind of creative aspect of our office -- is, we will tailor the communication depending on the need of the group that is coming or has need to further understand FDA processes. We can have very often a direct communication, where we might have a phone conversation or we might have a small meeting or we might travel locally to visit an organization in the metro area and learn a little bit more about what their needs and questions might be with regard to FDA process. We also give oftentimes presentations -- kind of FDA 101 Basic -- as well as information about the MedWatch reporting in, as well as the MedWatch reporting out. You'll hear that again. If you have questions on that, continue to ask.

We also do some national meetings that we attend and speak to. As you can imagine, the health-care professional community typically has an annual meeting, and we do try to participate. For example, with regard to the American Medical Association, it's someone from our office who is involved in representing FDA and collecting the comments with regard to any resolutions that are proposed by the House of Delegates to AMA.

We also are involved in providing educational webinars. We have something ongoing where we have a monthly webinar series for our patient representatives.

Again, the patient representatives are those individuals who have been identified and have come on board for participating as a special government employee and are available for participating in FDA's public advisory committee meetings as a member. Those individuals are actually voting members to those advisory committees.

We also conduct stakeholder calls. These are calls where we establish a telephone communication and we'll have an FDA expert oftentimes communicating about a new initiative or a safety message, in which we have a line open for the health-care professional community to engage FDA on very specific questions.

More recently, we do get involved in developing some of the multimedia communications as well.

That's the overview of what our office is involved with in communicating. I would like to introduce and ask Captain Beth Fritsch to come and tell us a bit about the MedWatch reporting-in process, as well as the consumer form.

CAPTAIN FRITSCH: Thank you, Heidi.

As Heidi mentioned, I'm planning to talk to you today and give you an overview of reporting in in MedWatch and how you report in. Also I plan to talk about the consumer MedWatch form that has been under development for the past year. I'm going to try to take you through the

process of how this evolved.

First of all, FDA's adverse event reporting is MedWatch. It has been around since 1993, so for almost 20 years. It's mainly used for drugs and medical devices. Most of the time when reporting in, most of the reports that are received are for drugs or medical devices. MedWatch can also be used to report adverse events for dietary supplements, for infant formula, and even, most recently, tobacco, as we now regulate tobacco as an agency.

Reporting into MedWatch is really how FDA finds out about postmarketing risk and safety issues. We receive reports of serious adverse events. A serious adverse event might include some type of life-threatening, requiring hospitalization, a birth defect, or disability. We also receive reports of medication errors. Those could be involved with the wrong dose or wrong medication. Lastly, we receive reports of product quality issues. This could be for counterfeit products. It could be for a product mix-up or some type of a device malfunction.

Basically, our discussion today -- I'm talking about reporting in. I know Heidi mentioned that there is a voluntary and a mandatory reporting mechanism. What I'm going to focus on today is the voluntary reporting mechanism. Basically, this slide is showing that anyone can report in a serious problem through MedWatch. The

reports come in from throughout the country, from Washington State, from Maine, from Florida. The reports come in from health professionals. They come in from nurses, physicians, pharmacists throughout the US. They also come in from patients.

This slide shows the MedWatch voluntary reporting form. This form is Form 3500. Currently it consists of about two pages to fill out for someone who is sending in a voluntary report. It's about two pages, and it contains about 10 pages of instructions. The available formats for this form -- it's available in several different ways. It is available as a paper form, which can be printed and mailed in. It does contain a postage-paid mailer. It can be faxed in. It can be submitted online. It can be completed online as a PDF and then printed and mailed in. Or one can contact CDER's Division of Drug Information at the toll-free number to request a form to be mailed to them.

AERS, or the Adverse Event Reporting System, is the FDA database that captures adverse event reports. This chart actually gives us the number of reports that are submitted by health professionals and consumers by year. As you can see, the reports since 2001 have steadily increased. It's actually about a fivefold increase since 2001. We did see a spike in 2009 that was a little greater

slope than previously. We're thinking that this could be attributable to the fact that the 1-800 number and also the MedWatch Web site are now appearing on prescription drug labels, they are appearing on print ads for prescription drugs, and they are also appearing on consumer medication information.

This kind of put us in a situation, in that a patient or consumer was going home with a prescription and they were reading the leaflet that came with that prescription and they were seeing this 1-800 number. They weren't really sure what that 1-800 number was for and what they were supposed to do with that. Some of the folks actually called that number, which takes you to CDER's Division of Drug Information, and they were requesting refills or they thought it was their insurance company.

That made us think that there was a gap, a real gap, with consumers. So our office, which kind of manages the MedWatch form, decided to embark on a program. Actually, it's a MedWatch education program. That's what we have decided to do and we went forward with that.

The two main components of the program: One, we wanted to have listening sessions. We wanted to talk to consumer organizations or consumer advocacy groups. We also wanted to develop educational tools to help consumers understand adverse event reporting.

What we ended up doing -- we did end up organizing three listening sessions for consumer advocacy groups in December of 2010. We asked those groups, how do you communicate with your constituents? We also asked them if they were using social media to communicate as well. We gave them the background of the MedWatch program and what it does.

I guess what's kind of important is what we heard from those groups. We did share with the voluntary form, the 3500 form, the form that I mentioned had two pages that a person would fill out and then 10 pages of instructions. What we heard was that this form was too complicated for consumers to fill out. We heard that the explanations were too lengthy for consumers of all levels. We heard that there was a high level of literacy that was needed for consumers to fill out this report. At the end of the day, many of the participants in the listening session mentioned and suggested that FDA create a consumer-friendly form for MedWatch.

The original goal of the MedWatch education project that I mentioned was really to develop educational tools to help consumers understand the importance of reporting adverse events into FDA through the MedWatch program. That's what we thought our real goal was. But after hosting three listening sessions with the consumer

advocacy groups, we learned that maybe our goal should be shifted to developing a consumer-friendly MedWatch form, and that's kind of the path that we went down.

The steps that we started with -- online, Canada and the United Kingdom each have consumer forms. We really used those as a starting point, to kind of look at how they were designed, what kind of information, how they were worded. That's kind of where we really started. We also used writers, and we consulted a plain language expert to help us develop a prototype.

We shared the materials within our FDA staff, through various centers and also various offices.

This slide is just going to kind of summarize the overall process that we undertook in developing the MedWatch consumer form. This process has gone on for approximately one year. We did hire a contractor. The contract was awarded in September 2010. The contractor helped us facilitate three listening sessions back in December 2010. That's where we learned of the need to develop a consumer-friendly MedWatch form.

Between January and June 2011, we again worked with the contractor very closely, the plain language expert. We reviewed the forms from the United Kingdom and Health Canada, and tried to put together a really good prototype.

In July and August of 2011, we actually took, not one prototype, but two prototypes back to the consumer advocacy groups that we had first engaged. We asked them to share their feedback with us concerning the design of these two different prototypes.

After that, we basically took some pieces of the two prototypes, some of each, and combined them into one form and finalized the draft consumer form.

After that, September 9, we published a *Federal Register* notice and we solicited the public for comments to the consumer form. The comment period closed on November 8. Currently we are in the process of reviewing those comments. Ideally, we are hoping that we can launch this form sometime in 2012.

This is a screen shot of the first page of the proposed consumer MedWatch form. As you will notice -- I believe you have a copy of this form in your packet -- the boxes are larger on this form. It's a bigger font, a little bit more white space. The total number of pages -- rather than the two pages, it's actually increased to three pages in length, but that's partially due to the increased white space, font, box size, et cetera.

Lastly, assuming everything goes well and we're able to make this form a reality, we are hoping to be able to promote the form and perform outreach, develop some

educational tools, and to kind of get the word out about it. We hope to go back to those consumer advocacy groups. They have been very supportive in the development of the form. We are hoping to work with them to promote the form as well. We think it's really important for patient advocacy groups to know and be able to let their patients know that such a form exists. During the process of the development of the consumer form, we outreached to librarians. The librarians are at the community level. We think they are accessible and we think they are a really good resource. They were also very helpful to us in this process.

We also plan to engage with health professional organizations, who can get the word out to the patients.

We also hope to take the message into colleges, particularly medical schools, pharmacy schools, nursing schools, for those who are undergoing education to learn about MedWatch while they are in school and to kind of take that message back to the patients that they treat and they care for.

Next, in terms of educational tools, we have worked with our contractor to develop widgets and also a button and a badge. These would be used electronically -- electronic tools -- and be able to further disseminate the message.

We also hope to develop a YouTube video and then publicize that. We hope to conduct some training sessions within the consumer advocacy groups, so we can train staff and they can go out and talk and train their constituents as well.

Lastly, electronic newsletters, e-lists, and Twitter -- I know Heidi talked a little bit about some of our outreach tools there. We do have two electronic newsletters. One is the *Health Professional Update*. That goes out to about 41,000 subscribers. We have the *Patient Network News* that goes out to about 7,000 subscribers. Our e-list for MedWatch has about 200,000 subscribers. We would like to send messaging through that. Lastly, we do have a Twitter account for MedWatch.

That concludes my presentation. I'm going to turn it over to Anna to discuss safety messages.

DR. PETERS: Could I actually interrupt with just a quick question? It may be, Anna, that this is what you're going to be covering, so please just let me know if that's the case. In terms of the committee being able to respond to some of the questions you have, I just have a quick question first.

It's absolutely great that you are making it more health-literate. Ten pages of instructions would probably be difficult. I didn't actually see that form. Also

making it accessible I think is terrific. But I do have a question about what the purpose of it is. What's the purpose of getting this information in? Will it eventually go back out? Maybe this is exactly what Anna is talking about.

DR. FINE: I can probably just touch on it and then maybe we'll be able to clarify more at the end of my presentation. Now we're going to talk about MedWatch-Out. Probably a common question that we do receive is, we report to FDA, and then what do I get back? Why do I report? Why is it important? The MedWatch-Out will hopefully answer your question.

With that, now that we heard from Beth on reporting into MedWatch, I would like to review the various mechanisms through which MedWatch reports back out to the public. That's sort of our logo, with the arrows in and going back out. It's sort of a full circle, we like to think.

Not only does MedWatch have its own Web page on the FDA Web site, but you'll also find two distinct products. The first is the MedWatch safety alerts. They are issued in a timely manner and they are product-specific. This can consist of -- not limited to -- certain examples, such as drug recalls, Class I recalls, drug safety communications, or even an early communication on an

emerging safety concern with a product. On average, they do range from about one to four per week, as Heidi has mentioned. There have been days where we might have had to send three or four per day. We don't look at the numbers. It's basically, is there an issue that needs to get out there? That's how the number that goes out is determined.

The second product is the safety label changes. Those are issued monthly. They capture the safety changes to a prescription drug product labeling, also known as the package insert -- what we like to think of as the holy grail for a prescriber, to know what's really in the label and knowing how to prescribe and use a product. With an average of about 45 labels per month, we have over 80 to 100 changes per month going back out to the community. Some examples would include changes to a contraindication or an adverse event updated to the label. This will affect the practice and whether or not this product still continues to be the right one for their patient.

In 2010, we issued about 169 MedWatch safety alerts. Thus far for 2011, we have around 130 safety alerts. We had 430 medical products in 2010 that were posted to our Web site with safety labeling changes. This is the piece that comes back out to the community. You report in, it's internalized -- that piece we don't work on -- and eventually the messages come back out to you on

what those changes might have been due to the reporting.

What am I referring to when I say we issue the messaging? The safety alerts, as Heidi mentioned -- we are in the Office of the Commissioner, so we have that broad view across the agency. They may also include drugs, as well as devices or biologics, sometimes special nutritional products or unapproved drugs. You may also find things with undeclared drug ingredients which we think might be important for a health professional. Your patient will be taking something that they think is a dietary supplement, when in reality there is an active ingredient in there, and that could be drug interaction. So there are a variety of things that are going out through MedWatch.

When we say they are issued, what we mean by that is that they are going out through a variety of mechanisms. That's sort of leads to one of the questions that we have for you and why we did a survey as well. We have the GovDelivery email account. It's an electronic email distribution. We have text messages. We have an RSS feed. You can also follow us on Twitter.

The MedWatch Web page not only serves as a place where you can find the most current and newest alert that's posted there, but it also serves as a historical reference. You can find alerts dating back as early as 2000.

How do you sign up to receive a MedWatch alert or

an email list, like 200,000 people already have? It's from our Web page. This is our homepage. This is also where you will find the most current alert, as well as links to our labeling changes, as well as ways to report into MedWatch. This is where you can sign up for receiving our MedWatch alerts. It's in the "Stay Informed" box, where you can also sign up for other various mechanisms of receiving these messages. What you enter is really just your email address. This is to also point out that the only information captured is your email address. We do not share or spam you, and we have no information on you or who's subscribing to our messaging.

Here is an example of our MedWatch safety alert. This is an example on the tumor necrosis factor-alpha blockers. It's with a warning for a risk for *Legionella* and *Listeria* infections and increased risk for developing serious infections with the use of these drug products.

This is an example just to show you what you would receive when you sign up for our alerts. We do have a consistent format, something that we have reviewed in years past on how to structure our alerts with the audience and the chunking and making sure it's very readable and user-friendly.

Here's an example of the exact MedWatch alert reproduced on the Infectious Disease Society of America Web

page. This is a health professional organization, and they are further cascading our information to their constituents.

Here's one more example of our MedWatch alert that resulted in an article on Medscape.

So we hope that the information is seeping into the community and that there is integration of this information into practice. This is just an example of things that we could find on Google search or a Web site or maybe through communications with our stakeholders, some health professional organizations. We ask them how they use our alerts.

As I mentioned -- how can you subscribe to MedWatch alerts? -- all we capture is your email address. We do have nearly 200,000 subscribed. Health professional organizations keep abreast of the information for the health professionals. But to better understand who our audience is and how satisfied they are with our service, we conducted a survey.

This survey was through a customer satisfaction with ForeSee Results, who has been used in government since 1999. It revolves around the citizen satisfaction utilizing the ACSI method for calculating the satisfaction score. The data for the survey was conducted from September 9 to September 30. Every time we sent out a

MedWatch alert during this time, at the bottom you had a static link. Anyone, if they happened to see it, was able to click on it and take our survey. The goal of the survey was really to find out who is subscribing to MedWatch, how they are using it, and how satisfied they are. Are we truly getting to the community? It's a difficult question for us to answer. Hopefully you could help us with that.

We had a 13 percent completion rate, with about 1,468 surveys completed during this timeframe. The survey consisted of general satisfaction questions, as well as some custom questions to better understand our audience.

At the bottom of each email, you will have, "Tell us how we're doing." We would hope that people would click on that and provide their feedback.

The ForeSee provides a quarterly index, and it benchmarks government Web sites. They have about 100 different federal government Web sites that use this mechanism and tool for disseminating surveys. We are, however, the pioneers in using this for a government email-type survey. When you go to the FDA Web site -- or maybe any other government Web site -- you might notice that after a few clicks, a survey pops up. That's how I mean that this is very different versus a Web page. In this case it was just a link that was provided in email.

It's rather difficult to benchmark us against the

other government Web sites. However, the average on comparison of the other hundreds that are on the Web site email surveys -- their score is in the 70s, 74. It has been escalating, 75, as people are trying to improve their usability. Our score was 82. We are told that scores 80 and higher represent a highly-satisfactory and that citizens are satisfied.

We wanted to know the role and who the people are who are subscribing to our survey. Some of the roles include consumers, which we learned. We always thought that MedWatch was for health-care professionals. As we're seeing, there is an escalation in how many consumers are now submitting reports. For the other, people were a bit more specific in trying to identify who they were. Some of those included medical, nursing, or pharmacy students, versus "I am a pharmacist," when the question was asked of what role you are in. One could be led to believe here that when you have about 31 percent of health professionals, perhaps with the other is when they identified themselves more specifically of the type of health-care professional they are -- we could say that maybe there are more than 31 percent health professionals who subscribe to MedWatch, but also noting that there are 41 percent of consumers that responded.

While health professionals and consumers are both

using MedWatch emails to stay informed themselves, the health professionals are much more likely to be using the emails in other ways professionally, such as informing their colleagues or patients or presenting the information at meetings or publishing in newsletters or even online, as we saw with the Infectious Disease Society.

This is an example of what they are doing with our emails. The ones that are in boxes are to show that there is a distinction between how consumers use and how health professionals use our emails.

Both consumers and health-care professionals are most likely to select other responses when you ask them, how else would you like to receive our messages? This is an important question for us, because we want to know if we are getting to the audience that we want to be getting to, and if there are other ways that we could perhaps distribute this information. It was interesting to find that, though we didn't put email as an option -- because we assumed this was an email survey and we asked how "other" they would like to receive -- you would find that perhaps it's a bias -- that I'm receiving it through email and taking an email survey, and that's how I want to receive your messages.

Comparing the two groups of respondents, health-care professionals are more interested than consumers in

text messaging alerts and podcasts.

One of the things that we learned from this is that we have consumers following MedWatch, a lot more than we would have perhaps thought, because we always thought that MedWatch was really geared towards health-care professionals. But the way that they are using it is slightly different. You will have consumers using it for personal information, whereas health professionals are using it to inform their colleagues or their patients and to keep informed of what's going on with practice. About half of the health professionals -- sometimes you'll have an alert and you're thinking, oh, no, it's 6:00, do we send it out? Health professionals may not be in the office anymore, and are they going to get it the next morning and are they going to read it? We were curious sometimes, because when I'm here at 8:00 on a Friday night thinking, do I even need to send this out or should I wait until Monday morning -- this was a question that we thought maybe would help answer it. But it really didn't. A lot of people at the end of the day would say, we're willing to get it any time. It's important safety information. As soon as you know about it, get it out there.

Beyond email, we learned that health professionals might have interest in video, podcasts, or text alerts and Facebook, and also for consumers outside of

email, Facebook and video are most appealing as means of communication for them.

Today Heidi provided an overview of the specific communications from the FDA Office of Special Health Issues to patients and health professionals. Beth highlighted the various ways to submit a MedWatch report to the agency and the 3500 form, as well as introduced the proposed consumer MedWatch form. I reported the various ways that the agency communicates to the public with MedWatch, including our robust GovDelivery electronic email listserv, as well as the survey that we conducted as an attempt to better understand our audience.

With this summary, we would like to thank you for your attention. We would like the committee to also consider the following discussion topics:

- Does the committee have any comments for us to consider regarding the consumer MedWatch form?
- Feedback that you might have on the development of educational tools to educate consumer reporting into FDA.
- Suggestions from the committee on other methods for dissemination of MedWatch alerts.
- Discuss other methods or tools to assess MedWatch safety alerts integration into practice.

Thank you.

DR. PETERS: Thank you very much. Why don't we go ahead and start?

Agenda Item: Committee's Advice and Concluding Comments, Session II

DR. MILLIGAN: That was a great presentation. I really appreciate it. This question is for Anna. I wanted to get you before you move from the podium.

I thought the survey information was very important and interesting. As an industry member, we struggle with this all the time. Were you able to get any information on whether or not your communications through the MedWatch resulted either in any enduring knowledge from the consumer or physician point of view or result in any change of behavior?

We are often asked to measure those sorts of criteria with our own communications from the industry with some of our medical communications and medication guides. I was curious whether you were able to gain any information on your survey about those two outcomes as well.

DR. FINE: That's an excellent question. The survey didn't have any questions that would have actually asked that question. I'm not sure if we were able to measure it. I think that's one of the reasons we like to also get into potential CME activities through our partnership with Medscape, because there you are able to

actually ask questions prior to the activity and post-activity: Did this change your behavior? Will you apply this?

But no, the survey did not address those questions.

DR. PETERS: Thank you. Shonna and then Craig.

DR. YIN: I have a question about the MedWatch consumer reporting form. I was wondering about the extent to which these forms have been looked at and tested with patients, especially patients with lower literacy. As I look through some of the information, I could see how things could be simplified a little bit more than they are now.

My second question is related to whether or not there is a plan to translate this to other languages.

CAPTAIN FRITSCH: For your first question, we mostly went to and worked with consumer advocacy groups on the consumer form. When we took the prototype form back to those groups, a couple of the groups did provide us some actual consumers to take a look at the form. I'm not sure what the literacy of those folks might have been, and I'm not sure if they would have been on the lower literacy level. I think we thought that it was important to try to get the form out. We know that if it does get approved, it will need to go through the OMB approval every three years,

and if we needed to make changes, we could do so at that time.

There's also still some comment period. I guess the public comment period closed, but we do have some comments that we are reviewing as well.

Your second question was about the various languages. That was a comment that we heard as well. Two of the consumer groups that we talked to along the way -- one strongly encouraged us to translate the form into Spanish and the other group was favoring several different Asian languages as well.

Again, our first goal is to get the form out there and publicly available. Perhaps down the road we can look into translating the form.

DR. PETERS: Craig, Noel, and then Val.

DR. ANDREWS: There are possibilities to easily get at the readability of this, different grade-level issues and literacy issues, similar to the patient medication information that's out there.

A couple of little things. We were just sitting here with questions. I was asking one of my colleagues who knows a little bit more. There is some information on here. Maybe it's on vaccines and other things, but I don't know as a general consumer -- things like lot number, NDC number, UDI. Are those common terms? I wasn't sure if

consumers would know these abbreviations that are on the form.

DR. PETERS: This is under medical devices?

DR. ANDREWS: Yes, it's Section B and Section C of the form -- perhaps lot numbers, NDC number, UDI number. I was just curious.

CAPTAIN FRITSCH: Those are some of the -- a lot of the products -- and we do understand that consumers may have some challenges with that. I think that's one of the areas on the form we kind of went back and forth on. I think a lot of folks internally to FDA -- it was very important for them, if those numbers were available, that they report them into us; if they are not available, then to leave that section blank.

I do have some colleagues here who helped me work on the form. Would you agree with that? Yes, okay.

DR. ANDREWS: What do those represent? I was just curious. NDC, UDI?

CAPTAIN FRITSCH: NDC is national drug code. It would be for a drug product. The UDI is actually for a device. Does that help?

DR. PETERS: Thank you. Noel, Val, Gavin, and then Bill.

DR. BREWER: I have a couple of miscellaneous things. One is sort of picking up on Sandra's question. I

had a very similar response.

Actually, even before I say this, I just thought it was great that you all were collecting data of any sort. That's a real step forward, and I think that's really admirable. It's very thoughtful. It's excellent.

I did wonder if there was some way of going beyond the process kind of evaluation to an outcome evaluation. Process is, did you like it? Was it satisfying to you? Then an outcome evaluation is more along the lines of what Sandra was talking about, trying to assess what kind of impact it has on the people who are receiving it. A study of behavior is a whole endeavor unto itself, but you could look at some more proximate things -- for example, what the main message is that they got out of the email they received. It could be a question as simple as, what's the main message that you think this email contained? Something like that might be very revealing and might start to open the door to some other kind of communication. It may tell you that you are getting it exactly right and that people are walking away with exactly the message you want or that they are walking away with 10 different messages or that there's really nothing -- they'll say something like, "I don't know."

Any of that information might be very useful for giving you feedback on thinking through what it is you are

communicating.

On this form, I didn't have a sense of whether you have done usability testing on it. It sounded like you have gotten a lot of consumer feedback in a general way, which is a little different than usability testing. There are people who have been on this committee before and some now who know a bit about usability testing. The things I'm thinking about are a little beyond literacy and plain language. It sounds like you have gotten feedback on that. I'm thinking of just the plain graphics issues. I'm thinking in particular about the Dillman book -- I think it's Don Dillman -- on survey design. There are a couple of principles that they recommend that this doesn't necessarily follow that you may want to think about following that may help create some -- increase readability in some ways and in other ways you could even perhaps increase it further.

For example, I'm having a hard time parsing elements here of questions versus responses and when one question ends and another question begins. There are a couple very small things that you may be able to get away with doing that would help sort that out.

DR. PETERS: Related to that, another type of study that you might consider doing, given the number of people who have signed up for this -- why are other people

not using it? Then using some of the same process measures, as well as the kinds of impact measures that Noel is talking about with them might help get at why it isn't used even more.

Val, Gavin, and then Bill.

DR. REYNA: I'm actually quite impressed. The document I have has a single page of instructions, followed by three pages of a form. So I'm looking at the right thing. It seems remarkably compact considering the complexity of the kinds of things you are trying to do surveillance on. I'm actually quite impressed. Not that it couldn't always be better -- all of us can always be better -- but I was impressed with the presentation and with the form.

One of the things I would mention is that the health-care professional outreach, the pages that we saw, and perhaps also the patient groups -- if there is any way to begin to take advantage of artificial intelligence or any other kind of technology to be able to pinpoint the targets of these messages. As a health-care professional that might be interested in lots of things, depending on the specialty, the type of patient you have, what the nature of your problems is, you have to go through all of this very useful information, but it may not be directly germane to you. The degree to which we can target these

messages to their correct recipients in the most efficient way, in some kind of a passive technology kind of way, where people don't have to select a bunch of boxes to finally get to where they want to be -- or at the other extreme, which is very common now today, which is the alert and reminder overflow, where there is an alert and a reminder on 50 things and 49 of them aren't quite relevant to you directly. We have an explosion of information. You have great information, and I think if people had sufficient leisure time, all of it would be probably useful to some degree. But getting the right message to the right person in the most efficient way in this massive information overflow I think is a real challenge. But I think technology could be useful here.

In a more general way, a quick note on the evaluations. If there is some way to ensure that the samples of feedback you are getting are at all representative or the nature of the sampling, that would be great.

My third point is a general one -- a very kind of hard issue, but one that I think we have to raise. In these kinds of reporting mechanisms -- and, by the way, I have no solution to this problem, but I think it's an important problem -- cause and effect. What you have here is a contiguity issue. What happened right after you took

the medication? What happened after you used the device or made a change? That's probably the best you can do. But as we all know, that's not cause and effect, because lots of things can happen afterwards that have no causal connection to the prior event.

There is also the issue of the patient or practitioner noticing something odd. Did anything strange happen? That's the sort of thing that would trigger this form.

I know that this works to some degree. It's kind of remarkable that it works, because the patient and the practitioner have to kind of know something they don't know yet. Anything odd here, report it. Until you really know what the issue is -- and once you get enough of these cases, you say, okay, there's a bubble here, and now we have to respond and figure it out. It's kind of a miracle that these things work.

Anything that could pinpoint causality better would obviously be a boon.

DR. PETERS: I think at this point, actually, we're going to stop and take a break, unless Lee has something to say.

Let's do one quick comment from Nan.

DR. COL: I'll be really fast. I loved it. The current prescription medications and over-the-counter

medications -- the average person takes 10 or 20 now. More space for that I think would be useful, because you could look at drug interactions and get at the causality issue.

DR. PETERS: And taking a break does not mean we cannot continue to bring up these issues, by the way, afterwards -- not that it's easy to stop anybody. Everyone is having some great ideas. I'm hoping that after a 15-minute break we'll have more great ideas and suggestions for the group.

Thank you very much. We'll see you guys back at 3:30.

(Brief recess)

DR. PETERS: We're going to go ahead and talk about MedWatch and talk about some of the interesting questions that our speakers have brought up today until about 4:15. At 4:15, we're actually going to switch topics back to our morning session, in order to continue to have a little bit of discussion. I know CDER would, in particular, like some more input on one of the questions in particular. We talked with them over the break.

But, in general, just to kind of reintroduce us gently back into the MedWatch issue, we talked quite a bit about how it's just amazing how you guys have done a really nice simplification of the form from before, but also have actually done some testing. Again, I think this committee

should over and over laud FDA for how much testing they are managing to get in of their communications. This isn't exactly a communication, but it kind of is. It's trying to pull information from consumers. It's great. There is probably some more to do around issues of health literacy and usability and some other issues. But the changes that have been made have been terrific.

I have a couple of quick questions, if I could, just because I didn't quite understand. Is MedWatch the total of the postmarket surveillance? Between the consumer input, the physician input, and the pharmaceutical input, is that postmarket surveillance for FDA or are there other bits also?

DR. MARCHAND: It's kind of a difficult question to answer, because MedWatch comprises the opportunity for input, whether it's a drug, a device, a therapeutic, a nutritional, and so forth. It goes into a central clearinghouse that ultimately then goes into individual databases by center. For the Center for Drugs, for example, it could go into two separate databases.

I also mentioned that MedWatch is postmarketing safety information that is spontaneously reported. There's a component that is voluntary, which is health-care professional or consumer, and then there's another component that's mandatory. That would be a sponsor

requirement and function. Actually, that's a 3500-A form, as opposed to the 3500 form. You can actually access each of those on the Web site and see what they look like.

There are slight distinctions.

I think it's fair to say, for the Center for Drugs, it represents the majority of the postmarketing information. It could very well be that there is other information that comes from outside of the US, for example, because this form is US-derived. So I can't say it's absolute, all of the postmarketing. I wouldn't describe it that way. But it represents the majority of the postmarketing information that is coming from the US.

DR. BREWER: Is it also the VAERS system, the Vaccine Adverse Event Reporting System? Is that included? I just wasn't sure.

DR. MARCHAND: With regard to the MedWatch reporting, that is a drug adverse event. It will go into the AERS system --

DR. PETERS: If I could ask a follow-up question, too, which is maybe a better rewording of something I attempted to ask before. Is the simplified form intended to increase consumer input -- so increase the number of people who input -- and/or is it intended to reduce the noise so that it can be used better in postmarket surveillance?

CAPTAIN FRITSCH: When we were discussing the form, it was kind of twofold. We wanted to educate consumers about when to report an adverse event. We weren't necessarily looking to increase the number of total reports. Over the past 10 years, the number of reports has gone up basically five times. But what we are seeing is the quality of reports -- sometimes when the consumers are submitting reports, they are not really submitting useful information, because they don't know what to include in the report. We're really hoping that this could improve the quality of reports and also allow consumers to know what to report.

DR. PETERS: That makes a lot of sense. Thank you.

I have a list of people who wanted to make comments earlier. I can go ahead and start with that. But feel free to pass if you have managed to forget your question over the course of 15 minutes. I have Nan, Gavin, and then Bill.

DR. COL: I already asked it.

DR. PETERS: That would be an error in bookkeeping. My apologies. So at that point, then, we have Gavin, Bill, and then Mary.

DR. HUNTLEY-FENNER: I think a number of questions I was going to ask have already been asked. I

just want to underline Nan's point about needing more room for additional medications -- I think that's a good point -- and also Val's point about the sampling issue. It seems like this is a great opportunity to use the form to actually see whether you are getting a representative sample or not. I don't know if Val has some answer up her sleeve as to how to do that, but I think that's something that ought to be considered.

With respect to this question that was just being discussed -- namely, the issue of the quality of the data -- I want to ask you about the increasing forms in responses that you saw in 2008, 2009. Do you know whether most of the increased forms were from physicians or from the general public, proportional to previous years?

CAPTAIN FRITSCH: We did have information about reporting either from health-care professionals or from consumers. It looked like during the increase it was actually coming from both groups. Perhaps consumers may be at a little bit higher rate than health professionals.

I kind of want to qualify my response by saying that in the existing MedWatch form that we have, the 3500, there's a box on there that says "Health Professional," and you have to check yes or no. If you are a health professional and you check yes, then it's counted as a health professional. If you check the box no, it's counted

as a consumer. The reason I'm qualifying my answer a little bit is that if that box isn't checked at all, then it's counted as a consumer.

DR. HUNTLEY-FENNER: It seems like that might be important to know, especially with regard to the noise question. You may find that you will get a higher-quality type of response from physicians. The two sources might be useful for different types of analyses. I'm sure you are all over that.

Finally, one small point. Sometimes these forms get printed out and show up as printouts. But you may want to put somewhere on the printout that the form is also available online and you can complete it there.

I notice there wasn't an email address for submitting the form. There was a snail-mail address. If there is an email address, you can probably add that, too.

DR. PETERS: Thanks, Gavin. Bill, Mary, and then Moshe.

DR. HALLMAN: I have a question and a recommendation. If I understand it correctly, you got a half a million of these in recent years? Something around there, 400,000 or something like that. Who reads 400,000 reports? Walk us through the process of how this works. Are there some of these where you hit the panic button, there's an emergency? Are these sort of done routinely?

How long does this take?

DR. MARCHAND: One of the things that maybe we didn't totally disclose clearly was that with regard to the MedWatch information that comes into FDA -- and I'm looking at Beth's specific notes; 830,000 MedWatch reports came to FDA in 2010, approximately -- it is not our office that reviews all 830,000 of those reports. In fact, of those reports that come in, they will be further triaged into databases and data collection of the different centers. The Center for Devices has a specific database, the Center for Drugs has a specific database, AERS, as well as a second database, and so forth.

At that point, electronically there are reviewers that will evaluate those reports coming in, in the context of other safety information that is available to them. That's not the responsibility of our office, and I can't necessarily speak to the specifics of, after it's triaged, precisely how it's reviewed by the safety review officers within the division and the Office of Surveillance and Epidemiology.

DR. HALLMAN: So if I understand it correctly, this is sort of additional information to give you clues when perhaps there is information from another source. So information comes from another source and you corroborate it with the database? It's not serving as a primary

indication that there may be a problem? Is that correct?

DR. MARCHAND: This is a spontaneous postmarketing safety reporting system. The agency gets thousands of reports. That is reviewed and evaluated in the context of all information that is available on that product. There might then be an outcome of a safety alert or a safety labeling change and so forth.

DR. HALLMAN: I'm still sort of -- so how is meaning made of these reports, I guess is the question. There has to be a human being who is reading these things. It's not your office. Who is it?

DR. MARCHAND: Who is receiving the report will actually be, for the example of drugs, a medical review officer within the Office of Surveillance and Epidemiology, involved in looking by therapeutic area, potentially -- it's how they may be organized -- and evaluating that safety information in the context of all known safety information. It might very well be that a signal is raised that they want to do some further review and analysis. Again, that's not our office. That office for the Center of Drugs is managed by Dr. Gerald Dal Pan.

DR. HALLMAN: So essentially there are human beings who are reading this. There's no artificial intelligence. There's no scanning of the database. That's a very large data set, even if split it a number of

different ways.

DR. MARCHAND: Not that I'm aware of. But maybe, given your questions, it would be fair to have further review of that process from the Office of Surveillance and Epidemiology.

DR. REYNA: To further clarify that question -- I was going to ask a very similar question -- in particular, what numerical triggers are there? Again, severity matters. A small number of a really bad thing is pretty bad. A lot of a not very important thing is not too bad, unless it was so common that it was really debilitating to many, many people. Somebody must contextually interpret this. Or are there real cutoffs for adverse events of various categories in advance?

DR. MARCHAND: You're right, somebody interprets it and they look at it in the context of the particular product and the particular patient population and the severity and the proximity and so forth.

DR. REYNA: I sense a data opportunity here to try to extract, at least post hoc, where people are forming their thresholds. I think that actually could be extremely useful on the other end, for both surveillance in advance, anticipating the nature of these categories in a systematic way, and trying to simulate this human intelligence.

DR. HALLMAN: Another recommendation: In looking

at the Form 3500, there are a number of categories here. One of the headings, I think, should be, what will FDA do with the information I submit? Which is not currently here. Implicit in that idea is, is it really worth my time to go through -- it's now only three pages, but it's a lot of questions.

Very specifically, I have a question about a category. When should I use this form? One of the reasons you should use it is if you used a drug, product, or medical device incorrectly which could have led to unsafe use, which doesn't make sense to me. If you used it, how would it lead to an unsafe use?

DR. MARCHAND: Maybe the directions weren't clear, that sort of thing.

DR. HALLMAN: Okay. Maybe that could be clarified a little bit.

One other detailed piece of information. Will the information I report be kept private? You say, "Your name will not be given out to the public," which is then followed by, "This information may be shared with the company that makes the product to help them evaluate."

It's not clear whether you are talking about their name or everything but their name. What does "this information" refer to?

DR. MARCHAND: The adverse event that occurred.

DR. HALLMAN: So if that could be clarified in the instructions, it would actually make more sense.

Finally, in Section B, where you ask about the strength, the quantity, the frequency, how it is taken, I assume that you want them to read this from the prescription, so it's what they should have been taking -- for example, two pills or two puffs -- rather than the four or eight which led to the adverse event that they actually did -- if there was some mistake in their use of this. This is what they are supposed to be doing, not what they actually did, which may have actually led to their event.

DR. MARCHAND: Thanks.

DR. PETERS: I have Mary, Moshe, Shonna, Kala, and then Nan.

DR. BROWN: I would like to echo Bill's comments. I think they are very to-the-point.

I would also like to commend your office. It's ironic that you had this education project and then it turned into a project that educated FDA. I thought that was interesting.

One way to assist patients to fill these things out or explain why it's valuable to fill them out -- I'm speaking as someone who has been working with medication safety and who has looked at these forms for many years -- one way could be a simple tutorial online that walks them

through filling out the form and explaining. Also I do think it's important for people to take the time -- and they have to be motivated in the first place; otherwise, they wouldn't fill out the form -- explaining where the information goes clearly and attempting to give feedback on what is collected, in some form. I don't know whether that's possible with all of the information that FDA takes in. But in the past I have always felt that those that we ask to give input on surveys deserve to hear something about the results.

This is outside of your purview, but I'm going to add it because it has been something that has been on my mind for quite a while. It might be very useful to do this same sort of thing for the FDA Web site. I and many of my colleagues have found the FDA Web site in general very difficult to navigate. I recognize that there is an incredible amount of information that you need to convey on the Web site, but I think there are ways that it could be improved. I would love to see you pass that information on to whoever is in charge of the overall Web site, that there is an opportunity here.

In fact, I just got an email from one of your sister agencies, SAMHSA, saying that they are embarking on a Web site improvement project and they would like input from the people on the email list for the Web site.

Maybe just your pages would be helpful. But even for someone who works with information a lot and is familiar with Web sites and how to navigate them, it's very dense and difficult to navigate.

CAPTAIN FRITSCH: One thing I just want to make a comment on about the Web site. When we spoke to librarian groups -- and there were two different organizations we spoke to of librarians -- one of the things that they said to us was that they would really like us to come back and speak at one of their annual conferences. They wanted us to talk about the consumer form, assuming that that would get approved and go forward. But the other big request that they wanted us to do was to kind of train the librarians on where to find information on FDA's Web site, because they had challenges with that.

I just think your comment is quite interesting.

DR. MARCHAND: Can I also just ask a point to clarify? Maybe you could expound on it a little bit. What, in your thinking, would be an ideal online tutorial? That is, I think, where we have interest in taking the next education step. In fact, we would like to have something that would be almost -- our thinking is maybe something kind of modular that could be taken to colleges, health-care professionals, health professional associations, and so forth. From your experience and thinking when you made

that comment, what would a great program look like?

DR. BROWN: I was thinking in terms of the consumers. It would be fairly simple, as short as possible, so that it doesn't take up too much of their time. But if they have questions -- maybe some of these things are ambiguous -- a tutorial would be helpful, just walking them through.

DR. MARCHAND: And having perhaps a dummy form to fill out -- actually, a hands-on experience kind of thing?

DR. BROWN: Yes, right, like a WebEx demonstration.

DR. PETERS: That's terrific. Thank you, Mary.

Moshe, Shonna, Kala, and then I have a few more names after that. Probably at that point we'll be close to finishing up.

DR. ENGELBERG: In the spirit of all the well-deserved commendations on the work you have been doing, in particular the MedWatch, and in the spirit of your third question about suggestions for dissemination, one recommendation and a couple of questions.

The recommendation is, I think you have a great story to tell that you could put together as a mini-case study and use it internally to promote more of this more customer-sensitive way of doing business, and also use it with partner organizations, within graduate programs,

undergraduate programs, where the lesson is about being more aware of the customer, doing pretesting, and so on, but the context happens to be this form, to increase awareness and uptake of MedWatch. I think it would be a great study.

DR. PETERS: I would second that, by the way. I thought that was one of the best things that you did, and other things were quite good, too. I think it was Mary who said that you used an education project to educate yourselves. I thought that was very nice.

DR. ENGELBERG: The question I have is leading maybe to a recommendation, but I need to clarify it. My understanding from your description is that to disseminate this to consumers, you have used mostly what I would call a pull strategy. If I'm a consumer, I need to go somewhere to get this. I'm pulling it from somewhere. It's not being pushed toward me.

DR. MARCHAND: I think that's fair, although Beth commented earlier on this more recent regulatory requirement to include the 800 number for MedWatch on prescription labels and so forth. I guess to the extent that you are getting a prescription, you then have pushed to you that 800 number and a very short comment: Report adverse events to 1-800-MedWatch.

DR. ENGELBERG: So that would be on prescription

drugs and maybe devices at some point?

DR. MARCHAND: Yes.

DR. ENGELBERG: Great.

An extension of that would be what some people call Web 2.0 community, the whole idea of information flowing in two directions and a lot of transparency, which isn't always the philosophy of government agencies, in my experience, to have that level of transparency -- but the whole idea of embracing the openness that technology provides and having a more public view of comments and so forth. For example, if there were a lot of comments coming in on some GE device or some medication, people could see it, particularly if you had some sort of visual catalogue of products and devices.

DR. BROWN: Something like a blog? Is that what you're referring to?

DR. ENGELBERG: What I'm thinking -- it's not exactly a good analogue -- if you look at Amazon, you can see a product and see people's reviews. That's what I mean by there being more transparency and more exposure. That would probably generate more buzz and more participation.

DR. MARCHAND: Good point.

DR. PETERS: Shonna, Kala, Nan, Mike, and then Craig.

DR. YIN: I definitely want to commend the FDA

for trying to make this form much more user-friendly.

I also want to echo the comments that Mary and Bill made about the fact that there's a section missing about why the consumer should use this form and what's going to happen with the information -- in particular, using that to motivate and activate that consumer to fill out the information as completely as possible. I'm assuming the more information that's in there, the more they are motivated to look up the serial number or the NDC number or whatever, that would give you more information. That would be helpful to others.

Just a comment about the tutorial idea. I was thinking it might be also nice to link from the form, where you could click on a certain part of the form. If you have a question about the NDC number, then you might click on it and it might show you the label, and here's the NDC number. That's where I should look for it, or wherever the serial number typically is for devices.

DR. MARCHAND: Good point.

DR. BROWN: Could I just piggyback on that and suggest one other thing? That is to give a definition of a serious adverse event. What is a serious adverse event that qualifies to be reported? I think there is a lot of confusion about what that definition is or how FDA defines that.

DR. PETERS: Kala.

DR. PAUL: This form isn't to be just used for serious, is it? I thought it was any adverse event that any patient feels the need to report. I don't know that you want to limit it in any way.

In talking to people from FDA in the break, I was really impressed with the amount of work that went into this and the thought that went into each of the words. I play with the words. It's interesting to hear how things I was thinking about had already been thought about and discarded.

I was wondering, is this form available online as a PDF or a document with fields? Will it be?

CAPTAIN FRITSCH: Will it be? We're hoping that it will be, once it's approved and it has gone through the rulemaking process. We are hoping it will be available online. Currently the draft is online under the Rick Communication Advisory Committee. It is one of the background materials. It is there.

DR. PAUL: There are certain aspects of it that are so much easier if you can fill it out as fields or if you can make choices available so that people can check off things and then "other" becomes just a field where they might put specific data as opposed to -- Mary already has her hand up. I'm not sure what she's going to say about my

suggestion. I'm just thinking of the way I like to fill out documents.

DR. BROWN: I agree with you. I agree with you, Kala. However, there are a lot of people who take drugs who don't know how to use the Internet very well or don't have access to the Internet. But a fillable PDF is a wonderful tool and it eliminates a lot of data errors. That's a good suggestion as one way to simplify that back-and-forth communication.

The other question I have is, do you plan to translate it to Spanish?

CAPTAIN FRITSCH: We did go through that in our listening sessions. We did speak with one of the groups. Right now I think our primary goal is to get the consumer form through the rulemaking process and make it a reality, and then kind of go down the road from there. We did have inquiries about making the form available in Spanish, as well as a number of Asian languages. That might be something that would be addressed in the future.

DR. PETERS: Nan, Mike, and then Craig.

DR. COL: I have several comments. I'm worried about the "nocebo" effect, where people imagine that they are having side effects because the idea is planted in their heads. One way of trying to get at that is by, when people are talking about the date the problem occurred,

asking them if they have had this before. It's not uncommon. Teasing out causation is often more difficult. Somebody may have had headaches all their lives. That's a different scenario than if someone has headaches when they start taking a different drug, which may or may not be related, and somebody who has never had a headache before, who then gets one.

I think also little things -- the date the problem occurred. It implies that it kind of started and it's gone. You may want to get when it started and how long it lasted.

The other thing is, a lot of people -- they start taking a drug -- there are a lot of drugs that you actually start at a very low, low, low dose, and the side effects don't happen until you actually get them up to a higher level. Statins are a great example, the antidepressants. They may have started taking the drug a long time ago, but you may have just had to bump the dose, and that may have been when the side effect kicked in. So you can get a dose change.

Also there's inconsistency. You only ask about "if you know it" about the company name, not other areas. I think in the general instructions you say, give us everything, whether you know it or not. You can sort of get rid of some of those words.

DR. PETERS: Mike, Craig, Bill, and then Sokoya.

DR. WOLF: I'm just going to deal with the things that haven't already been brought up. I do agree with the minimize free-text response options again. I completely agree that this is a form that definitely should be primarily -- not only, I think, my recommendation would be that it should be an online submission form, not just a PDF to download, but it should first and foremost drive people to do the online form, and only offer this as a backup. We definitely underestimate how many people are online who have high-speed access, whether it be in their home or have immediate access elsewhere.

Also you might even want to consider the possibility -- we do a lot of work -- I come from the perspective of doing a lot of work with leveraging health technologies, like electronic health records -- again, going back to the learned intermediary idea, that this could be -- if you do need all this information or you want all this information, if you want the NDC code, if you want the -- this could be better leveraged if you linked into pharmacy software or electronic health record software, had a learned intermediary, whether it be the physician or a pharmacist who has a professional mandate to kind of be engaging with patients and again dealing with safety and adherence issues, that they could help expedite this form,

especially if it was online, especially if these fields had auto-complete functions where you have literally -- if you're asking for 1,000 -- there are thousands of potential prescription medications, on average, according to MEPS data. Patients take six or seven medications, on average, over the age of 65. If you have 10, 20 medications and you want them all, you could do this very, very quickly, leveraging the electronic health and electronic submission form versus something in paper, which again means the data would be available to you so much more quickly, and probably more accurately, too, I think, if you had a health professional guide through this form.

The other thing -- this is just a prototype. This is not something that -- in the 835,000 cases, you have used an old form, not this form.

CAPTAIN FRITSCH: The form that was used for those 830,000 is the voluntary reporting form, the Form 3500. This one is not finalized yet.

DR. WOLF: I think Noel brought up this point earlier, getting usability testing. If there was any data or if you are about to get data, even if you improve upon all the recommendations that are being made and you start seeing that there are data fields that are just going incomplete, that gives you some guidance that the item is bad or that people are struggling to find the information

or just don't know it. That might help you -- again, the shorter form, the better. People are going to be more likely to use it.

To Valerie's comment earlier about -- I don't know if you were getting at this, but this idea -- I was curious, because if it's a physician and consumer that could be filling out this form, in some regards what you don't know is if the physician is filling it out because the consumer -- I'm assuming in a lot of these cases the consumer is reporting to their provider and not going directly in. I'm wondering, if it's directly from the consumer, if you see that lower threshold -- I had an irritated throat -- versus the physician kind of discarding anything that might be viewed as something that they will dismiss that doesn't need to be reported. That might give you some guidance as to what patients are -- I don't know. I thought there was something that may be based on your comments about the level of threshold for a patient versus a provider report of side effects.

DR. HUNTLEY-FENNER: There's a recent news article, apropos comments just now, about state departments of public health using grocery loyalty cards to track purchases in the case of illness outbreaks, and using those data to quickly identify which products are at issue. I think there's an opportunity there to use pharmacy data

maybe in the same way.

DR. PETERS: I think I might actually insert a question of mine. I have been wondering about it for a bit. The 1-800 line has been on prescription drug bottles for some time. I don't recall exactly how much time you said. But I'm wondering, since that has been on prescription drug bottles, is there any evidence of some unintended consequences -- for example, patients reporting to MedWatch, but not to their physicians? If not, it seems to me that that would be data that would be worthwhile trying to get a feel for. I think, in the end, while the postmarket surveillance is really important for the population as a whole, the patient as an individual really needs to be reporting that to their physician as well.

I have Craig, Bill, and Sokoya.

DR. ANDREWS: Actually, I was thinking a little bit along the same lines. I'm going to broaden it a little bit. As you can see, we get excited about consumer research here. That's a good thing.

I want to tease out -- we were talking a little bit earlier, and Moshe was talking about push/pull issues. Do you have any tracking data on exposure awareness in general, where you could slip in a question here? I talked to somebody else about what percentage of the general public may know about this. I was just curious on the

different sources. If you would slip in a question -- how did you learn about MedWatch? The question is, is it from a physician, a pharmacist, librarian, stumbled on the Web site, heard it on the street. There are a lot of sources -- the 800 number. That's very important, because you can turn around with a POR or tailored messages back to those constituents. So it might give you some valuable information.

DR. ENGELBERG: Just a real quick insertion. Per Ellen's point, it may be useful to add the question, did you report this to your doctor, on the form as well.

DR. PETERS: I would even go perhaps a little further than that: Please report this to your doctor.

DR. HUNTLEY-FENNER: I often do risk analysis work and FMEAs or PHAs, if you know what those things are. In trying to identify degree of severity for incidents that fall below, let's say, a hospitalization concern, I will often ask, is this something that you would call your doctor about or is this something that you would just sort of treat at home or is this something that you would go to an emergency room about? I think questions like, did you call your doctor, are a great way to assess severity that falls below "I was hospitalized."

DR. PETERS: Bill and then Sokoya.

DR. HALLMAN: Very quickly, because this form is

also supposed to cover nonprescription drugs, OTCs, herbal products, and those sorts of things, it would be great if you could collect the UPC code information on this. Eventually we need to be moving to databases that link products and UPC codes so you can actually search something in your cabinet by UPC and see whether it's there or not. So if you change one thing, I beg you, put the UPC code on there.

The form currently says, at the very bottom, to keep the product in case the FDA wants to contact you for more information. How long should I keep my product?

In the very beginning, you very appropriately say, include as much information as you know. I assume that you want to be sensitive rather than specific in terms of getting reports. My concern is that there is a lot of information here. I'm not sure I would know all of the information. Do you want to repeat in a couple of places, fill out as much as you know, so that people don't think, well, I don't have all the information, so I'm not going to turn it in. So just repeat that instruction.

DR. PETERS: Sokoya.

MS. FINCH: First of all, I want to thank you for all the work that you have done with the MedWatch product. I have been processing how to ask this question. One of the things that works with different cultures is stories.

People adapt to stories versus numbers or the qualitative -- the stories would be qualitative. I thought about the question that Valerie asked, that there may be a couple of little things that happen, but they may have devastating impact, and so the little is big. I just imagine that that big and that little becomes a major outbreak, but among a certain subset of folks. Then you implement your protocol, and things take care of themselves. So I imagine that there is this great story that comes out of it, that somehow between MedWatch and the doctors and those people doing intervening and getting this group of people together, there is a story that comes out of it.

I was just thinking, have you thought about using stories to give a good outcome to a bad adverse situation, which gives other people hope that the system really works?

DR. MARCHAND: I know in our discussions with regard to the education part of going out and having the conversation with health-care professionals and patient groups and consumers and so forth, we have tried to source several examples, where it has been one, two, three different reports that have come into the FDA that have resulted in some significant labeling change, for example. Maybe it's a boxed warning. It manifests in some modification. So we have done it by example and probably

could benefit from making it more story-like than the very specific numbers and names of products and so forth, to make it more appealing with more of a storytelling.

CAPTAIN FRITSCH: The other thing that I want to mention about the MedWatch education project that we were working on -- one part was the listening sessions with the consumer groups, the second part was developing educational tools, and the third part was educating health professionals with potentially a continuing education program. Our contractors did develop a standard slide deck for us and they have put together a script for a continuing education project. One of the things that they really wanted to do was give a real-life example and use some of those real-life examples. One of the items was, every report makes a difference, and then there is an example of how submitting an adverse event report to MedWatch made a difference in a patient's life or resulted in a labeling change. So they have worked with us on that.

DR. PETERS: A very interesting idea. I actually like that quite a bit, because it can help to propel people wanting to use the form, but also propel a motivation to do it right and to do it well, because I as an individual want to help other people. So I very much like that idea.

I think, in general, the discussion actually has been wide-ranging -- hopefully, not too wide-ranging for

you guys. It has been very interesting from our standpoint. As you can see -- and I think Craig pointed this out -- we really like to talk about this stuff. It's important. It's things that can make a difference to the welfare of the American public. I again applaud you for the efforts you have been taking in this direction. The idea of improving postmarketing surveillance, which in the end is what you're getting at, is critical to the welfare of the US public. It's critical to long-term health. I think that the efforts you have taken in terms of improving the form get at that direction.

I didn't want to have this overlooked. I think Valerie's idea about using technology to do better data extracting over time -- that might even interact perhaps with some changes in the form. I wondered whether the drop-down menus -- and I apologize, I forgot who brought that up -- could even inform the data-extraction process, but also whether a data-extraction process over time could inform changes to what the drop-down menus themselves should be.

But I think that idea is very important, because the problem that you are dealing with is so important. You have to figure out, among these 400,000 reports you said you get, where the signal is and where the noise is. It's a really, really critical issue.

I again applaud you to being open. I suggested one possible unintended consequence, that patients might not report to their own physicians. That's the kind of thing that perhaps you should be a little bit open to. But you guys have been incredibly open, in terms of learning from what you have been doing and changing direction. You started off with an education project, but then changed direction, because you learned something, that the form itself needed to change.

Then also just coming to this committee is a sign for us that you are open to feedback. Hopefully, the feedback has been helpful. We appreciate your coming and asking our advice. Do please let us know if there's something more that we can do for you in the future as you move along on your projects.

DR. MARCHAND: Thank you very much. Your comments were very helpful and obviously reflect the depth of knowledge of the topic. I think we'll take this and see if we can incorporate those comments into the introduction of a consumer form. We appreciate it.

DR. PETERS: Thank you.

I wonder if we might want to take a five-minute stretch before changing topics. Let's take a five-minute breather, just to kind of cleanse the palate, if nothing else.

(Brief recess)

**Agenda Item: Committee questions and Discussion,
Session I (continued)**

DR. PETERS: I must say, there's a little bit of method to my madness in terms of giving us a brief break, the mental palate cleansing. I'm hoping that we might be able to stay a little bit later today. We are going to try to finish up our session from this morning, because the folks from CDER cannot be here after today. Basically, anything we have to say on these issues -- and they are very, very important issues -- we really need to get done today. And we have a lot going on tomorrow, as Lee just pointed out.

The FDA, in terms of what they do -- and I'm going to talk just about the health side. There are lots of other products that FDA regulates. But what they attempt to do is to support health decision making and, overall, to improve the welfare in terms of health of the American public. The idea behind providing quantitative information in promotional materials and advertising has to do with -- the question we are faced with is, will that help the FDA do the job that they are here to do?

What we started talking about this morning and we'll continue talking about now is that the FDA wanted us to better appreciate -- and I think we do now -- the

complexity of providing quantitative information. It is a very complex world that the FDA faces.

At this point, I'm not sure that the committee has consensus on a number of issues. And we don't have to come to any kind of consensus. What the FDA, and CDER in particular, would like to have feedback on are the questions that they provided. I do think we have some consensus that if they were to provide quantitative information, it's not entirely clearly yet what format should be used. It's not entirely clear. For example, one of the points that I thought came out very clearly from our discussion earlier is that sometimes ambiguity is the key piece of information. What do we know -- we haven't talked about this at all -- about presenting ambiguity, if indeed ambiguity is that key piece of information?

There may be some other things that people have thought about along the way.

In particular, what CDER would like to get some additional feedback on before we leave today is question number 3. Question number 3: If no scientific evidence from the risk communication literature is available for some of the cases above, how can the FDA get a scientific basis for how information should appear in promotional labeling and advertising to improve health-care decision making?

We do know a lot already. But I think what CDER is asking -- and, Dr. Abrams, please correct me if I'm wrong -- is, what other kinds of studies should be done?

MR. ABRAMS: I just want to make a comment. That's exactly it. I know some committee members have stressed this point. I think it's real important. We are talking about promotional advertising. We're not talking about other forms of communication. It's easy to get into a lot of other topics, but I think we really would benefit if we realize this is just promotional materials and advertising.

DR. PETERS: I knew you all were not going to be shy. I'm going to go ahead and pick whose hands I saw first. Nan, Craig, and then Noel.

DR. COL: This is assuming there's no data on how to communicate stuff. Is that what the question is intended -- there's no data on communication, not what to do when there's no data on the risks that you are trying to communicate?

DR. PETERS: I believe that's correct. It's basically about the scientific basis for the risk communication itself. We don't deal with the medication data. We deal with scientific evidence about risk communication.

DR. COL: When you don't know whether there is a

risk or not to communicate, how do you communicate whether an absence of information means you don't know anything or an absence of information means you know that risk is not present so you didn't mention it, so it's not mentioned because it's truly not a risk?

Anyway, if that's not what we're talking about, I was thinking that one of the areas where you could do this is just look at how other fields, analogous areas, where people make really complex decisions -- buying a car, making decisions about mortgages, where they are weighing short- and long-term risks and benefits. Some are soft and squishy, like whether it's a sunroof versus whether it's safe, got airbags. There are tools that other areas have developed for helping people make informed decisions. Perhaps looking at what other areas have done as a starting point --

DR. PETERS: Craig?

DR. ANDREWS: A combined issue. I remember in health claims there was an issue of not having complete scientific agreement. I don't know if that's included in this, when you say no scientific evidence. Maybe there are conflicting studies out there. That was a big issue, I remember, on the health claims. Anyway, I'm kind of combining that with our question.

DR. PETERS: I think the question is related

to -- and correct me if I'm wrong -- question number 2. We talked within question number 2 about various case examples where the data were complex, where the data are not as clear as, here's the precise point estimate for the benefit, here are the precise point estimates for the side effects. We talked a little bit -- and maybe we need to talk more -- about what kind of evidence is still needed so that our committee or FDA themselves can figure out what we should do around quantitative information.

MR. ABRAMS: That's correct. What we're trying to do is not what data is out there as far as drugs. What we are saying is communication data and things like that. Question 2 identified a lot of complex challenges. You can't just pick endpoint. How is the best way to approach these challenges if there is not evidence or data out there to communicate or to select this information to be communicated. So that's what we're looking towards, if that makes it clearer.

DR. PETERS: Noel and then Moshe.

DR. BREWER: I'll address the basic question maybe the next time I talk, but there are two points I wanted to make before that I haven't had a chance to make, so maybe I'll just make those.

The first is that there is this whole nice systematic review that was just done that said to use

numbers. Then, by the end of our last session, we were saying, don't use numbers. I wanted to point that out. I think that's a little weird. I do think, actually, there is a place for presenting numerical information. I appreciate that in our desire to simplify things, our intuition tells us to simplify it by stripping out numbers. But I'm not sure the data necessarily are following our intuition on this one. So I do encourage the FDA to use the data, to the extent that they can.

That sort of leads to the second point. My second point is that the question 2 list points out all these really interesting, intricate, complex situations -- and not just one of them, but issue after issue after issue -- where giving numbers may just not be doable. I do appreciate that.

But I can see someone reasonably saying -- I'm just imagining, let's say, in a week, *The New York Times* has an editorial: We proposed the drug facts box three years ago, four years ago. This idea has been kicking around since the last administration. What's wrong with the FDA? Why haven't they adopted it?

I think it's fair, as a conclusion from the conversation I have heard today, to say, because the complexity of the issue goes vastly beyond the simple situation that was presented in the original drug facts box

and the original drug facts box studies. That's my take on this, which is different than when I walked in. I walked in thinking, let's go, let's get this thing implemented. Now I'm thinking, I don't know, it's much more complex than I thought.

DR. PETERS: Moshe and then Val.

DR. ENGELBERG: The more we talk about this, the more I think maybe the purpose of the information, in whatever form it is, is motivational as much as informational -- that is, to trigger some kind of action. I'm thinking, particularly in the context of promotional labeling and print ads that are the size of a cigarette pack, it's just not practical to put in a whole bunch of stuff, which is what I think, in part, led to the "let's not focus on numbers so much." If in reality a decision point is for me to think maybe this medication is for me, therefore I will call my doctor -- so the decision point is, will I call my doctor or not? Therefore, I think studies would focus on calling the doctor as an outcome, as a dependent variable, rather than ending with understanding and more cognitive outcomes.

DR. PETERS: I think that's an interesting point, that idea that, because we have these learned intermediaries, who, in fact, are the funnels through which we actually get medication, one potential thing that FDA

could study would be, does the provision of quantitative information versus not encourage more people to ask their doctor and talk to them? I think that's a very good point.

Val and then Gavin.

DR. REYNA: Again, I'm going to say some things I'm probably going to say tomorrow also. It's like saying, will words help people? Saying will numbers help people is like saying, will words help people? It depends on what the words are. It depends on how the numbers are presented.

Just to give a quick synopsis, I think people extract their own gist from numbers, but you can't just throw the numbers at them in a disorganized way. You have to decide, what is the essential bottom line that people need to be motivated? You just tell them, if there is any problem at all, call your doctor. Well, I get 1,000 messages like that a day. How do I know that that's something meaningful? So you have to give them something, some nub of the essence that captures some amount of meaning.

That leads to the inevitable question, what's important? You have to really think about that -- just like the person who is watching those adverse events coming in and in that signal, they say, wait a minute, something has changed, this is important. You have to make a

decision. I would say, go to expertise, people who are experienced practitioners, experienced patients who have insight into these things. Capture the nub of what's important sufficiently to motivate people to seek some additional information. The key numbers presented in a simple, gist-like way may be very powerful in eliciting people to extract the message that you want. It depends on how the numbers are presented. It depends on how the words are presented, whether people get that essential meaning out.

There are data that suggest that people make decisions on the basis of this essential gist. The good news is that it's a boil-down thing. Maybe you could get enough finite space. But extracting that gist is not -- you can't just copy words and have people get a meaning out of it. There are empirically supported methodologies, experimental methodologies and techniques and even mathematical models that have been used to extract the meaning of information, including numerical information. I would suggest that there is a process that could be gone through for that, so that finite information could be provided about the essential content that people would need.

DR. PETERS: In terms of that essential content, I guess the question I have is, can you give an example of

how one could give a patient the nub of the essence, as you said?

DR. REYNA: The first step -- and again I'm going to say some of this tomorrow -- you can't communicate a message if you don't know what it is. So you really have to think through -- and gist is not just less information. That's a kind of fast and frugal approach. That's not fuzzy-trace theory, where you just present some of it and good luck with the rest. The gist is the digested meaning. So you really have to put all the facts together and say, what's the pattern here? What's the bottom line? What would matter to people? I don't think that's an infinite set, by a long shot. What the data seem to suggest is that for most people that have a certain type -- there are some common scripts and common gists from the information. But what people would have to do would be to decide what the essential information is. Are there four or five messages here that are bottom-line essential messages that person would need to know to make an informed decision?

There's no avoiding that step. If you do on the one hand and on the other hand, and you try to be exhaustive, that's not going to capture the gist of the message. You really have to think it through to what the essence is here, what the bottom line is, and then separate that from the values that would be retrieved that you would

apply to these message. These are two different things. They can be separated and have been separated empirically.

I can give you examples of procedures that have been used to extract that, if you want me to. I don't know how long I should go on.

DR. PETERS: What might be more helpful would be to provide them with some of the work that you have done in this area.

DR. REYNA: Delighted to foist my reprints upon you. My condolences in advance.

DR. PETERS: Hey, it was by invitation.

How about Gavin and then Nan again.

DR. HUNTLEY-FENNER: Regarding the importance of numbers, there seems to be consensus around the need to provide physicians and health-care professionals with accurate, clear, concise information, subject, of course, to the increasing use of gist reasoning by experienced professionals, which I think we'll learn about tomorrow. I think there's no question about that.

But the question arises, what do you make of how the general public responds to these sorts of data? What is it that we would like patients or potential patients to do when they are provided with risk/benefit information? It seems to me that there is consensus around that, too. We want folks to have an informed conversation with a

medical professional.

One of the ways I have been thinking about this is, you're a person, you are considering using a medication, there is an advertisement that you are presented with, and you have the option of going to a number of different places to get more information about it. Ideally, whatever information is presented in the advertisement should lead you to go to the most credible, specific, high-quality source that you have available to you. If you are going to have a standard box, for example, its success will be measured by how well it moves people the variety of sources of high and low quality that are available to a high-quality, in-depth, pertinent conversation with a physician who knows them.

That may not involve numbers at all. If it does, then we can sort of figure that out. But it seems to me that ought to be the study. If we are going to invest in research, the question would be, what kinds of information drive people to the high-quality sources and what kinds of information support high-quality conversations with medical professionals in the end?

DR. PETERS: I do have to return a little bit here to Noel's point, though, which is that the systematic study that was presented to us this morning shows that there is a value of quantitative information being

provided. It helps to convey the magnitude of the risks and the benefits. It is preferred by people. People understand the information better when provided numbers. That has more to do with conveying the magnitude of the potential harms and the potential benefits.

There is a complexity, though, to coming up with those numbers that FDA has to deal with. I think what, for example, Gavin, you are pointing out is that one of the studies that they could do, in conjunction with, perhaps, other studies that they might want to do, is to look at the extent to which providing numeric information or not improves these kinds of conversations. In the end, it is the physician who is making the ultimate prescribing behavior.

DR. HUNTLEY-FENNER: Yes. And by the way, I don't mean to say that one should never provide numerical -- I think there have to be sources of numerical information that are aimed at consumers, the average person. The question is whether we take a one-size-fits-all approach. That is, there's a standard vehicle for communicating that information that goes on a print ad, that shows up in television advertisements or on the Internet, that gets printed with the product. I don't think you can have the same level of information or quality of numerical information in all of those sources.

So you have to really think about, what's the goal here? If someone is looking at a 30- or 45-second commercial, what are we hoping for them to get out of that? If we're going to present them with a box with numbers in it, game over, and we've lost. If we're going to present them with something that says, "By the way, if you're considering this drug and you have heart disease, talk to your doctor about side effects," then I think there's the possibility that you can expect those types of conversations to occur.

DR. PETERS: I think that's a very good point. One of the things that I'm hearing you say is that TV in particular presents some of its own very special challenges and that quantitative information in those cases may simply be too difficult. I'm not sure if anyone has ever tested that before. Maybe we have some comments on that. Bill, maybe you can go right after that.

We started off this way earlier, and people seem to agree. I still wonder to what extent, if we have agreement around the room that there is a consistent format that could be used, but maybe needs to be modified for TV -- because you can't capture all the numbers in a 30-second ad -- the person watching the ad can't possibly digest that kind of information. If that's a simplified format, something that looks consistent with it, but has

more quantitative information, let's say, could show up in a print ad or on a Web site.

DR. HUNTLEY-FENNER: Sure, that may, for example, allow you to identify -- at least prepare you to search for quantitative information if you are information seeking. You have seen the TV ad. There's a specific format. You see another ad in a different context that has more detailed information. You will know exactly where to go to get the quantitative information that you missed in the television presentation.

DR. PETERS: Bill, I think you had something specific to say about it.

DR. HALLMAN: I agree. There is some data around how people actually take in information from television, especially around news. A lot of these drug ads are actually part of the 6:00 news, because they are targeted to that particular population. It turns out that while television is presumably a visual medium, actually people listen to television and television news more than they actually watch it. So if you had a visual box with this information on the TV, it would most certainly be missed by lots and lots of people. There would have to be some sort of a voice-over that would communicate this information to make sense.

DR. PETERS: And I have to apologize. Lee just

pointed out to me that we are focused on print advertising in particular here. My apologies for that. But I still think that's very interesting.

Nan, Vicki, then Mary.

DR. COL: I'm confused. I see an inherent tension. Maybe it has already been addressed. There's this tension: Is the goal of the print advertising to persuade people to do something versus is the goal of the advertisement to help people make informed decisions? For instance, if the advertisement is about getting a flu vaccine or using smoking-cessation products, where there's a legitimate role for persuasion -- in other areas, there's going to be a tension between the companies that are promoting a drug or -- their purpose for having the print is to promote the use of that drug. The purpose of labeling, of FDA's involvement, is to ensure that the patient is making an informed choice.

I'm trying to come to grips with what we're trying to do here. It seems to me that if there is a dichotomy between persuasion versus informed decision making, as being different goals, the benefits of the treatment are typically going to be covered very well by whoever is promoting it, by the company that is making the ads. The concern is that they may not be projecting the risks and harms adequately. What would seem to be the

objective of what we could do is set some minimal standards for talking about harms. But I think if our goal is informed decision making, when you talk about informed decision making, it's not just about talking about the benefits and harms of a single treatment, but it always has to be in context with whether the patient is aware of the alternatives, which include not just other drugs, but doing nothing and lifestyle changes.

I'm just confused. We are talking about informed decisions. I think we may -- I don't know. What is the goal of this?

MR. ABRAMS: I think that's an excellent point. It's advertising. The purpose of advertising is to sell a drug product. This is not activity that is being done by FDA in the interests of public health. It's being done by the pharmaceutical company to sell their drug product. FDA steps into this to make sure that what the company is saying is not false, it's not misleading, and it's balanced. People should not overstate the efficacy of a drug. They should not minimize the risks. We want to make sure of that. But it is advertising to sell a drug. Our role is to make sure it's accurate and balanced, and if we can improve it in quality, that's good. That's what we want to do here in the interests of public health.

But we are bound by regulations. We cannot force

companies to do certain things beyond our regulatory authority. I think that's an important point when we talk about objectives here.

I think we don't want to lose sight of the fact that the agency is working on many, many other communication initiatives to get out to the decision making that you are referring to, which is so vital here.

DR. PETERS: If I could add just very quickly, because I'm not sure how much we have discussed that here today -- you mentioned promotion shouldn't overstate the benefits. There are not a lot of studies, but there is some data out there that shows that when you provide quantitative information about the benefits, people's perceptions of the benefits decline, that people have lower perceptions of the benefits, as if they had an expectation of higher benefit and the numbers brought it more in line, perhaps. I just wanted to point that out. This goes back to your comment also, Nan.

Vicki, Mary, Bill, then Moshe and Noel.

DR. FREIMUTH: This feels a little out of context right now, but there was an earlier lengthy discussion about focusing on having people talk to their doctors as an outcome. I just want to add a caution here, for two reasons. One is, we know a lot about doctor-patient interaction. It's not always ideal. Patients are not good

at asking questions, and often there isn't the time to have that kind of informed discussion.

The other point is, we know a lot about compliance. A lot of patients decide to start on a drug -- or maybe not start, but at least get a prescription for a drug but never get it filled or discontinue taking it. I come out of all that saying that we have a responsibility or FDA has a responsibility for including a number of levels of information. That's what I keep coming back to. Several people have said it before. But if it has to be something very brief initially on a print ad, then I think it needs to be than just "talk to your doctor." There needs to be another level of information where the consumer who wants to pursue it on their own can get access to more than they can get in an advertisement.

DR. PETERS: Thank you.

Mary, Bill.

DR. BROWN: I think Vicki stated my issue very well. I have nothing to add.

DR. PETERS: Bill.

DR. HALLMAN: Ditto.

DR. PETERS: Moshe and then Noel.

DR. ENGELBERG: I'm thinking about what Nan said about what's good for industry, what's good for decision making, and marrying that with thinking about this from

both a motivational and an information processing perspective. In my opinion, when we are blending information processing and motivation, that brings up the importance of personal relevance as something we want to trigger with the communication.

As I think back on the lit review that was presented, which was very good, it had different variables than I might suggest. I don't know if the committee as a whole would support this or not. But I can envision a program of research -- I'm trying to get to an answer to this question or put something on the table to consider -- and I can imagine, of course, a matrix. God forbid we don't have a matrix. In the rows there's cognitive -- the cognitive ones are something about understanding efficacy and understanding risk -- not understanding in detail the risk, but understanding that there is risk. Maybe that's sufficient -- not "there's risk, call your doctor," but enough for people to take it seriously. Maybe there are those two cognitive variables. Then the affective one would be the personal relevance, and the behavioral might be, not "call your doctor," but it might be information seeking. I suspect a lot of people who read an ad, before they call their doctor, are going to go online and type in Zantac or whatever it is. It's not realistic to expect people to immediately go to their doctor. Maybe it's some

sort of structured information seeking.

So I can imagine a program of research in terms of next studies that would cross these outcomes, cognitive, affective, and behavioral, with different key message attributes.

DR. PETERS: I think I would add to that that there is risk to not taking a medication. So the efficacy, in some senses, has to be compared to not taking it. Risk exists, but, as someone pointed out earlier, there's always a baseline risk of all of this. In some senses, I think it also again has to be in comparison to not taking it.

I'm not sure I would agree that having -- I think what you mentioned was just simply the idea that risk exists. But I think it has to be risk exists on top of what you would normally encounter.

DR. REYNA: Any drug has risks. That is one of the things that sometimes people don't necessarily know, however, that they are really incurring a risk. They really think that safe and effective means 100 percent safe. That is part of, I think, a public education context. But above and beyond this drug, which risk is in excess?

DR. PETERS: I would agree. That's sort of a more general public education program that FDA may have even tried to tackle a time or two. I have forgotten some

of the earlier discussions in this committee. But it's not something you would tackle in a promotional ad, for example. I don't think you guys could regulate that, if I had to guess.

Noel.

DR. BREWER: I'm thinking of question 3 here in terms of how FDA can get a scientific basis for some of these things that are missing. It does seem like having a list of a few of the gaps is useful. You are in a pretty good place for identifying some of those. It's one of several logical next steps from the systematic review that was conducted. In some ways, the systematic review identifies what some of those gaps are. In some ways, it doesn't. Your list of 2 a through g kind of nails it, I think. I think many of those issues are not particularly well addressed in the report.

A next step is putting some money behind it. I realize that no one has a big pocketbook anymore. But a center of excellence or participating in some other NIH-wide RFA could be quite practical or quite useful. I know that FDA participates in several and has certainly spent some substantial money on other risk communication things, for example, related to the FDA warning labels. I think there are also a lot of people who can do this quite efficiently. I'm not sure that the amount of money has to

be particularly large. What I do think, though, is that it has to be really strategic research. Scientists coming in and trying to answer questions for their particular theory or their particular general approach may or just what occurs to them may not be as useful as ones who really fundamentally get what it is that you all are looking for. So having well-defined gaps and then calling for evidence that would fill them I think would be really very practical.

Another line of research that I think is interesting -- whether it's research or just a practical learning process -- there are going to have to be some kinds of rules for integrating this information to come up with a quantitative number of simple "gistified" information, if I can make up that word, Valerie, where you take whatever sort of complex information that's out there -- maybe conflicting or hard to get your mind around -- and try to figure out how to boil it down. There has to be some process for doing it that's better than not better.

Then we also have to figure out who is going to do it. I'm assuming it's not the FDA. I'm assuming that this is something that we are all expecting industry will come to the table with, because it's industry that provides the labels. This is not something where the FDA has an

office that's going to be churning these out for the 10,000 or 100,000 products that you all regulate. Regardless, there's a burden here. Just saying you ought to do it is really not going to be helpful. It's, I think, necessary to say, you should do it, and this is how you would do it, or this is, very concretely, what it might look like, and then identifying whether that burden is a reasonable burden.

DR. PETERS: Kala.

DR. PAUL: Tom, this is a question. We have been all over the map with this. Now we're back down to print ads as what we are discussing. We are actually discussing something that would, in effect, replace what's currently the patient brief summary or add quantitative information to it. It seems to me there are an awful lot of ramifications if companies are using their med guides or -- they don't even have patient labeling. They use their PIs on the backs of the ads. It's a far-reaching -- if we are demanding or asking for quantitative information, risk information, in these print ads, we are asking for potentially far-reaching changes in the current labeling, unless we are just adding something like a box on the front of the ad.

MR. ABRAMS: I think Kala's point is an important one. What we do here is not just, let's add a box or a

page. What will be the implication? That's the first decision. Do we do it? If we do it, what does it look like? Then does it replace anything? I think it would be a very simplistic approach to say this should be added to everything, and everything else stays the same. I think we have to look at this whole thing in that context that Kala outlined. So we would do that.

DR. PAUL: The other thing is, when we talk about gist, at some point, for each of the indications, for each of the safety pieces of labeling, somewhere along the way, either the company or the FDA has come to some point at which they decided the drug could be marketed. In looking at the data, there must be some gist point in that data that they are using to say this is safe and effective and can go on the market or stay on the market. So maybe that information actually exists in some format, and we're not really talking about reinventing the wheel. There were two studies or there were six studies, and so for each indication or each patient population, that gist data does exist in some way. I think the question may be more critical. Let's even assume that it does. It's the multiplicities of it. Are you going to list all the indications on the back of your ad or are you going to do it by indication for whatever that ad is showing? Do you have to show all the patient populations who had adverse

experiences or particular adverse experiences? Those are the kinds of things that we might have to wrestle with -- the breadth of it, rather than the fact that there are different pieces of information, as we were discussing.

I'm trying to make that point. It seems to me that the decisions to market were either based on a gestalt or they were based on one particular set of gist information.

DR. ANDREWS: Kala's point is a valid one on the brief summary. My feeling is that you don't want unintended consequences here. If you add the box and then manufacturers feel legally obligated to include all the same information, maybe you are moving to a 2-point font in a document that's very small to begin with. These are some tough issues. I do agree with perhaps taking a holistic approach to this and the message that would be sent to the manufacturers based upon what you decide.

MR. ABRAMS: I think it's an important point. I think it points out -- and I don't want to go out of the scope of this meeting myself -- we have to look at all the different factors. A good example of that is the brief summary. We have a draft guidance out now to improve the brief summary. Nobody would say taking the risk information from an approved product labeling and just putting it in is beneficial. This is important

information. We have a draft guidance. We want to make it as best as possible. So we did three research studies to get data to do that. We are actually revising our guidance to incorporate that data to help guide our policy.

I think it points out how complex this issue is. You can't just change one thing without thinking about everything else and without thinking about the other initiatives that FDA is involved in.

DR. PETERS: Bill, Sokoya, and Nan.

DR. HALLMAN: Just a caution. When we talk about this process of "gistification," I am doing research on qualified health plans right now, and that is an extreme example of "gistification," trying to get to the gist of scientific evidence. I can see us getting into that hole, trying to say two studies suggest, but one does not, that blah, blah, blah, and you get these very legalistic statements that don't work for anybody. So we can go too far in trying to get to that.

DR. REYNA: That's not gist, though. That would be verbatim. That would be all these details that are not integrated. Gist is the bottom line where you put them all together.

DR. HALLMAN: I understand.

DR. PETERS: Sokoya.

MS. FINCH: I hear what you said, Doctor. I'm

trying to go outside of the box, because it looks like we kind of have slim pickings in terms of what we have, because you want to make sure you have everything you need in that one shot when you start to do the work on the project. I was thinking about a market analysis that's based on rigorous research that gives you the indicators that you are looking for. What makes people change their attitudes or their beliefs in terms of just picking up that product and believing in that product? I'm thinking outside of the box in terms of maybe research under anthropology or maybe sociology or psychology, just in terms of how people change their attitudes and behaviors as it relates to their wanting to take this product and call it their own and say, wow, this really works, it takes care of the job.

I'm thinking there has to be some level of psychology in that. There may be some research out there that can speak to that and, again, PR firms that may have done market analysis, if that makes sense. It's totally outside the box, but I'm thinking that probably the further you go out of the box, you may be able to find some of the answers you're looking for.

DR. PETERS: Nan and then Noel.

DR. COL: I'm trying to "gistify" my thinking here. I'm thinking that we talk about the side effects as

being an ulcer or disease or this and that. The gist of it is, really, what we have been talking about is that we want to avoid serious complications, and if we can, then we also want to avoid less serious complications, and we want to get the benefits. I don't know if it makes sense, but it makes sense to me -- some sense -- because if you don't have something, all these serious things are all -- you want to avoid all of these things equally and you want to avoid all these minor things equally. But these things are not equal to that. So that's the gist. It's very bad and bad.

Why couldn't we have a food labeling box where you just had chance of serious effects and just lump all the serious effects, so you could say, for this drug, the chance of serious effects is 5 percent, the chance of non-serious effects or minor effects -- whatever the term is -- is 20 percent? That way, if you're looking from one drug to another, you could -- and then you also have chance of death, because I think death is a big thing, and even if it's zero, it should be there. So if you have death, serious, and minor stuff and had those chances quantified as best you could -- we have that information -- and just had that, you could compare across products. Then you would have basically just three things. Then if you wanted to read more, you could read more. But at least you are

not going to get swamped in -- this is liver disease. I don't know what that is. I know what heart disease is. It gets the gist -- I don't know.

DR. REYNA: That's in the spirit of some of the things I was going to mention. Some of the difficulty here that we are kind of talking around is the issue that for some people a particular outcome is a more horrible thing. Cognitive disability, to some people, is almost worse than death. You have to understand enough of the content themselves to be able to make your own decision, so you can extract for yourself, this is really awful, or this is something I could live with. That is the dilemma you face about pulling out the essential meaning.

However, in practice, when these things are talked about by people who really have experience in it -- experienced patients, experienced clinicians -- there is convergence. There are not infinite numbers. There are small, finite numbers. There are three takes on this. There are basically three major ways to look at it, sometimes two major ways to look at it. Most people don't want to die, that sort of thing.

Part of the reason why people hesitate to get other people's gist information is, for them, 10 percent is low; for you, 40 percent is low. They want to get their own gist. That's part of the issue here. But that can be

empirically addressed. Again, there's a small number. When we are talking about real drugs with real side effects and experienced patients who have some insight and experienced practitioners, it's not enormous alternatives -- so far. This is an inductive problem, but so far.

DR. COL: I think the problem with the way things presently are is that there is this long list of things and you can't make sense of it. Even providers, who know what these things mean, can't make sense of it. If you don't have any specific knowledge, it makes even less sense. It's just a long, scary list.

What is it we are trying to communicate here? We want people to understand, when there are serious risks, that there are serious risks. We want them to get a sense of the magnitude of the serious risk. That's the most important thing, before they know whether the risk is heart disease, liver disease, bone disease. Then they could unpack it later. But we have to figure out what is really the most important thing that we want to communicate. If we have these tools -- I don't know.

DR. PETERS: I just want to make one comment on that if I could, just very quickly. There are potentially some pretty big unintended consequences there. I like the idea that you are coming up with in terms of sort of

packing things together. I think that that long laundry list of 20 side effects is a difficult one.

I'm going to go across your two categories and do an exaggeration, just to make the point that I want to make. Let's imagine that you called a serious consequence mad cow disease, a Jakob-Creutzfeldt kind of thing, and I'm going to come up with one that's not really serious, but let's say it's headaches. Let's just imagine that those two things were together within "serious." One of them had maybe a 10 percent chance of the risk occurring and the other had a 1-out-of-10,000 chance. They got packed together and then you come up with some likelihood of a serious side effect. I realize I'm exaggerating here.

What if the patient has heard about the Jakob-Creutzfeldt, the mad cow disease, symptom and ends up thinking that what ends up being about a 10 percent risk is the risk for that?

DR. COL: That goes with the whole problem with the labeling for the risk -- what's rare, what's common, how you unpack things. I would suggest that there are actually those catastrophic events, and I would think that there is catastrophic, because those often -- even in tiny, tiny things, those tend to drive a lot of decisions. Osteoporosis treatments are often driven by this incredibly rare jaw necrosis, which is -- but that's what people

remember because it's catastrophic. But if you said, are there catastrophic events, and what is the likelihood, at least then you could compare that one is 1 in a million and the other one maybe is zero at this point.

So I think how you come up with the labels -- but I think that that catastrophic is a really important -- and the you would have to have some reasoned -- and maybe it's catastrophic, very serious, severe, whether it's three or four. But I think the way we do it now, it's just so confusing. I don't know how we can do comparisons, because ultimately I think we are going to have persuasion. We are going to have companies wanting to persuade people to buy their products. That's the way the world works. Yet we have a consumer who wants to be able to compare, at least on some general level -- and right now you can't because -- you simply can't because you have no sense of magnitude and severity. This would give you both.

DR. PETERS: Good point. Noel and then Kala.

DR. BREWER: I completely agree. Having headache and death in the same sentence is just hard to follow.

Picking up on the question -- at least my take on what question 3 is about -- I'm trying to imagine more what exactly a mechanism would look like, what the FDA's needs might be. One of them seems to be speed, given that there is, I think, pressure on this issue and there's a strong

internal interest to move forward. A traditional RFA might not give you all enough control or enough closeness on this, so I guess a contract is sort of how it works. But my hunch is that some of the expertise you need is not in the contract houses. You probably need people who are a little more university-based to be at the table to give some of this sort of higher-level expertise and this more current theoretical cutting edge. At the same time, because it's such an intensely applied and focused question, it seems to me also that FDA people have to be very present at the table, not one of these things where you just hand it off to someone else and say, here are four things, go and come back.

Those are some of the characteristics of the mechanism that seem like they are important.

I would love to hear more about these three studies. You mentioned them several times, and I kept thinking, oh, gosh, I guess I didn't do my homework. Maybe I didn't read. But I was talking to Ellen. She hadn't heard them either. Can you tell me about me about them? Have we seen those papers? Maybe you could summarize them for us. I apologize. I feel like I just haven't followed those.

MR. ABRAMS: I don't want to take the time up, and I'm not the best person to speak to it, but a complete

executive summary and report are listed on our Web site. Lee can provide that Web site to us. That has a complete report of the three studies and our analysis of it.

DR. PETERS: Lee, if you could provide that to the whole committee, then people could choose to read or not.

Kala and then Moshe.

DR. PAUL: One of the things that I think the group has reached some sort of consensus on -- at least I'm hearing this -- the information that is the most important is that type of thing that would make somebody decide not to pursue the drug based on the potential for a catastrophic event, which we would call a very serious adverse event, which really boils down, for most drugs, to maybe one or two. We are not talking about a whole laundry list usually. It's one or two. For many of these drugs, if something is found in the postmarketing period, we don't have incidences. So that's another issue in terms of the quantitative presentation of the data. We don't have a denominator.

We also have seen in other things that the FDA has put in place that statement at the beginning of med guides and the patient package insert that says, what is the most important information I need to know? The question is, where are we going with trying to improve that so that

patients use the available tools maybe in a little bit more effective way to make those decisions -- I don't want to even ask my doctor about this drug? We have already got a lot of this stuff defined. I think we made this incredibly complex, looking back on it, talking about 6 percent as an example, because that's what was in the literature research. Six percent incidence of a common adverse experience, headache, is not the kind of thing that we are talking about. We're talking about something that is much less commonly seen, and when patients actually see that 1 out of 10,000 or 1 out of 100,000, all of a sudden it changes their perception of whether this is something that is really something they have to be worried about.

To me, there is a lot of talking we have done about something that goes away when we put it in the context of one or two very serious adverse experiences that may or may not shape the patient's view, for which the risk -- not the outcome, but the outcome and the probability of that outcome -- may be very low, or the drug wouldn't be on the market.

So I put that back out for the general conversation about where we're going with this.

DR. PETERS: Moshe.

DR. ENGELBERG: Two things real quickly. One is to echo what Kala said about, in order to direct future

research, the importance of really identifying what goals need to be achieved by the communication.

Number two, I'm thinking, even with all we have talked about, about numbers and words and so on, it might be useful to do some zero-based thinking -- start from scratch and pretend we need to come up with a universal symbol. At the airport there are the conditions that are orange or yellow or something like that. If there are symbols like that that could be used to convey a constellation of things related to risk, and it's not absolute -- it's not some percentage is always orange -- but it's contextual, like we were saying before -- a 5 percent risk for one thing might be no big deal and for another outcome, might be a big deal. I think, Noel, you were saying that. What I'm suggesting is that kind of zero-based thinking and maybe just thinking beyond words and numbers.

DR. PETERS: Do we have any other questions?
Gavin?

DR. HUNTLEY-FENNER: I was just going to ask a question. My assumption -- and maybe this is incorrect -- is that often when you have these types of risks, catastrophic risks, a couple of things are true. One is that the benefits of the medication far outweigh the catastrophic risk. Maybe you are talking about something

that will save someone's life, and it may be the only product on the market, for example. The other is that in some cases you are talking about risks that really accrue to persons with additional health conditions that doctors need to be monitoring or you need to be carefully thinking about as you are embarking on a new course of treatment. In other words, they are not taking place in a kind of vacuum. It seems to me that that's an important piece of the puzzle that we ought to be thinking about.

DR. PETERS: Thank you, guys, for the opportunity, for the opportunity also to CDER to get to consider these issues. Some of what I heard coming up -- and this is partially just reiterating what other people have said -- is identifying what the goals of the communication are. In particular, a topic that people brought up several times over the course of the day is, what information would change decision making? What information would actually change what a patient would do anyway? That would probably include catastrophic risks, but that would also include probably the likelihood of those catastrophic risks. Whether other risks also need to be in there as the context -- perhaps it could be important to understand that a 10 percent likelihood of a headache, for example, is so much bigger than this 1-out-of-10,000 risk of a catastrophic side effect. If that helps you to

better understood the gist of the likelihood of that catastrophic side effect, that could actually end up being important to have in there. I don't know. It's an empirical question.

This idea of taking a holistic approach -- if the provision of quantitative information is just kind of slapped down on top of whatever is there right now, it may be too much. There may be too much there for consumers, and less numerate consumers in particular, to be able to consume that information and that kind of a quantity. So taking a holistic approach seems like a very good idea.

We had some very good ideas around potentially packing together side effects. I didn't hear that for benefits. I think there's less need to pack together benefits. To me -- and I just want to reiterate this -- the provision of quantitative information, nonetheless, while we haven't had complete agreement about whether it should be provided, does give people an idea of the magnitude of the benefits and the magnitude of the risks, whether it's a very catastrophic side effect or if it's the overall benefit. Maybe it's not as high as people think.

Another theme that kept coming up over and over is that success in these kinds of communications may be about moving people to better conversations with their physicians. Again, the physician in the end is that

learned intermediary that we as patients need to provide on. There's the idea of communicating about the gist so that we can get beyond superficial knowledge of a 9 percent risk to an understanding of what that means, whether that's good or bad.

In terms of further studies that have been done -- I think Noel actually said this quite well -- there have been a number of gaps that have been pointed out throughout the day today. I'll reiterate something I said earlier. Part of the data that you have available has to do with ambiguity. I think understanding how to communicate that ambiguity, whether it's quantitatively or not, may end up being quite important, and then not losing sight of populations that are more vulnerable, not losing sight of people who come from other cultures, who are less numerate, older, maybe the combination of the two. We wouldn't want to provide information that has unintended side effects, that in the end kicks back and ends up hurting some proportion of the population.

Are there any other final words that anybody wants to add before we stop for the day? I appreciate everybody's patience. We have had kind of a long day and a lot of topics, and I appreciate your willingness to stick in there and continue to think about things.

At this point I think we'll leave FDA with your

own job of thinking further through things. We will look forward, if possible, to hearing back from you at some point about what kinds of next steps you have ended up taking, what ended up being useful in our advice and you were able to act on -- perhaps what wasn't as useful even.

Lee, any last words?

MR. ABRAMS: We just want to thank the committee for the insight. I found it very, very interesting. More importantly, it's very productive. It will provide insight for us to go back and discuss this and have a method to do our evaluation. We thank the committee for all the insight and for staying so late. Thank you.

DR. PETERS: Great. For the committee members, we meet back tomorrow morning at 8:00 a.m. Thank you.

(Whereupon, at 5:26 p.m., the meeting was recessed, to reconvene the following day at 8:00 a.m.)