I'm putting on my teacher hat now. There's some benefit there for multiple forms of communications. I mean, you have advertising, sales promotion, web-based things, but the key is to have some synergy across there, a single message. That's very, very important. And, obviously, more information is not always better here. And I hear you loud and clearly, maybe there's too much there, and the shopping bag analogy was quite good.

My second area, I just wanted to talk a little bit about study design, so I'm going to put on a researcher hat now. And I have a few questions. This was screaming out for maybe some sort of quasi experimental study, where you might have CMI, PPI, the Med Guides. I know tomorrow we're going to hear a little more about the OTC Drug Facts Tabular presentation, with controls, too.

So, for example, you might have people coming in with sophisticated, or

unsophisticated knowledge from their physicians, so maybe none of this stuff is actually working. Maybe they already know that, or maybe are biased from what they're hearing from their physicians.

Are you aware of any sort of studies in this area that might have pitted some of these against one another? And let me talk a little more about that. It's more than just kind of perceptions; do I understand? Well, of course, I understand, but maybe accuracy, comprehension questions, survey issues, as well. Has there been any attempt at all to take a look at that? Kind of a loaded question.

DR. OSTROVE: We know that there have been some studies that have looked at perceptions; for instance, specific Medication Guides. I am not aware of any studies that have pitted any of these against each other, or even in kind of the quasi experimental sense that you're raising. I'm

not aware of any. Jodi, are you?

MS. DUCKHORN: No, but I also wanted to add that it's hard to sort of pit them, as you're saying, against each other, only because, as I was mentioning, if you have a Med Guide, then you don't have a PPI. You could have a Med Guide and CMI. In that sense, you could pit them, if you will, against each other, or if a Patient Package Insert was, at some point, changed into a Medication Guide, which that happens all the time, you could sort of pit them then. But a lot of times, that information changes. I understand exactly what you're saying, and my answer is no. I would love to know if you know of anything now?

DR. ANDREWS: More of an academic than regulatory, it's interesting mix between those areas. There's also some other issues, too, on the order of some of this material. It seems to bounce around a little bit, and I noticed that if you take a look at the OTC

Drug Facts, they group all the negative information together under warnings, but it seems to bounce around a little bit on some of the others, so there might be some ordering effects. And I know we're going to get into this later, but there's a lot of juicy ideas here for, I guess, academic, or other research. Anyway, thank you.

DR. OSTROVE: And we would encourage that.

DR. DAVIS: So I have on my researcher's hat, also. And I want to discuss evaluation of understanding and usefulness, also. So, I have a comment, and I have a couple of questions. Like, who evaluates that, and how do they evaluate it?

My research indicates that asking people if they're read something, if they've understood it, or asking doctors or other providers if they've counseled patients, doesn't answer your question. And, for instance, even besides lying to you straight

up, I mean, how much did you read? Did you read the essential thing? Did you under - what keypoints -- what's the need to know, and what's the need to do? Does the provider counsel all patients with all the essential need to know and do, so how much? But the other comment I have, in other FDA - I guess I'm on the Drug Safety and Risk Management Group - what I have found is, sometimes manufacturers say they do this, but then it sounds kind of shaky once you start probing them. They often contract this out to other groups, and they say well, we did pilot studies, but when you start pressing how did you confirm understanding, it kind of falls apart.

Then, the final thing is, if you all have been evaluating through national surveys since `92, what have you found? `82, I mean.

DR. OSTROVE: That's interesting. Here's the issue. Actually, the last survey

we did, which Jodi can speak to more specifically, was in 2004, but what we don't have is information about understanding. What we're asking is people who have filled a prescription within a specific period of time, we're asking them whether they were orally counseled, or gotten written information. We'll ask them, for instance, well, did the - were you told how much to take, how often to take it? Were you told about refills? Were you told about precautions? Were you told about side effects? And in terms of those given written information, we'll ask about what type of information they got, whether it was a brochure, an instruction sheet, stickers on medicine information. In 2004, I happen to have the data here, in 2004, 91 percent of them reported having gotten instruction sheets, but we don't have any detailed information about whether they understood those. And even if we did, of course, it

would be kind of general, so we have the general numbers, but we don't have the specifics about what they're getting, and their understanding of the information that they're getting. At least, we don't have the specifics about written information. We have a little bit more in terms of specificity about what they remember they were told orally, but that's what we've got.

MS. DUCKHORN: One of the things worth noting, at least, in that particular collection, that series, is that there is an -- it was amazing how there was almost no change over the course of the 20 years, or whatever, 15 years, or 20 years that the actual study was done every time, so we are never asking about actual understanding, but it was simply receipt of this type of information.

I wanted to address some of your questions.

DR. DAVIS: Right. Just, often a

lot of stuff is just a check-off, did you do it?

MS. DUCKHORN: Right.

DR. DAVIS: Rather than was it useful, was it understandable?

MS. DUCKHORN: Which is why we're saying -- well, you saw, we're providing feedback saying that that's not acceptable to us for the assessment piece. The assessments are done 18 months, three years, and seven years. Those are the minimum assessments.

We request in the sort of contracts with the sponsors, or with the manufacturers, that they provide to us methodology 60 days prior to going out to the field and doing the research. We actually don't really have to approve that methodology. They can go out and do that, whatever it is that they're going to do. But if they don't sort of - I don't want to say clear it through us - but if they don't run it passed us, and then they submit something,

and we go this is junk. You guys have all these biases in here that you didn't account for at all, we can send them right back out to the field. And we can provide recommendations at that time, so it is in their best interest to run the methodology passed us prior to going out there. Otherwise, they've wasted their time and money.

And you're right, a lot of them are contracted out. They're still, ultimately -- the sponsor or the manufacturer is still, ultimately, responsible for that, because it's in their contract with the Agency, their REMS, their Risk Evaluation Mitigation Strategy, which is sort of that contract, that they are going to be responsible for that. They do the evaluation, they do the assessment, they send the results to us.

Social scientists, myself, and at least one other person at this time on my

team, and we're looking to hire more, will be reviewing these assessments. We won't have our hands, at least at this time our plan isn't to have our hands on the data, but actually to look at what they're submitting based on, hopefully, methodology that we've reviewed, and I don't want to say approved, but we've reviewed and agreed with, or at least negotiated in some way, shape, or form. Does that help?

And then the other thing about it, again, getting back to the question. So we review the methodology. We also review the questions, the actual instrument in the case of it's a survey. And so, that gets us back to these questions. It would be nice to have some kind of consistency across the products so we can actually, ultimately, look at the usefulness of a Medication Guide, or whatever it is, as a tool to mitigate risk, in addition to within the product having some consistency.

DR. GOLDSTEIN: And just to follow-up on some of the questions already, the idea of usefulness as a construct is interesting, but it's limited. And we're already heard. What we want to achieve is beyond usefulness, to action, and confidence, and the ability to make adjustments, patients being able to make those adjustments based on their experience. So to what degree has the FDA, and others directing the FDA, considered going deeper, and looking at patient safety?

We're at the National Transportation Safety Board today, so if we look at this from a safety perspective, how can we insure the safety of the use of medication, and do we want to know not only understanding, even beyond that, the degree to which people know what to do, and actually ask them what to do after they're received the various interventions that they're getting.

MS. HENDERSON: I would say that

that's where we're trying to head, and that's why we're here. That is -- I think, Dr. Goldstein, you have it just right. That's where we want to be. We want to assure that patients are using their drugs safely, and appropriately. So however you define that, yes, we want to start looking at outcomes, and not just checking off boxes, so we're most interested in your thoughts about that.

DR. GOLDSTEIN: So, to follow-up about that, so to what degree can we look beyond just the single intervention? I know we want to look at the usefulness, and the effectiveness of the CMI, and the other kinds of tools that are delivered at the pharmacy, or in the Patient Insert, but to what degree can we get to the point where we're talking about a safety system, that includes the context in which it occurs, the information delivery, as well as other things, as well as who's involved in that, and how it leads to the multiple levels of influence that we

might want to engage?

And it's kind of interesting, if I could just -- can I go off on a little tangent, because it's amazing that we hear the National Transportation Safety Board, and having just been on an airplane, and knowing what the airline industry, and the regulation of that has done to safety of travelers, when we go on a plane, like I did yesterday, there are different levels of information that's provided to people on the plane about what they should do. And there's the announcement that's made from the travel attendants, that's one level. Then there's the card that you have that's in your seat. But then if you're in an exit row, the flight attendant comes down and they ask you, first of all, are you prepared to participate? And do you understand - now, it would be better if they actually asked me what I am prepared to do, and do I know what to do? But then they don't just rely on that, if something

happens, then they come and they assist those people in the exit row. And there's also a big sign right on the window or the door about what to do. So I think we have to think about all those different levels.

The materials, yes, are really important, the system is really important, who's involved in that system, targeting those who need extra attention, because they're the ones who we want to count on when we get a medication and there's a problem, what to do about it.

MS. HENDERSON: Well, I will just -- I don't know what more I can do but to agree with you. You and I would have a great time if we could be a plane for a few hours. The FDA is part of this system. I guess, in answer to your question, what is fair game for you? You guys can get together and discuss the quality of care provided by the healthcare system around the safety of patients, as long as you would like to. It's

an important issue, probably for everybody around this table who's ever touched healthcare.

We are only one part of the healthcare system, and we are most interested in your advice today about things that the FDA can do in our role in the healthcare system. As that affects the other pieces, feel free to discuss that part of it, of course, but we are most interested, and one of the reasons we have picked written information is that it's something that we know that we have control over in one way or another. And there are other parts of the healthcare system, what the doctor tells the patient, what the pharmacist tells the patient, how the nurse delivers the medicine, or whatever, that we really have little -- we have some influence, and we play in part of the system, obviously, but we think we have a very important role in providing information to the other pieces of the healthcare system,

all the way to the consumer that can be useful. And we're interested in making that as useful as we can.

CHAIRMAN FISCHHOFF: Thank you. I'd like to sort of bump up Betsy and Sokoya to have them speak first, and then Sid, and then myself, and then we'll have a break at 10:15.

DR. SLEATH: I just wanted to re-echo what Dr. Davis said about how you assess whether people understand things. You can't ask them whether they understand it, because they're going to say yes. So sitting here, I was thinking that one possibility is, can you come up with key messages for the drugs that the patient should be able to get from these leaflets, and then just assess that? Did they get it or not? There's research that when they look at providers and patients talking, where researchers look at whether the provider assesses whether the patient got new concepts to very specific detail.

And then the other person I wanted to bring up is Dan Morrow, who actually has done work in Transportation, and work on designing leaflets for patients, where they do a lot of great, often experimental trials where he's really looked at - he's a psychologist, how people process information, and the best way to present it to them with headings, so I'd encourage you to look at that.

And I would be tough on the sponsors, because I saw your slide about some of the proposals that you got, and they just don't look rigorous at all, so I would encourage to be tough, and maybe require randomized trials of, if they get a guide, and if they don't get a guide, and the difference in getting these messages, because I just think it's crucial.

And then, I wondered if the sponsors assess by literacy level, and do they also assess by different languages?

That's just kind of some questions that I thought of. Are they not only assessing comprehension in English, but also Spanish, et cetera?

MS. DUCKHORN: Okay. So, I guess I first want to address, or clarify, the list of questions that we are considering are just sort of the first set of questions. The second part of that would clearly be risk-specific, and do somehow comprehension testing, or recall testing. Do you even understand what you would do? Which of the following would do if this happened to you? And try to make it at least a little bit not so obvious what the answers are, to come up with some way to assess the actual key messages, the key risks. It's not just those, do you understand, did you get it? Because, you're right, we understand that. We know that just saying yes is very simple, and that means nothing. But having those questions first would say that someone said

they understood it, but then when it was time to answer the questions, they couldn't demonstrate that they actually understood it. And, again, I don't know how much of that is good to know, versus we really need to know it. Maybe it's just better to simply ask them about the specific risks, and not did you understand it? But I think from our perspective, it might be nice to know, did they say they understood it? They checked yes, I understood it, and then later when they were actually asked to demonstrate somehow that knowledge, they couldn't. So that's one thing.

And I guess second is, I appreciate you're telling us to be tough on the sponsors in their assessments, because we don't feel like what we're getting right now is really, I don't want to say what we're looking for, because we don't have really specific things that we're looking for, but we don't feel like they're getting at the

right sort of actual patient comprehension, or evaluating the actual effectiveness of that tool, as a risk minimization tool.

And what I would ask of you all is, how -- you're talking about sort of randomized trials, and that sort of thing. How are sponsors supposed to get a hold of these patients without violating HIPPA, and without going to specific doctors. I know that's one of the questions they have, and it's one of the questions we have, too. We're not sure how to tell manufacturers to get these patients, and do it in a random and fair way so that they're assessing high-income/low-income, high-literacy/low-literacy, minority populations, getting at everybody without cherry-picking, without going to specific - if you go to a suburban pharmacy versus a rural, I mean, without feeling like they're really cherry-picking. So I sort of put that back to you.

MS. FINCH: Yes. Thank you again

for your presentations.

I have the same exact question as Betsy, but I'll take it a little further. The results of the evaluation on the 2000 goal, I wanted to ask the question, does that include bilingual languages, as it relates to the -- I see, no.

MS. DUCKHORN: No.

MS. FINCH: So it's basically English. And where are we with bilingual, or other cultures that are pretty much rising to larger percentages across the country in terms of being fluent with language?

MS. DUCKHORN: There is no requirement that actual labeling be written in any other language besides English. And some sponsors, some of the manufacturers have said that they're going to translate the patient information. We don't have anybody internally reviewing that, so they say that they'll do a verbatim translation, and I've seen things that have been translated into

English that you can clearly -- verbatim, that you can clearly see, while it's verbatim, it doesn't take the message, and actually turn it the right way. So even if a sponsor has somebody certify that it's done correctly, it's still not, necessarily, the same message that we're presenting in English. There is no requirement. I guess the short answer is there is no requirement for any other languages, and we certainly didn't assess any other languages in terms of the Consumer Medication Information. That was only English. And, actually, I think pharmacies can produce CMI in other languages, because there is no rule about that, either. CMI is sort of, it has to be useful information. I think that was one of the exclusion criteria in our evaluation, is that if it wasn't in English, then we didn't evaluate it. That pharmacy was actually kicked out of our sample.

DR. WOLFE: I just want to briefly

expand on the answer that was given to Dr. Khanna's excellent question, was why was this limited to estrogens, and OCs?

Around the time that this regulation in 1970, and finalized in 1980 had been finalized, I wrote to Dr. Alexander Grant, who was the Associate Commissioner of Consumer Affairs at the FDA, and said just how extensive was this? And, indeed, as you suggested, benzodiazepines were included in what was supposed to happen. And his letter to me said these -- it was ten drugs, or classes of drugs, it wasn't just ten individual drugs, and they represented over 300 individual drug products comprising 16 percent of all new prescriptions. So it was a fairly extensive program, and it was, I think, cancelled for fairly arbitrary reasons, the private sector clearly hasn't come through.

The second comment I would make is on this methodology of how we do these

assessments. I do not have any ownership or stock in the Rand Corporation. I think it's not-for-profit, as a matter of fact, but the methodology there clearly included whether readers learned significant amounts of important information, so it wasn't just did you read it? Did you understand it? They actually checked learning. So, again, I would just urge you to go look back at the methodology of that study, which was an FDA-funded study.

In addition, they obviously, I don't know whether in advance or whatever, they stratified the results by reading level, so they actually had information about that, as well. So I am always not just as I am aging thinking about why do we have to reinvent the wheel. I think that FDA probably has, in addition to this, some other previous studies on assessment that can be built on in terms of what you demand of these people who are putting in these requests to

get part of the Stimulus package.

DR. PETERS: I wanted to follow-up quickly on something that Dr. Goldstein said earlier. I liked your idea of thinking about this in a safety context, but I also wanted to add, we've talked about this a little bit before, but there's a benefit context here, too, that we have to make sure that we're sensitive to. And, also, testing comprehension of what those benefits can be.

There's lots of data looking at - not lots of data - there's some data looking at benefits and adherence, for example. So you can see the influence of health literacy and the ability to stay within a safe and beneficial range for Warfarin, some very interesting data there. There may be other issues involved with things like statins that have kind of invisible benefits. But I just encourage us to keep in mind the idea not just of safety, but also the benefits of all these drugs.

MS. MAYER: Just as sort of an overarching statement, we regulate drug products and devices very carefully. FDA has looked long and hard, and has very high standards, generally, on what is required, particularly of drug manufacturers. And, to me, since from a patient perspective informed consent is really the foundation of medical care, that is, that patients have the information they need to make treatment choices, and their sources for that information are limited in society, often to direct-to-consumer marketing, and a few other sources. This opportunity, to me, represents a very important way that FDA can interact directly with patients to provide accurate information.

And I hadn't known the whole history of this really until beginning to read materials, and hearing the presentations today. And it's just very clear to me how crucial this effort must be to have a single

- I think it should be single - source of really comprehensive, clear, understandable, unbiased risk and benefit information. And it seems to me as if this is sort of a pressure point now with the failure of the initiatives on the part of the industry, where FDA actually might find some ways, perhaps with our help, of sort of seizing the regulatory authority to really once and for all make this happen, and not simply leave this process up to manufacturers and outside developers.

MS. LAWSON: That's sort of, I guess, a lead-in to my question. Now that you have the results, and they're not that favorable, do you have a time line for revisiting the regulations to determine what you can do, and when you proceed to do that?

MS. HENDERSON: I would say that we don't have a time line for finishing, but we have surely begun in earnest. I mean, as soon as we knew the results of this survey,

we began internal discussions right away that led us to you. I mean, you are -- we starting meeting immediately with various stakeholders to try to understand what these results meant, where the failures have occurred, and so I would say that we feel with you a real sense of urgency. I don't -- depending on where we go will depend on how long it takes to change whatever it is we're going to change. It's just almost impossible for me to give you a time line, but I would say that we feel a real sense of urgency within the Agency to, I think, seize the day, and figure out what is the right thing to do for the patients we serve. So you are a very important step in that process.

CHAIRMAN FISCHHOFF: Let me thank the presenters for, obviously, having gotten us going, focused in a good way.

We'll take a break now until 10:30, and then we'll start with the presentations on the evaluation.

(Whereupon, the proceedings went off the record at 10:20 a.m., and went back on the record at 10:39 a.m.)

DR. FISCHHOFF: Thank you very much.

We'll begin the next session with the report from Carol Kimberlin on the evaluation of the consumer medication information.

Thank you.

EXPERT AND CONSUMER EVALUATION OF CONSUMER MEDICATION INFORMATION - 2008 FINAL REPORT

DR. KIMBERLIN: Well, thank you to the committee. And we especially want to thank Jodi Duckhorn from the FDA for providing much support, and being very dogged in making sure that we got the deliverables in on time, so we appreciate that.

I'm going to start us off, and then I'll turn it over to my colleague, Almut Winterstein.

The research questions that we

addressed really mirrored the 2001 study. What percentage of shoppers filling prescriptions were given any written CMI beyond the label directions? What percentage of the CMI adhered to quality criteria as determined by a national panel of pharmacy experts? What percentage adhered to criteria that consumers were asked to use to evaluate the quality?

And how did these experts in consumer evaluations of the quality differ in the 2001 and 2008 studies?

For the 2008 study we had two medications that patients were newly prescribed, and went into pharmacies to have filled. The National Association of Boards of Pharmacists purchased electronic lists of all retail pharmacies in the continental United States.

A sample or 420 pharmacists were selected using random selection procedures, and the sub-contractor, Second to None, hired

professional shoppers to pose as patients and present these two prescriptions.

We trained and provided training materials to Second to None so that the shoppers would use standards protocols for playing the patient role and answering questions in the pharmacies.

The physicians were recruited by the FDA in local areas to write the prescriptions. Then all written material dispensed in the pharmacies were sent to the University of Florida for evaluation. And then we conducted both the expert and the consumer evaluations.

Now we had two expert panels that we relied on to assist us and advise us in this research. We had four clinical experts from the University of Florida and Shands Hospital and the community of Gainesville, which formed the development expert panel. And that panel reviewed standards and criteria that were used in the 2001

evaluation, as well as the 2006 FDA guidance document, which came after that initial evaluation.

The panel examined FDA approved labeling and other professional monographs in the standard drug compendia.

The panel developed explicit criteria, then, within each of those standards to operationally define CMI for the two drugs that were being used in this study.

I'm not going to go over this, since Jody already covered the standards, but just to point out that the first five really have to do with the content; the sixth is more of a disclaimer or general information encouragement to ask questions.

The scientifically accurate, unbiased and up to date. And then eight is really the formatting to assess how legible, readable, comprehensible the information was.

After the development expert panel operationalized for the two study drugs, then

we had a national panel of eight pharmacy experts who reviewed and made comments on the expert evaluation form. Forty CMI were rated independently so that we could see reliability and make some alterations where there was any inconsistency in applying those criteria. And we continued that check as we collected data.

The scoring procedures varied slightly from the 2001. Raters were asked to indicate whether each item in information identified by the specific subcriteria was present or not present.

In 2001 they had present, partially - the criteria was met, partially met, or not met. So we did not use that partially met level.

For criterion seven, the scientific accuracy only involved the information that was actually in the CMI, so it was only errors of commission. We didn't do a separate evaluation of whether there was

information missing, because that would have been covered in criteria one through six.

For criterion eight the format, the expert panel assessed four of the readability criteria, and the staff assessed explicit measures such as font size, amount of white space around text, line length, use of bullets and reading level.

Adherence of CMI to criteria were also reported as a percent of total possible points obtained for the overall aggregate score of all of the subcriteria.

For each individual general criterion that is identified, that Jody identified as the standards for CMI, and then for each individual subcriterion that operationalized each of those criterion specific to the study drugs.

Means and standard deviations for aggregate, and the general criteria, the eight general criteria, were also reported.

In order to compare to 2001

findings, we categorized the percent of possible points of information that were covered in the content area, and also where the criteria was met in the other standards.

Level zero, no written information was given.

One, zero to 19 percent of the possible subcriteria were met.

Twenty to 39 was level two, 40 to 59 level four; 60 to 79, and level five, 80 to 100. So this was completely congruent with the 2001 study.

We also did a consumer evaluation study and the evaluation form was identical to the one that Svarstad and Mount used in the 2001 study. It was a five-point semantic differential scale where low scores were equivalent to low quality.

So nine items asked how the consumer would feel about the leaflet if he or she were taking the medication for the first time. The remaining three were overall

opinions about readability, comprehensibility and usefulness.

And these items were summated and reported as average percent. And standard deviation as well as that five-level frequency distribution that matched the 2001 study.

In the 2008 study for the consumer evaluation we had 14 site coordinators in 13 states that each recruited 12 to 20 consumers. We had all materials approved both by the University of Florida IRB as well as the IRBs in each of these institutions or agencies that we were - where the site coordinators were located.

They used snowball recruitment, which was the same as 2001, from clinics, churches, apartments, parents organizations - a variety of groups.

Consumers did have to read CMI in English, have no training as health professional, not have diabetes or

hypertension or taken any medications in the same class. We wanted them to be unfamiliar with the medications from their own - from the point of view of their own health history.

Now the results: 365 pharmacies dispense the medication for the study drug. What we found when we went to the targeted pharmacies, some of them were closed. Some of them did not want to dispense the medication or ask for identification from the shopper since this was a new patient in that pharmacy. So we did have 365. Six percent provided no written information beyond the label directions. So that means that 94 percent did provide some sort of written information. And that falls within the 95 percent confidence interval for the target of 95 percent, or 95 percent falls within the confidence interval.

The CMI ranged from 33 words to nearly 2,500 words, so there was great

variability in the amount of information that was provided.

The guidance and the standards say that all of these CMI should have the publisher and the date of publication included in the information.

Forty three percent of the CMI we looked at had no published or identified, and of the remainder, 56 percent were First Databank, 42 percent Wolters Kluwer; so there are really two publishers of this information. Some of the results of the overall quality of the CMI, somewhere between 70 and 75 percent had the level IV or higher in terms of quality of CMI. And the mean, though, was 60 percent - about 60 percent of all of the items of information that we were looking at to indicate the quality were met, the criteria were met.

And this is per criterion. And I think the notable items are the directions and what was included in the directions was

not just directions for use, but directions on how to monitor the effectiveness and safety. So it's really that monitoring that there were items that were included that were less likely to be met than actual directions for how to take.

The format was also one of the lower items. And we will go into some of the specific criteria, subcriteria, for those.

The accuracy of the information that was provided was very high. So that if the information was provided, it was judged to be scientifically accurate.

Now the percent that dispensed CMI, that met that 60 percent threshold which was defined in the 2001 study, you can see the low categories are the directions and the format. And in comparison to the 2001 study the directions for use were less likely to be met in the 2008 study, and I think because of the increased emphasis on knowing how to monitor therapy, not just what the patient

could do themselves, but what they understood the physician would do or should do to monitor effectiveness and safety.

The format, it appears to be reduced. But in the 2001 study there were four medications used, and there was one that was an extreme outlier. It was sublingual nitroglycerin, and that had 47 percent, that one medication, that met that 60 percent threshold. If you looked at the other three, they were really closer to the 8 percent that we found.

So the highs and lows then in category three, which was problematic, was - we wanted the patients to have the information about what action they should take, not just that they had the information but what should they do with it.

So asking about lab tests for lisinopril, anticipating how frequently - knowing what to anticipate in terms of how frequently those tests should be run; asking

about blood pressure readings, or self monitoring their blood pressure; overdose symptoms; not just - one of the items was what do you do if you have an overdose, and the typical advice is call the poison control center or get to an emergency room.

But some CMI had the National Poison Control Center number there. So that was an additional very useful piece of information is the patient needed to call.

Now administration with or without food, that was seen in both of these. But what wasn't seen was the monitoring.

In terms of the formatting, the problematic areas in terms of the FDA guidance document, black box warnings were not in bold or in box. Often they were in bold face type - I mean all caps type which is harder to read. There was not the bolded text for emphasis which was recommended.

Bullets in terms of outlining the information so that it is easier to read and

using bullets for important points, that was not - very rarely seen.

Only 10 percent were written at or below the eighth grade reading level using the Flesch-Kincaid reading level test.

And in terms of the space between lines, the recommendation is that it be at least equal to 2.2 millimeters, so we had calipers, and we were measuring this, and 15 percent - only 15 percent - met that.

So the text is very dense. It is very - there is very little white space between lines, or around text.

Now the items that were generally met, and again, these are pretty much the same as were generally met in the 2001 study, they used both upper and lowercase lettering by and large. They didn't use italics or ornate type phrase, space, good ink/paper contrast, limited use of medical/technical terms that weren't explained.

Other low scores for the different

drugs. Angioedema can be fatal for lisinopril. The action when you experience a serious side effect to stop taking the medication was not explicitly provided.

A physical description of the drug, other precautions in the case of lisinopril were given only 41 percent of the time; dates of publications were typically not provided, brand names were typically - now these are generic medications, but so the advice that brand names be included was not typically provided.

The contraindication of a contrast agent with metformin was often not provided.

And usual dosing was not.

We looked at the question of pharmacy ownership. By and large the chain pharmacists had longer leaflets, and so they did present more - there was definitely a relationship between the number of words and the number of the criteria that were met. And that is one of the issues. You just get

credit for putting in more facts, and not demerits for overloading with information, which I think is one of the problems with this.

In terms of the content, then, the chains were more likely. But the formatting, the independents were more likely to meet those formatting criteria.

And again, the chains had longer leaflets, so there was just more content there, or more word count.

The consumer rated quality of the CMI, the means were 65, 66 to 70 percent of the possible points that could be awarded were awarded. And the - about 75 percent scored at - 75 percent scored at or above the 60 percent threshold.

Now what was concerning was that the items that were most problematic, according to the consumers, were print size, line spacing and ease of reading, which are exactly the ones that were identified in 2001

as being most problematic.

So if you compare it with the 2001 study, the real differences are that there - there were more at the level four, which was the 60 to 80 percent that were met. So that you had a higher percent that met that threshold criteria, but the items that were lowest in the consumer's mind were the same as the experts, and that had to do with the formatting, readability, comprehensibility.

I'm going to turn it over now to Almut Winterstein, who will give you some examples of what we saw with specific areas of concern.

DR. WINTERSTEIN: Good morning. I get to do the fun stuff. I get to show you examples, and share some anecdotes with you.

But before I do this, I'd like to start with an analogy. Many of you are interested in patient safety, and I know that many of you or probably all of you will remember the patient safety report, the

Institute of Medicine report that came out, and a lot of discussion thereafter. And there were a lot of analogies that were drawn to traffic, aircraft, and various other safety environments. And I'd like to draw an analogy to risk communication or leaflets. All of you have bought a laptop, a washing machine, any other tool you may use. And you may, before you see some of the examples I am going to show you, I would like you to recall the last manual you have had in your hand when you bought a new laptop or so. And what you may notice is that the format for a laptop manual is actually better than what you will see here, even though laptops typically don't kill people, and they don't improve health and make you happy maybe or unhappy, but they don't really do anything with the most precious good that mankind has, which is health. They also typically come in multiple languages. Now we will argue that of course they come in multiple languages

because they are sold in multiple countries, but of course the same is true with drugs. They are actually available in Europe as well, which covers many languages, and in that sense it wouldn't be so difficult to translate English drug information in other languages.

So keeping this in mind, just thinking about what we typically have available for our computers or washing machines; also there is typically an area that talks about troubleshooting. If your computer doesn't work and a certain light blinks, what are you going to do? And it actually goes through the most common troubles, aka side effects you may have. And it gives you very specific, explicit ideas about what your action step might be. And again, I'd like to ask you to look - pay attention when I show you some of these leaflets to see whether you find the same type of troubleshooting advice provided in

leaflets.

So this is outside of the results we provided for the direct research questions related to this contract we had with the NABP and FDA. This is really more exploratory analysis just to find out what else was there, what kind of interesting information could we derive from those leaflets we had.

So the first question we asked was, are some publishers better than others? And there were two main ones. You have seen this, First Databank and Wolters Kluwer. And when we looked at publisher versus content, either content quality or format quality, you remember that those first six criteria explicitly asked if specific content pieces are included in the leaflets, and then we have this format criterion that talks about how the information should be formatted and displayed.

There was no significant difference between those two publishers. But

there was also significant variability of leaflets within one publisher, which was quite amazing. Because what we had expected was that pharmacies buy this information from publishers, and pretty much go ahead and print whatever they get.

Now what we found was, here is, for example, a leaflet that was done by First Databank. First Databank is identified as the publisher. This leaflet has I think 2,500 words, 2,400 words, one of the longer ones. These are front and back page, so this is not two leaflets; that is one leaflet. So lots of information on here, and that met a lot of quality criteria on here. I think that had a quality score of about 80 percent.

Here is First Databank again. And obviously this looks very different, obviously way less words. In fact these were 760 words. It had 30 percent of content criteria met, so very very different.

And this was actually quite

interesting one, this area that we show here. There is a note in this leaflet that says about side effects, see also a warning section - there is no warning section on this leaflet. So it refers to something that is actually not present, which suggests that something has been taken out, and we don't know by who and how it happened and why people did that, but it simply is not there.

Here is Wolters Kluwer, pretty much the same thing. A leaflet that met 81 percent - I have a little cheat sheet here - 81 percent of all content criteria; had 2,050 words. And here we have Wolters again with 136 words and 11 percent of criteria met. Interesting that it's meeting anything, because there is not a whole lot on there.

So one question we really like to ask is, how do publishers select this information, and what happens to this information when it gets into pharmacies, and what are they doing with this?

And that is really not totally clear to me. Also looking at the larger leaflets, I went to the package inserts for metformin, and this is only the section on precautions. Just - this is even a little bit larger font size, but you see how much information is on there. None of the leaflets had all of this information.

So my question is, what kind of criteria are really being used to select the information that goes into this patient information, into the CMI, and what not? And who does that? Is this a pharmacist, a physician, a sociologist, a psychologist? Who within First Databank actually makes the decision what goes in and what goes out.

Now with the volume what you noted is that the more information is there, the more content you hit. It's pretty much a shotgun approach obviously.

So but the question of course is what is the right amount. So if I have a

5,000 word leaflet, I pretty much have the PI, then I have pretty much everything in there that I need, and the patient has all the information that is necessary. But is this really what we need? And to go back to the analogy about the laptop, we all know those really thick manuals we get, then we look at the short instructions. There must be one little card somewhere that tells us how to do the quick start here.

So is this useful, and is this really what we want? Or is there really a threshold for information overload?

So would it make more sense to have actually less, and should we have punished leaflets for giving too much? And obviously we did not do this. You know how the content criteria was set up.

Now one issue beyond that is that what we noticed is that there as lots of redundancy. So here is one leaflet that has not a whole lot of information. Here is a

leaflet that has almost no information. Here is a leaflet that has quite a bit of information. And if you look at the word, efficiency, we decided to call it, these are the leaflets that met at least 80 percent of the content criteria; not format, just content criteria. And within those leaflets there was a range of more than 1,000 words difference. So there were some leaflets that managed to provide 80 percent or more of the content with 1,100 words, for less than approved 1,400 words for metformin. And there were some that needed 2,100 or 2,400 for the same. So there is a difference of more than 1,000 words, and that's what I think goes back to this efficiency issue.

This is not quantified, but a lot of this has to do with disclaimers. We saw leaflets that had disclaimers in every single section of text they were providing, for the side effects, for the precautions, for the contraindications. It would say in every

single place, this is not all of the information. There may be more, and you may want to talk to your physician or your pharmacist, and basically this information is not very reliable anyways.

And this would be repeated every single time you would go to a new paragraph.

It may not really be the best way to provide information.

This is a graph between - just to illustrate this a little bit more - between content quality and word count. And what you see is that the quality leveled off at some point. The XX is the word count here, the content quality is on the vertical on the Y-axis. And you see at some point the more words you provide you hit a level of no return - there's nothing more you can really provide.

So that definitely I think could be chopped off. Whether this is all, or whether there even could be information

spared because patients don't need them anyway, and they won't really benefit from it, I think is a question that is still out to be answered.

Now about the format, how to organize and present the information, just a couple of more examples. Here is one leaflet that actually had a drug description. You will see a little graph of how the tablet looks like, and there is at least some sections here, so that is actually one of the nicer ones I think.

This is a leaflet that actually has both drugs on one page, one is metformin, and the other one is lisinopril. And you see that the text is just crammed and, I mean, I would have a hard time reading this, and wouldn't enjoy it.

Here is another one where at least we have blocks of text, but you see that these blocks of text, at least we have headings, but you see that these blocks of

text are really long and not easy to read. Here this is even worse obviously.

And then just to finish this part of showing you examples, what is the issue about distracters? I believe Debbie or Nancy this morning - I think Nancy this morning talked about there may be other information provided that may not - shouldn't really be on there. This is the back side of one - no, actually not - well, it's a leaflet that could be folded. So we have nutrient news here. We have all kinds of things. That is the back side of one of the leaflets.

Skin hair and nail tips, that's always good to know. And then there was one which we didn't include here but I will mention it anyways, that actually had a Bible verse right on top of the publisher, for whatever that might be good in a CMI.

So there is a lot of information that may distract, and that may not be such a good idea to include.

So I think there are a couple of clear ways to improve leaflets, but that is not the whole story, and we have a lot of questions that are still open.

Just to illustrate this, this is our idea about how this - how this information is currently generated. We have this universe of drug information which of course is not complete. There is all this new stuff coming out, as we all know.

I'm a pharmaco-epidemiologist. I'm generating this new information. Then we have a data warehouse that selects this information somehow. Then we have a pharmacy that prints it, and then we have a patient that consumes it essentially.

Now the first part here is, it actually doesn't look like the universe. It looks like more like this source of more and more information where we actually really don't know whether it is relevant or not.

We know that more side effects are

included in the labeling than are actually necessary. Many side effects are clinically irrelevant. Many drug-drug interactions are theoretically but clinically not manifest.

And we know in many instances really not whether it's important to know this or not, not for clinicians, and not for patients.

Many of you may be aware of the research that is currently ongoing related to clinical alerts, clinical decision support systems, which is the same idea. You have drug information that is now provided to providers. And providers complain about the clinical irrelevance of the alerts that are provided. This needs a lot of cleanup; and the same of course concerns patients.

So right now the PI that is generated has not only to do with clinical relevance but also with legal issues, obviously. And the evidence base for the labeling information is obviously - is often

not present.

Then the - however this of course is the core source for the information that is selected by the data warehouse for the CMI. So I like to ask then, what are the selection criteria for content? This is to me a complete black box, and I haven't seen anyone defining those selection criteria, and we will come back to this on the next slide. Is this done based on patient relevance? And what does patient relevance really mean? Again I will come back to this later.

What about updates? How fast is this information really changed? Those of us who are commissions know that drug compendia, like Micromedex or CP Online, and so forth, usually have very frequent updates. Now this is happening on the provider level, but what is happening with CMI? Do we know whether this is updated quickly as well? The publisher date was often not on the leaflets. So we weren't really use how timely this

information is updated.

And then with respect to the format, do those data warehouses actually format this information according to the FDA/CMI recommendations, or - so is it essentially the pharmacist that screws this up at the back end, and is the original formatting actually good? Or not? And wouldn't it be nice if somebody made a really good step on formatting it correctly to start out with and then we are done with this part.

Lots of questions that we were not able to answer.

Now for the pharmacy portion, who is making those modifications and why are they being made, and does it really make a lot of sense? You saw that content was missing. You saw that the format varied tremendously. And it appears that the format varies within publishers, but also within pharmacies of the same chain.

With respect to updates, I

mentioned this already.

And then the other really interesting part here, what about individualized information? This discussion came up when we talked to our clinical expert panel that was trying to define what information should really be on the leaflet.

Now both drugs, metformin and lisinopril, have off-label uses that are evidence-based. Metformin is used for polycystic ovarian syndrome, frequently has good evidence that backs this up. Lisinopril or all ACE inhibitors have solid evidence for diabetic nephropathy.

Now however, both indications are not approved, and FDA guidance suggests that unapproved indications shouldn't be mentioned.

We had long discussions about this. Now you have a patient who is filling a prescription for metformin, and this prescription says this drug is meant for your

diabetes. And that's the end of it, and she has polycystic ovarian syndrome. I don't know how this relates to compliance, but at least I would ask a couple of questions if I hadn't been told by my physician this drug is typically used for something different.

However it creates a lot of uncertainty. And would it make sense if the indication were known to include those off-label uses? And how of course would we decide what is an evidence based off-label use or non-evidence base off-label use, since the FDA review obviously is missing, so we don't have the rubber stamp on whether this off-label use makes sense or not.

So we collected information on off-label use. We didn't include it in the criterion for the evaluation. And it varied tremendously. Half of the leaflets didn't talk about off label use at all; another half mentioned that it could happen, and then a certain portion mentioned specific uses,

which, personally, I find might be helpful for those patients who use it for those indications. But it's an open question.

The more individualized this information could be, I think the more helpful to the patient. I think that is all very clear, but this obviously requires a completely different vehicle than what we have right now. If we have one leaflet, that will not fit all patients. If we had something that was more integrated, where let's say we would have electronic medical records, and a leaflet could really be generated or tailored to the medical information that is available for a patient that might be a completely different approach, to me a very appealing, but obviously it's a little bit along the road.

What about those disclaimers? How many disclaimers do have to be on a leaflet? And does it - do those disclaimers have to be in the body of the text? Can they go

somewhere else? Do they really have to be in this text, crammed everywhere?

It's an easy question, but one that unfortunately was, I think was very disturbing for many of these leaflets.

Another question that came already up, was how does this information change when it is really handed over by a pharmacist who points out that this is actually the leaflet to look at. Forget about the coupons and everything here; this is the piece of information you need, that you really may want to look at, because this is the piece of paper that tells you about your drug. Or pharmacists potentially really taking a highlighter and highlighting the areas that are important for patients. I mean this information could actually be individualized if a pharmacist took the time to do so. And since I'm a pharmacist, Nancy, I would like to strengthen what you said earlier. OBRA isn't really implemented very well. Our

profession doesn't do a good job. And it would be really interesting to see to what degree, if that were better integrated, to what degree a normal generic patient leaflet could become more effective, and could result in more comprehension if there was more verbal counseling that travels with it, and it was a package.

So then lastly the patients, how do patients use leaflets? Is this PRN? So if I suddenly have a side effect and I go and look it up. So is this really a reference for me? Or do I read the whole thing before I use it? And then a more philosophical question which I think is important; what do we want this leaflet really to accomplish? Do we really want this leaflet to establish solid self-medication management skills in a patient? And if so, none of these leaflets is able to accomplish this right now. I want to make this very clear. This is not what we evaluated. Many of the actions that were

recommended for side effects or contraindications were very generic, that did not go beyond, call your pharmacist or your physician.

This is not an action step that I consider appropriate when a patient has early symptoms of lactic acidosis. So in that sense, really clear action steps for monitoring of safety and effectiveness are not spelled out. They are not spelled out in the PI, and they are not spelled out - consequently they are not spelled out in the CMI. So that may be a completely different piece of information that needs to be added on that is currently not there.

And then lastly, determinants of comprehension. Is every patient the same? Would leaflets need to be tailored towards different levels of health literacy? Different types of patients, patients who are more computer literate, versus patients who don't want to have computers? Could it be

combined? Is there really one size fits all? Or do we need different approaches?

Which brings me to my last slide: future research questions. And I mentioned I wanted to come back to how is this information being selected.

What information in the label is clinically significant? This has nothing to do with CMI. We do a lot of studies in our teaching hospital related to drug-drug interaction alerts, and such. And just to share one anecdote or one example with you. Amiodarone and haloperiodol has an absolute contraindication because of the potential for QT prolongation. It is frequently used in CICUs, cardiac intensive care units. We actually did a study in more than 300 patients. We saw a median QT prolongation of zero milliseconds, and an average of nine milliseconds. Baseline QT was about 500. This is not a big deal. It is a theoretical contraindication which doesn't seem to be

clinically very manifest. There are many like that. But in many instances the evidence is not there, which is a big problem not only for consumer information but also for clinical decision support system and provider alerts, or provider information.

So what criteria for CMI specifically should be used? The clinical significance, the severity? Should we tell only patients about those things that can clearly produce harm? The prevalence? So everything that is very common because that could happen most often.

What is important for self management, should we focus on this? So omit the pieces that a patient wouldn't be able to handle himself, or herself anyways. What is relevant to an individual patient? So should we actually have some type of decision tree depending on what the patient's medical history is, and how important is legal protection in there, and all these

disclaimers that I mentioned before.

Are there better media than a leaflet? This question was asked already this morning before. Is there a threshold for volume? Is there one? Should we actually research what volume of information a patient can actually digest on a leaflet, and use this threshold to select the information that goes on there?

How does verbal counseling during dispensing change all of this?

And then the last question, which was already mentioned this morning as well: How does any of the above affect comprehension and patient's ability to make informed decisions? What I mean with this is, it was actually funny, we were talking about how to communicate information to patients. And we were trying to communicate research findings. And the way we communicated these research findings, this morning was, 75 percent of the leaflets met

the minimum threshold for usefulness. And probably everybody in the room asked this question: so what is the minimum threshold for usefulness?

The threshold was 60 percent which is arbitrary. Our previous - our colleagues who did this study previous in 2001, may have flipped a coin. I have absolutely no clue. Sixty percent sounds better than 50; it's more than half, though 60 could be produced by content only, or by format only; we don't know what was in there. We did not rank the information by any way or fashion. It is simply 60 percent of whatever was there.

And then is this enough? Is this 60 percent enough to result in solid comprehension? We have no idea. And we don't know whether 70 percent of them meeting the 60 percent is good or bad; we don't know.

So again an analogy, if we were reporting the efficacy of a new anti-hypertensive, then we would say that 50

percent responded with a clinically significant change in blood pressure, we would know about that clinically significant change in blood pressure is.

So I think somehow we need to have some way to define comprehension in a similar fashion, and we have tried to do some work parallel to this FDA study on this, which we still need to analyze. But one thing that was already clear from this is comprehension was not really affected by formatting very much, and there are a lot of problems with comprehension for sure. Comprehension did not affect consumer ratings of these leaflets. Consumers could rate leaflets very highly yet did not understand the information that was on there. So these seem to be two completely different constructs that need to be considered.

So a lot to address. And I'm sure I asked more questions than I answered. But I guess that is a part of science too.

QUESTIONS AND ANSWERS

DR. FISCHHOFF: Thank you both for your - for the presentation and for the work that it was based on.

Since I didn't get in last time. Maybe I'll start.

So much of our work, our own research, has dealt with this question of how do you set priorities. And the way that we have come to think about it is that the answer comes from either risk analysis or decision analysis. Is that the priority? I need to be told first the information that is most material to the decisions that I am going to make. So that will be some combination of probability and consequences, and my ability to act on that.

And that's a tractable but a nontrivial question to answer, I think, in different situations. And you can think of in these situations and many others there are two interdependent decisions. One is, do I want

to try this product or not? And then second, how is it going? Do I want to stick with it, or do I need to try something else? Or get help quick?

They are interdependent. You could say, I'm going to try it. And then there is a whole other set of issues. Or then sometimes you say, I don't think I could use this. I'm not going to - I shouldn't buy it. So in your laptop analogy, if I have to read the manual I don't want this product.

And other places, or if I can't use this safely, then if I can't tell when things are going wrong.

I was thinking while you were talking about one example - this was Donna Riley's, one of my engineering student's dissertation. There was a place about 10 years ago, the Chlorine Council, the Consumer Product Safety Commission and EPA were interested in the possibility of voluntarily regulating products that had methylene

chloride in it, which had been declared a probable carcinogen by the IARC at that time.

So the question was, could you bring risk levels within tolerances for home users on the basis of labels? And so what Donna did is she built a model of the dermal and respiratory uptake of methylene chloride for people using paint stripper was a case in point, really nasty if you have ever tried it.

And so she discovered that there were really two things that you needed to know about using paint stripper. One was that you absolutely had to open the window; and second, that you had to have a fan blowing out. And if you did that you could bring down the respiratory uptake enough that you could perhaps be within tolerances in terms of carcinogenicity, and with a high probability be within tolerances for carbon monoxide uptake, because it causes heart attacks from its volatilization.

So we did this very complicated,

kind of intricate analysis, to discover there is actually just a simple message. You look at the labels, they came from the same school, same design school who produced the labels that you had there. If you picked through them you found that some of the labels of products that are on the market had the information that you needed if you could just find it. And you would find it if you read the warnings, but not if you read the instructions. You would find it if you read the stuff in bold, but not if you read the - you could either find it on the front, but maybe not on the back. So it was hit or miss on whether you would find it. And some of the labels just didn't have that information there at all.

So our conclusion was that in principle people could do things that would enable them to use this - to use a paint stripper in a way that brought the risk very low, but that a voluntary regulatory - a

voluntary system which was in place there, without any sort of behavioral or decision science input was not capable of delivering that information.

So I sense that there is an analogy here that we need a disciplined way of deciding what the priorities are, and then some sort of system that ensures that that expertise is brought to the task.

DR. KHANNA: Thank you. Thank you very much to Carole and Almut for their presentation.

I was interested in Almut's comment about many side effects being clinically irrelevant, with the implication possibly being that maybe they didn't need to be included in these guides, which would make them less dense and more readable.

That particularly struck me because I had just read the email to Dr. Zwanziger from a woman, a consumer named Jenna Markle who stated specifically that the FDA should

require all adverse events to be reported on the consumer information whether or not they are - regardless of percentage or causality. For example they cited Singular's prescribing information only lists adverse events equal to or greater than 1 percent.

So having that background I wanted to ask our friends from CDER or Dr. Ostrove whether the FDA does have a threshold where we require adverse events or side effects to be reported? Does it have to be clinically significant? Does it have to be greater than 1 percent?

MS. HENDERSON: Reported in the labeling, in the professional labeling? You know I don't know the answer.

DR. KHANNA: Actually either professional or consumer. Because this consumer is talking about the consumer information.

MS. HENDERSON: I don't know the answer to that question. Do you know, Jody?

MS. DUCKHORN: For consumer labeling we actually tend to go with what the professional labeling says. I don't know - we look for some kind of statistical difference between placebo and drug. And there is clearly a threshold, but we don't decide what it is.

With the new professional labeling format, we tend to go toward what is listed in the highlight section of the label. But even having said that, sometimes there are still others that the reviewing divisions feel should still be included in patient labeling.

So as long as it is in the professional labeling, and not as a post-marketing, not seen post-marketing. As long as it is in warnings or precautions or adverse events, then we will list it.

DR. WINTERSTEIN: Side effects can be added without proof of causality. They are frequently added without proof of causality, and they are added by the manufacturer, not by

the FDA.

DR. KHANNA: It sounds kind of unclear. Okay, Dr. Ostrove is nodding, enough said.

DR. OSTROVE: Well, the thing is, different drugs have different profiles. But beyond that, depending on what the drug is being used for. So you have to look at the benefits and the risks, and I think the determinations are kind of made on a case-by-case basis.

I actually, I don't think any of us here know whether there are specific objective criteria that are being used. So in some ways we are not the right people to ask. And we would need someone from - from the review divisions or the Office of New Drugs, to give you a solid answer.

All I can do is give you an impression. As Almut mentioned, at least in the past manufacturers have been able to add side effects, but we also review those at some

point. So at some time that can change. So side effects might be added, and then they might be taken away if FDA determines that they shouldn't be in there.

So there are lots of different things going on here. It is a very complex situation.

DR. WOLFE: I think this will hopefully clarify it a little bit, but I don't begin to have the full answer to this.

In the labeling, let's start with the threshold labeling, part of the label concerning adverse reaction is in fact, as I suggested before, is from randomized control trials. And those are the tables where less than 1 percent, whatever, because there you have got a denominator.

On the other hand, most of the drugs that have been taken off the market in this country were not because of randomized controlled trials. Vioxx is a sort of unusual example. It's because of average reaction of

course.

And so in addition to the table that is usually there with the incidents that occurred in the randomized controlled trial, there is a list, often a fairly long list, of other adverse events that had been put in there.

I would guess - I don't know that, because I have never been nor am I ever likely to be inside a drug company. But I would guess that the lawyers for the drug company are very prominent in the decision making as to whether you put something in. Because a standard, I am told, in product liability litigation amongst others is the failure of the duty to warn.

So if they do not put in something that let's say shows up 5 or 10 or 20 times, which may be in the rare category, don't list it outside of the RCT information, the company may get into trouble.

But I think the answer that Nancy

gave and Debbie - I mean I don't think that it is standardized at all, except those are the two categories. I think those two categories are always in there. But the decision as to what you put in, which is probably the origin of this letter that we were all handled, in terms of the ones that are from spontaneous average reaction reports, is pretty arbitrary.

DR. WINTERSTEIN: I'd like to add one small comment to that. Because my professional training, even when it is in the clinical trial, the clinical trial is not powered to look at safety. A phase three study that leads to efficacy will look at specific safety concerns that may have evolved in the phase two or phase one, or even the preclinical phase. But the power rating in the trial is focused on the primary efficacy measure.

So even if you had that table of these were side effects that occurred in more than 1 percent of the patients, you don't know

whether they were caused by the drug or not.

So most of the side effect information we have seemed to happen more often than in the other group, but we are not totally sure. That is what you get. Every labeling change thereafter is predominantly generated by pharmaco-vigilance, so essentially spontaneous reports either to the FDA or the manufacturer, and the manufacturer as the bulk of those. And they are added as suggested by Dr. Wolfe typically because of liability issues.

So the idea is, the public has a right to know, which is obviously true. But at the same time you have no idea whether there really is a causal association or not.

Many examples, one of the most prevalent right now, where the question is still out, is cardiac arrest for stimulants in ADHD. We don't know whether there is a risk or not, but it is already included in the labeling, even though there is still a study

going on trying to answer exactly that question.

DR. FISCHHOFF: Okay, thank you.

John, Mike and then Craig.

DR. PALING: I have many thoughts about this whole topic. But I will restrict myself to three brief ideas immediately following these last two presentations.

I felt there was an implication that those CMIs that we saw displayed were not adequately communicating with the public. It is my opinion to the contrary that they vividly shamefully communicated to the public the true message: we don't care.

I think that we are all surrounded not just by commercial messages, but by people who consciously know how to appeal to you as a reader, and to get their message across.

Now in saying what I have said, and I feel that very strongly, the real message is this is being done because we legally have to, and in fact, I think if the truth were

admitted, most people would feel, well, they are never going to read that. Yes, it's all there.

So that is one thing. I think, and I'll come to my third point which relates to that.

Second point is this: I've sat in many meetings, as we all have, where how far should we go communicating the risks is one of the many topics discussed. These documents are well intentioned attempts to cover all the salient points.

But I would like to perhaps disagree with what I think one of my colleagues said earlier, that I think a total paradigm for all risk communication in health care should be to do two levels of information: one needs to know, and the second, you should know, and you should ask for it, and should be encouraged to ask for it if in fact you feel a need to do so.

I think, and this is my empirical

opinion, that we do a disservice if we are trying to judge the great massive overriding document, whereas in fact I would encourage for all of these risk communication media that we should think of a two-level approach: need to know, brilliantly presented with good formatting, should know, and for those that want to cover their back ends and need to legally, also well formatted and clear, but made immediately available to anyone who asked.

Now my third very controversial point, which will not surprise my FDA associates, to whom I have made many outrageous suggestions off the record before, hoping to be able to make a difference to this process. I think the problem with this is that these unsatisfactory documents do not get public exposure for the contorted obfuscated communications documents they are.

Wouldn't it be wonderful, is my suggestion, though this committee could not do

this, if some patient advocacy website put up some of these, not to ridicule them, but to make a positive reinforcement with an award, voted for by whoever wants to go on the website, to comment on whether this could be made more clear and why. Not to try in anyway to diminish the complexity of risks, benefits and consequences, and all the gray areas of levels of knowledge and all of these other things, but in fact to put the harsh light of public opinion on the inadequacy of these CMIs as I see them.

DR. FISCHHOFF: Mike and Craig.

DR. GOLDSTEIN: This may sound similar in some respects. I want to thank the presenters again for raising as many questions, perhaps a lot more questions than answers.

I do think it's a matter of figuring out what the right questions are. So it's really really important that we get that right. In the broadest way, the question is,

what are we trying to accomplish? That's a quality question that I have learned from my colleagues who do this for a living.

And the how do we know that what we are hoping to accomplish was accomplished with whatever we are testing?

And it does get to narrowing our focus on what is really really the priorities, what is really really the most important things for people to know.

Because if we are really looking at the quality of the communication, we want to make sure those key high level important messages are getting through, and that is how we should be rating the quality of these devices or tools or resources.

So I would just encourage us to be really really thoughtful about those questions, looking at the outcomes we are hoping for, and I would say they are safety, knowing the key things that we want patients to be able to know and do with these

medications, and how they are going to respond once they are using the medications in an effective way.

And there is a nice list that our second presenter, Dr. Winterstein, provided, of some ways that we can narrow our focus, sharpen our focus, make sure we are asking the right questions and getting the right answers.

And we will talk more about those I think later.

DR. ANDREWS: I also want to thank Carol and Almut for a fantastic presentation and insight into this area.

It was funny, I was talking to some pharmacists and physicians leading up to this, and I asked a physician about the PPI, and he said, oh the legal document. Which was an interesting comment.

And I started to think about this, and I saw your future research questions here, what criteria for CMI content selection should be used? And I spotted legal protection.

And I'm in total agreement with what John is saying here, because obviously there seems to be two different purposes, two different levels of information. The irony of this is - I notice this is a different federal agency that dealt with consumers and the processing of advertising - is that small print disclosures or disclaimers did not get you off the hook in many cases at the Federal Trade Commission, the Kraft case, Stouffer case, and others, which is interesting, it's more consumer focused on that.

But the other thing I noticed, and I wanted to ask Carole and Almut if they had noticed that the CMI has moved toward more of a legal document, like the PPI, less consumer friendly. And then I'm thinking of analogies of direct-to-consumer advertising, the OTC, drug facts, compared to like a brief summary, the PPI.

So I just wanted to know their thoughts on the CMI and how that might have

moved over time.

DR. KIMBERLIN: I was on the expert panel for the 2001 evaluation as well. Certainly there are more items of information, just more facts presented now, in most of the leaflets. But it is highly variable. And I think the disclaimers, and the extensive list of side effects, and some repetitive precautions and contraindications, sounds like it's written for legal purposes.

I mean it reads like that, so I would say that that has been more of a focus, certainly now in the CMI, that we evaluate in 2008.

And those - but those examples, I thought what was interesting is how much variability that has to be attributed at the pharmacy level. Like the first Databank, the extensive 2,500 words, and then the 600 word, those were exactly the same publisher, exactly the same data publication. The information expired at the same time. Those should have

been identical, and they are not. And the one where the Bible verse was embedded in the CMI had to be at the pharmacy level.

DR. FISCHHOFF: Let's have one good thing that the staff has done is to get us first in line at the food court by scheduling. So let's have - we have three quick comments, and then we will take our break. We will meet back here promptly at 1:00 because our public comment period will be there.

So Tim, Ellen and then Sue.

DR. LESAR: Thank you. I appreciate the presentation. As someone whose desk is 10 steps away from a counter where we are handing these CMIs over regularly to our patients, and listening to conversations, I wanted to reiterate the point related to what are we here for, what is the actual outcome.

And the criticality of the outcome is extremely important, and coming from the drug safety side, we sit on where we sit and

evaluate drugs and their safety versus benefit. Many of the drugs are at the margin of - the risk-to-benefit ratio is pretty marginal at best, and only achieved in controlled situations. Certainly when we take these drugs out into the public domain, they are not used as well, they are not used as specifically, and they are used in patients at a greater risk.

So we know we see poorer outcomes in terms of efficacy and higher rates of adverse events. And so the critical point is, if we know that these drugs have marginal benefit to risk, it is certainly important how patients use the medications, and that they have the appropriate behaviors that optimize outcomes and reduce risk, is very critical. And that is what we are talking about, how does that occur.

Really it occurs through this communication that we are talking about. And while I appreciate the ability for experts to

review documents, for certain criteria, I also go back to some of the things we learned in drug safety, which is surrogate endpoints are often questionable, and lead us astray.

So sometimes I believe that evaluation of a document for its meeting certain criteria is really a surrogate outcome. What we really can do - this is just throwing out some suggestions - is thinking about the med guides, which often are targeted, looking for specific targeted behaviors to occur where that patient or warning, whether or not those couldn't be specifically evaluated whether that behavior that you want that patient to have, as we were saying, whether they know when to get a lab test, or what to ask the physician for, it seems to me that that could actually be tested to see if the documents actually make that patient behave. That is, did you take the medication before food or at bedtime and at the right time.

So you are actually asking the endpoint behaviors in trying to determine whether that had the impact.

So I would stress that I think much of the effort I think should go toward trying to measure outcomes rather than criteria that are varied in surrogate point, like formatting and things like that, I think those things lead us to that point and help us, but I think that outcomes are extremely important.

DR. FISCHHOFF: Ellen and then Sid. And I understand that you will be here through the meeting, so if we have additional questions that we can ask you later on.

Okay, thank you.

DR. PETERS: I enjoyed your comments. Your comments, as well as some of the other ones, are pointing towards a discussion we have had before about risk communication really needing to be more of a strategic process. And so you were just talking about some drugs having really clearly

a marginal risk-benefit kind of ratio, and so that the kinds of information perhaps that needs to be prioritized in terms of consumer perception, and tested in terms of consumer perception, has to do with careful directions for use, and for monitoring of side effects.

Other drugs might be a little different. But if we think about risk communication as a strategic process, part of what I think we need to do is, we need to identify who is going to identify this most important information?

And it seems to me that this discussion needs to be not just part of this committee, but it needs to move back perhaps into the drug review panels, with people who are evaluating the drugs themselves, at the same time evaluating what is it that is the key information here that therefore should inform how we actually communicate this to patients, whether it's in a CMI or a PPI or a med guide.

DR. FISCHHOFF: Thank you.

Sid.

DR. WOLFE: Just a couple of quick comments. One, the voluntary versus the more preferable I think regulatory nature of this is why at the level of the pharmacy as was very almost comically pointed out in this nice presentation that we just heard, the pharmacist decides I only want to give this part out or that part. And that is perfectly consistent with the voluntary approach. I think this is just a good argument against the voluntary approach.

The other thing, in terms of what you need to know, the priority kind of thing, the FDA went through a very good process, and many more than we participated in commenting on the new design of the professional labeling. You now have - it's coming in over a longer period of time than I would like - but when we new drug comes on the market, up front are the most important things that the

physician needs to know.

Now there may be some difference, and there probably are differences between what the physician needs to know and what the patient needs to know, but there is a lot of overlap, and I think this can be an important guidance towards thinking about the design of medication guides, the evaluation of them, and so forth.

DR. FISCHHOFF: Okay, thank you.

So I think Lee will give us some last minute instructions, then we will meet back here at 1:00 o'clock.

DR. ZWANZIGER: Thank you very much.

I just wanted to remind committee members that when we adjourn temporarily, please don't continue discussion off the record, and I'd like to ask anybody who is planning to speak in the open public hearing today to come and see me just for a moment.

Thanks.

(Whereupon, the above-entitled matter went off the record at 11:52 a.m. and resumed at 1:04 p.m.)

OPEN PUBLIC HEARING

DR. FISCHHOFF: Okay, let me welcome everyone back for the open public hearing portion of our meeting.

There is some - I guess it's my turn to do the official announcements. So both the Food and Drug Administration, FDA, and the public, believe in a transparent process for information gathering and decision making.

To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial

relationship that you may have with any company or group that may be affected by the topic of this meeting.

For example the financial information may include a company or a group's payment of your travel, lodging or other expenses in connection with your attention at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationship.

If you choose not to address this issue of financial relationships at the beginning of your statement it will not preclude you from speaking.

I should note that in addition to the statements that you will be hearing presented orally the committee has also received written statements which are in the folders of the committee members.

So we have the following people