FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PREGNANCY LABELING SUBCOMMITTEE

OF THE

ADVISORY COMMITTEE FOR REPRODUCTIVE HEALTH DRUGS

10:11 a.m.

Tuesday, September 12, 2000

Chesapeake Suite
Hyatt Regency Hotel
One Metro Center
Bethesda, Maryland

ATTENDEES

SUBCOMMITTEE MEMBERS:

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ATTENDEES (Continued)

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ATTENDEES (Continued)

GUESTS AND GUEST SPEAKERS: (Continued)

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FOOD AND DRUG ADMINISTRATION STAFF:

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DIANNE KENNEDY, R.PH., M.P.H.
SANDRA KWEDER, M.D.

C O N T E N T S

PROCEEDINGS

(10:11 a.m.)

DR. GREENE: I think we're going to get started please.

I'd like to thank everyone on the committee for coming, and Jayne has the usual conflict of interest statement please.

MS. PETERSON: Good morning. I'd like to read the conflict of interest statement for the meeting.

The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the committee participants, it has been determined that since the issues to be discussed by the subcommittee will not have a unique impact on any particular firm or product, but rather have widespread implications to all similar products, in accordance with 18 U.S.C. 208(b), general matters waivers have been granted to each special government employee participating in today's meeting.

A copy of this waiver statement may be obtained by submitting a written request to the agency's Freedom of Information Office, room 12A-30 of the Parklawn Building.

With respect to FDA's invited guests and guest speakers, Dr. Gideon Koren and Ms. Julia Scott have reported interests which we believe should be made public to allow the participants to objectively evaluate their comments. Dr. Koren would like to disclose that he's a researcher for Duchesnay, Ltd. and receives consulting fees and speaker fees from Duchesnay, Ltd. Ms. Scott would like to disclose that she's a member of Pfizer's Health Advisory Board.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement and their exclusion will be noted for the record.

With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you.

DR. GREENE: Thank you.

I'd like to ask the committee members to introduce themselves please, starting with Ms. Scott.

MS. SCOTT: Julia Scott, National Black Women's Health Project. I'm a consumer representative guest.

DR. FRIEDMAN: Jan Friedman. I'm a Professor of Medical Genetics at the University of British Columbia, currently on sabbatical at the CDC.

DR. KOREN: I'm Gideon Koren. I'm Director of the Motherisk Program in Toronto, and I'm a Professor of Pediatrics, Pharmacology, Pharmacy and Medicine.

DR. WISNER: Kathy Wisner from Cleveland, Ohio. I'm a Professor of Psychiatry and Reproductive Biology.

DR. GREENE: I'm Mike Greene. I'm Director of Maternal/Fetal Medicine at Massachusetts General Hospital. I work at Harvard Medical School.

MS. PETERSON: I'm Jayne Peterson, FDA, the Executive Secretary for the subcommittee.

DR. ANDREWS: I'm Elizabeth Andrews, Director of Epidemiology at Glaxo Wellcome and the immediate past President of the International Society for Pharmacoepidemiology.

MS. CONOVER: I'm Beth Conover. I'm a genetic counselor and I coordinate a teratogen information service in Nebraska.

DR. WIER: I'm Patrick Wier. I'm a preclinical scientist in reproductive toxicology for SmithKline Beecham Pharmaceuticals.

DR. KWEDER: Sandra Kweder, FDA.

MS. KENNEDY: Dianne Kennedy, FDA.

DR. HAMILTON: Holli Hamilton, FDA.

DR. GREENE: There will be two people joining us via conference call, as soon as we get the technical glitches ironed out. Those will be Christina Chambers who is an epidemiologist with the California Teratogen Information Services and Dr. Lew Holmes who is a Professor of Pediatrics at Harvard Medical School and works at Massachusetts General Hospital.

So, I think we're ready to pursue the program. The first speaker, please, is Dr. Sandra Kweder from the FDA.

DR. KWEDER: Good morning, everyone. I don't have any slides. My job is just to try to paint a picture, a very brief overview, for you of why we're having this two-hour meeting preceding the combined meeting of the Pregnancy Labeling Committee and Pediatrics Committee this afternoon.

As you know, we at the agency are continuing in our efforts to develop a new regulatory framework for pregnancy labeling. I'm not going to talk about the specifics of that today, but I think it's important that you understand that in addition to that labeling initiative, we have several others ongoing at the agency.

One in particular is that the agency is in the process of reformatting the entire package insert, the

whole thing, soup to nuts, in addition to this little piece that we're working on. The goal of that project is to make labels more user friendly and informative to clinicians who have their hands on them at the moment. We need to be thinking about that effort and how our piece, the pregnancy piece, dovetails with that, and that's why we're here today.

Whenever any new regulation is published, it has to have what's called an implementation plan, and Dee Kennedy will tell you a little bit more about that in a few minutes. But the point of having an implementation plan is so that parties that are affected by the rule, in this case the pharmaceutical industry, will know when they need to conform to the requirements of the regulation. That's all part of a good regulation. Here's what the new rule is. Here's when you have to be in compliance with the rule.

Typically for regulations, and particularly when we're talking about regulations that deal with labeling, the implementation plan, or schedule for compliance, is based on how long a product has been on the market. New products first; old products last. To make everyone change all at once and not have something like a schedule would be total chaos for the industry and for us. We just could not possibly keep up with that and review them all and do a decent job.

Well, we're at a point now with the development of a pregnancy labeling regulation that we think we need to start to think about what an implementation plan would need to look like. The most important aspect of that to consider in our minds is whether some products or some types of products need to be put on what one might consider an accelerated plan for implementation. In other words, which patients need today consults? That's one way to think about this.

In a few minutes, Dee Kennedy is going to give you a little more detail and background to try to help you organize your thoughts in this area. As you hear Dee's presentation, keep in mind that our questions to you aren't which individual drugs should be on such a list, but rather when you consider the individual drugs that come to your mind as being appropriate for such a list, what is it about them that makes those products qualify in your mind. Because we could never come up with an individual list that would suit everyone. So, the key is what are the qualifiers. In other words, help us establish the criteria for the fellows as to what are the criteria for today consults. When does it qualify?

Now, this might seem to be a bit of an odd task to request your advice on, but our goal here is to establish some reasonably simple but clinically relevant

criteria that will allow us to then go back and apply to agents on a case-by-case basis without being arbitrary. It's important for us a regulatory body to operate by principles and not just make arbitrary determinations.

So, that's why we're here today.

In the way of updates, I thought I would just mention in follow-up to our last meeting about six months ago where we discussed pregnancy registries, there was a workshop at the International Society of Pharmacoepidemiology last month, that Dr. Andrews was at and Dr. Hamilton and Dee Kennedy, beginning to address issues in methodologies related pregnancy registries.

There are two meetings coming up in the near future that will focus on studying the clinical pharmacology of drugs in pregnancy. There's an NIH workshop on methodologies in this area that's being held here in Bethesda on September 25th and 26th, and there will be a much larger conference sponsored by FDA and NIH to try to focus on the need for this area of research in pregnant women. That's going to be held in Washington on December 4th and 5th. We'll make sure that all of you who are at the table receive printed materials on that so hopefully you can plan to attend.

With that, I'm going to turn the podium over to Dee unless Jan has a question.

DR. FRIEDMAN: I'd like to ask you a question about what you said at the very beginning. You said this is in the context of a revision of the entire label.

DR. KWEDER: Yes.

DR. FRIEDMAN: Is there a time table for that revision of the entire label implementation?

DR. KWEDER: That project has been in development for years. The format has been presented at countless meetings. My understanding is that that proposal has left the agency, which means that it's somewhere else in the process whereby rules get approved to be published in the Federal Register. Groups that have to look at them include the Office of Management and Budget, the Department of Health of Human Services, and various other parties. Our understanding is that that has left the agency.

Whether or not there will be any action on any new regulations before the presidential elections remains to be seen.

DR. FRIEDMAN: Is there an implementation plan associated with that?

DR. KWEDER: There will be one. There will be a proposed one. That will come out as a proposed rule. Because its so far-reaching, it will come out as a proposed rule with a proposed implementation plan which will be time-based, and then there will be a comment period before

the rule is finalized and implemented.

Does that answer your question?

DR. FRIEDMAN: Sort of.

DR. KWEDER: You want to know when are we going to see the new ones.

DR. FRIEDMAN: No. I want to know whether there's a 5-year period, a 3-year period, a 10-year period that we can think about in terms of the time that the labeling with respect to drug use in pregnancy might be implemented.

DR. KWEDER: They're pretty standard. Dee is going to show you an example of one that I think will give you a flavor. I don't think it's exactly like the one that's on that plan.

We're always in a tight bind. I don't mean to try to avoid directly answering your question, but I have to be careful. We're always in a tough spot when we're talking about regulations that are in process, particularly something that, from our standpoint, is close to final and is outside of the agency. Our lawyers get very nervous when we talk detailed specifics.

I will say that the one that Dee is going to give you an example of is pretty typical, and my recollection is it looks similar but I can't confirm that it's exactly the same.

Any other questions?

DR. GREENE: One thing I'd like to do before the next speaker just one moment is just to ask Dr. Dattel to introduce herself please.

DR. DATTEL: Yes. But for the traffic, I would have been here two hours earlier. I'm Bonnie Dattel, Professor of Obstetrics and Gynecology, Eastern Virginia Medical School, Associate Director for the Division of Maternal/Fetal Medicine, and Assistant Dean for Women's Affairs.

DR. GREENE: I'd also like to acknowledge that we've gotten our technical problems ironed out, and Tina Chambers is on the line.

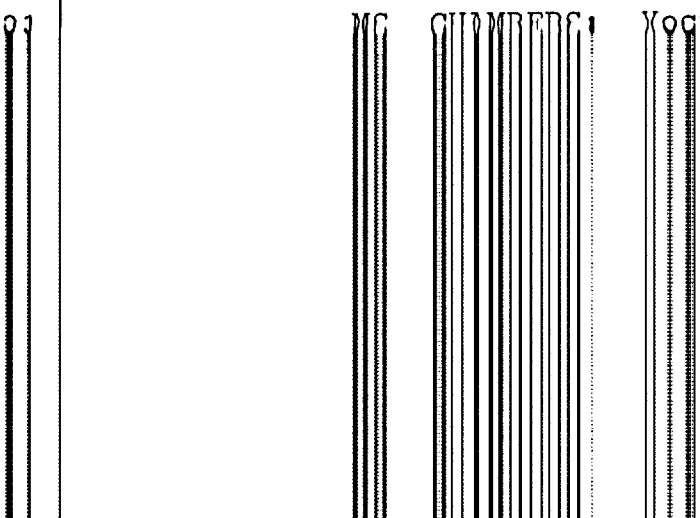
MS. CHAMBERS: Hello.

DR. GREENE: And Lew Holmes.

DR. HOLMES: Yes. Hello.

DR. GREENE: The next speaker then please.

DR. KWEDER: Let me just clarify. This is Sandy Kweder. Lew and Tina, could you hear me through the system here?



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DR. GREENE: And Lew Holmes.

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DR. GREENE: The next speaker then please.

DR. KWEDER: Let me just clarify. This is Sandy Kweder. Lew and Tina, could you hear me through the system here?

MS. CHAMBERS: Yes.

DR. HOLMES: Yes. We could hear you wiggling in response to Jan's question very well.

(Laughter.)

DR. KWEDER: It's easy to make those kinds of

comments when you don't have to sit at the table.

(Laughter.)

MS. KENNEDY: Bonnie, don't feel too bad that you came in late. There were a lot of us who were right up to the wire. I was on the Metro at 10 till 10:00 thinking I was going to have to speak at 10:00, so I was kind of glad that we were a little slow starting this morning.

I want to thank everyone for agreeing to come and help us out this morning. The joint meeting this afternoon with the Pediatrics Advisory Committee had been planned for quite a while. Then this morning's meeting was an add-on recently, and we just wanted to take advantage of having you all in town to get your help on one aspect of the Pregnancy Labeling Rule which, as Sandy has already told you, is the implementation plan.

We won't be discussing the details of the rule today, but before we get started, I just wanted to go through and remind you of what the history has been of the Pregnancy Labeling Rule.

Actually three years ago today, FDA held a Part 15 hearing to solicit input from the public on how we can best assure that health care providers and women get the best possible information about the use of drugs during pregnancy. We were particularly interested in learning about the practical utility and the effects and the

limitations of the current labeling, particularly the system of using the five different pregnancy categories to reflect what's known about risk.

Based upon what we learned at that Part 15 hearing and comments submitted to the docket, the FDA Pregnancy Labeling Task Force developed a concept paper on pregnancy labeling which described a draft model for pregnancy labeling that we thought began to address the concerns and recommendations that had been given to us. The concept paper was presented at the first meeting of this group, the Pregnancy Labeling Advisory Committee, in June of 1999. At that time we solicited your thoughts and recommendations on the concept.

We continued to work on the rule and we briefed this group again in March of this year on the status of the project. We are continuing to work. We meet on a weekly basis, and hopefully we'll have the proposed Pregnancy Labeling Rule published sometime the first half of next year.

However, as I said, we're not here today to talk about the specifics of the new rule. We need your help and recommendations on a different facet of pregnancy labeling and that, as you've already heard, is the implementation plan.

To avoid placing an undue workload burden on

industry and on the agency, any new regulation will be phased in over a period of several years. That's what's called the implementation plan. All new regulations must have an implementation plan when they're first proposed in the Federal Register.

We do plan to come back to this group and present the rule in its entirety as soon as it is published. However, we can't publish it without an implementation plan first, which again brings us back to why we're here today.

First, a little bit about the factors that we consider when we're developing an implementation plan. What is the universe of products that are going to be affected by the new rule? How much of a burden is it going to place on industry to comply with the new regulation? And what about the workload and resources that we have to have available at FDA in order to review the new labeling that's submitted? Most importantly, what about the public health need? Are there certain products or categories that warrant new labeling sooner than other products?

And here, Jan, is an implementation plan, an example. This is the basic framework for a plan. For example, applications that are submitted on or after the effective date of a new rule would be required to use a new format at the time the application is submitted. For older

products, the new labeling is required based upon the length of time the product has been on the market. For example, products that have been on the market less than a year prior to the effect of the new rule would have up to three years after that effective date to comply. Products that have been on the market one to two years prior to the effective date would have up to four years, and so on, to the point where perhaps those products that had been on the market five years or more may have up to eight years after the effective date to start using the new pregnancy format.

In this particular example, all marketed products would eventually be required to revamp their labeling into the new format, although it is possible that some older products or certain categories of products would be exempted from having to comply.

Now, even though this shows you a typical implementation plan, we aren't here today to discuss the timing for the phasing in of the requirement overall. I just wanted to show you this to illustrate that with the basic plan, even with the regulation requiring a new format, it will be years, if even then, before the older products would have to revamp their labeling.

We would like to know from you all if there are critical products or categories of products for which it's not reasonable to wait for many years to have more

informative labeling. Should we develop a list of priority products for accelerated implementation of the new pregnancy labeling such that these products would be required to revamp their labeling in perhaps one or two years after the effective date of the rule?

Our goals for this morning are to seek your advice on whether accelerated implementation is needed for certain critical priority products, keeping in mind that a basic implementation plan based on time in the market will be in place and will take care of the majority of products. If you do support the idea of an accelerated implementation plan, then we'd like to obtain your recommendations on what criteria we should use to identify priority or non-priority products. It's possible that you could come up with recommendations for us for products that you think would never need to have their pregnancy labeling revamped.

Our preliminary thinking is that there are two general categories with considerable overlap that might benefit from an accelerated implementation plan. First, products that a woman might be taking before she realizes that she's pregnant. Those would be the inadvertent exposures during early pregnancy. And also products used to treat a woman during pregnancy. These could be for conditions related to the pregnancy or for conditions that a woman might have who also happens to be pregnant. From

your perspective, should either or both of these be considered, and how should we identify and rank products within these categories?

A large percentage of pregnancies are unplanned, and women of reproductive age take a lot of prescription medicines. Therefore, we can assume that there is a significant amount of inadvertent drug exposure early in gestation.

Are there certain products for which it's important to provide useful information as soon as possible in the labeling that would be helpful to the physician when he's counseling a woman who realizes that she's pregnant or became pregnant while she was taking a prescription medicine?

To give you an idea of the most frequently used categories and specific products used in women of reproductive age last year -- those would be the ones that might possibly be the most likely to be subject to inadvertent exposure -- you can take a look at a table in your background materials. Actually it's a table that was just handed out to you this morning. It's data from the National Disease and Therapeutic Index. I want to point out on that table that products with an asterisk next to the name are those that have been on the market less than five years, and you can see that there are very few of them.

I'm not going to actually show you the data up here this morning, but I do have these tables as overheads if you find, when you're in your discussions, that you want to have the data shown so that you can talk about it.

If you do think that inadvertent exposures are a concern for us, what criteria should we use in identifying those products most in need of the new labeling? The volume of use in women of reproductive age? The potential harm or toxicity to the fetus? Whether therapy is chronic versus episodic? Maybe the extent the current labeling fails to adequately address inadvertent exposures or perhaps the frequency that teratogen information services are queried about particular products. These are just some of the ideas that we had, and I'm sure that you can come up with others that will be helpful for us.

With inadvertent exposures, one group of products that has been suggested to us as an important one for new pregnancy labeling and a group you might want to consider are those products that are currently classified as pregnancy category D. Those are the products whose labeling states: Drug X "can cause fetal harm when administered to a pregnant woman." And that's followed with whatever human data and any pertinent animal data, and concludes with: "If this drug is used during pregnancy or

if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus."

There are not that many category D products. When we searched the online PDR, we came up with a list of 97, and you have that list of products also in your background materials.

In addition to category D products, you might also want to consider category X, whose labeling states that they're contraindicated in pregnancy.

Pregnant women do take prescription medicines for therapeutic needs. Should we consider certain of these products as priority? To give you an idea of the types of products that are most frequently used in pregnant women, you can take a look. There are four tables in your background material from Medicaid and HMO databases. While the data are relatively old -- I think the most recent is from 1995 -- they do give you a flavor of what's out there. It's probably not that much different from what happens today, given that the newer products are very slow to be used in pregnant women. I don't believe that any of the products that are on those four tables were less than five years old at the time period reflected.

Again, think about the need for information and the fact that with the basic implementation scheme that it

could be eight years or more before the older products would be required to update their labeling, if even then.

If you decide that certain needed therapeutics should be included in an accelerated implementation plan, then what criteria should we use to identify them? The diseases or conditions most likely to require drug therapy in pregnant women or perhaps the products that are used most frequently during pregnancy?

Should we consider will changing the labeling modify clinical practice? Old products are more likely to be used in pregnancy. Will providing an updated labeling change that at all?

Perhaps we should give consideration to the extent that good information is available that is not in the labeling. We've been told before that for products routinely used during pregnancy, that there are already resources out there that provide prescribers with the information that they need, and so, therefore, we should focus our efforts on those products that are likely to have inadvertent exposures and have no information available.

I'm sure you all can come up with other ideas for discussion as well.

As you develop the criteria that we can use to identify priority products for accelerated implementation, if at all possible, please provide us also with some

suggestions on how we can actually use the criteria to identify the specific products that meet the criteria.

Just as a reminder, Sandy has already told you, we aren't interested in your developing a list of products for us. While examples of products will foster your discussion, what we are most interested in is a set of critical factors that make a particular product a priority or not in your mind. Those criteria are what we'd like to walk away with today.

Thanks.

DR. GREENE: Thank you.

Questions?

MS. CONOVER: Yes. When I was thinking about things ahead of time, I have a couple questions just about what kinds of agents fall under this regulation. So, for example, are things that are over the counter under this? And there are drugs that are prescribed and over the counter, like ranitidine or something like that, that are frequently used by pregnant women, and then also things like vaccinations. For example, influenza vaccine is something we get asked about all the time. Is that something that's included in this?

DR. KWEDER: Most of the new regulations that come out of the agency that affect drugs affect biologics as well. So, a vaccine would be covered for the most part.

The over-the-counter products are a little difficult. There are a couple of ways that over-the-counter products get that way. As a general rule, over-the-counter products like antacids and that sort of thing would not be affected by a new rule. Products that might be affected are over-the-counter products that also have prescription forms. They have NDAs.

Ranitidine is not over the counter in this country. It is in Canada and most other countries in the world, but it's not over the counter here. No. Actually it is. I'm thinking of omeprazole. I'm sorry. And Claritin. But ranitidine would be affected, yes. The nonsteroidal anti-inflammatories that have NDAs that were prescription first would be affected.

We would have to work to sort out how to translate whatever this was into the over-the-counter labeling because over-the-counter labeling, as you know, is a lot different than prescription drug labeling. A lot different. But they could potentially be affected. Certainly the prescription versions of them would be.

MS. CONOVER: And one more question. What about dextromethorphan, which we always argue about amongst ourselves even? Drugs that aren't proprietary anymore.

DR. KWEDER: Generics.

MS. CONOVER: Generics.

DR. KWEDER: That's one of the reasons that regulations that affect labeling often give longer periods of time for products that are very old. One of the reasons for that is that it's a much bigger burden for a generic drug company to have to revise labeling. They're not set up to do that. They're manufacturing houses and they don't typically have the resources or medical expertise to comply with these kinds of changes easily. It can be done, but it can be tough.

If you think about generic companies, there are many of them. How many companies make your favorite pain reliever? There are lots. And all those labels have to be the same. So, getting all that organized, working with the generic companies, and even on the part of the FDA, that's a lot of work, that most people don't think of, but it's substantial.

MS. KENNEDY: I just wanted to clarify something that Sandy had mentioned about the over-the-counter products and the labeling. I just want to make sure that everybody knows that if the product is over the counter and has an NDA, a prescription form, that that labeling is what would conform with what we're talking about. The labeling that would go actually with the over-the-counter product would not be in the format that we're talking about, but it would be some subset of what's

contained in the official labeling.

DR. KOREN: Preparing for these questions, we are counseling mothers, 200 women a day, and we follow them up. So, we have a lot of input in what bothers women. So, clearly I think the list Dee showed is very exhaustive, and the criteria, as you showed, cover anyone one thinks. But clearly you cannot throw this because this means everything. So, you need to be more specific.

One suggestion is to use knowledge and experience as it comes to see where the need is the greatest, and I'll give a couple of examples. Yes, one approach is the most common things. Common things bother women and high levels of anxiety when women find out. They didn't plan the pregnancy and so on, and we are aware of this.

But then as Beth said, I'll give an example. Dextromethorphan out of the blue became an issue two years ago when someone took a chick embryo and found out some change in some brain receptor. All the news media in North America quoted that scientist saying, I wouldn't give it to any woman and so forth. So, here is an example of an area of a very old generic drug that became and issue, and we get many calls. Women are even considering terminating pregnancy because they took it.

So, I give you an example, within the huge

umbrella of generic, old drugs, of something that became an issue. It would serve for me as an example that the agency may want to consider that this should be addressed with more information before, say, acetaminophen which, by and large, does not seem to be an issue unless it's an overdose.

DR. KWEDER: So, Dr. Koren, are you saying that perhaps we need to always ensure that in any implementation plan where there appears to be a public need, the FDA can go beyond criteria and require it, if there's new scientific information that changes the landscape or raises public anxiety?

DR. KOREN: I think the main objective of this effort is to ensure that women get better service and better health, and their needs should be addressed by their concerns. And the concerns are huge when misinformation, for example, enters the market, as often is the case.

So, out of the large group of commonly used products, I would try to use wisdom to choose those that are really an issue, either because of misinformation or the message is complex, for example, NSAIDs. NSAIDs in the first and second trimester are probably not at an increased risk, but in the third trimester with ductus arteriosus, they are. So, the message is a little bit more complex, and one has to address it in more information, using the

up-to-date counseling methods we have developed over the last 10-20 years.

It goes to drugs that women need. I'll give another example, not of a particular drug, but antidepressants. Many women stop cold turkey their antidepressants, ending up with suicide attempts, with hospitalization, and so on because someone told them that the label at the present time is not informative. The label at the present time says we don't have data even when there is data.

I won't try to be too specific, but fluoxetine is the example. The product monograph still says there is no information. It's not just there is information. There's even meta-analysis and neurodevelopmental studies, but nothing of that is now in the product monograph to help thousands of physicians in America to counsel women.

So, again, I would be more specific to identify areas where lack of information has really put women at risk or suboptimal therapy. So, for example, for me antidepressants would be before insulin or before diabetes where there are very rigorous protocols among perinatologists and obstetricians. Antihypertensives probably should be up high because we have several teratogens among them and then there are those that are not clear. The data is not yet clear.

So, I guess the criteria you gave, Dee, are good, but they are very large. I'm sure that the agency cannot deal with all what is there. So, within these two, the most common ones and the most needed ones I would use another level of wisdom to choose those that are really a problem, and that can be done using what's published. There's the Organization of Teratology Information Services which serves in America and Canada millions of women every year. Then there's, of course, the whole academic OBG and subspecialties to identify areas, because otherwise it will be an implementation you cannot implement. It will be to do everything.

So, this is kind of my input into it. To focus on these two areas and the places where there's the most impact on a woman's life.

DR. GREENE: One point I'll just make that Dr. Koren brings up is one that's been made in this forum before, and that is the problem of updating labels. As information becomes available, there doesn't seem to be a requirement or a good way to update labels. Your fluoxetine example is a good one.

Yes, Dr. Wisner.

DR. WISNER: I think my initial thought was more as a clinician. What I really would like to see is much more and better information about the category D

drugs, as Dee mentioned. Yet, if I think about implementation, to me it seems like selecting those drugs may be somewhat of a setup in that you then select perhaps the most complicated set of drugs to apply the implementation strategy to. Perhaps if I say, well, I'm just thinking about the implementation, I might select a range of drugs amongst the current system so that the actual implementation of the new design could be done across a variety of drugs, and the learning process of doing that for this initial set could then be better applied. I'm just worried about selecting the most complicated drugs to start a new implementation plan with.

MS. CONOVER: Actually in teratology sometimes it's easier to prove risk than to prove safety. Some of the D drugs in certain ways are easier for us to handle.

DR. FRIEDMAN: I'd like to make a comment and then ask a couple of brief questions. I also urge you to put the category X drugs right near the top because many of those are seriously misleading when seen in the context of inadvertent use. So, they may be contraindicated in pregnancy, but some women will, nevertheless, take them and then will think that they're just a disaster for the fetus when there may be a risk that's not so great. And I think that needs to be clarified.

My questions have to do with two comments that

Dee made. One is you said twice that there are some drugs that might not be done, and it seems to me that that would be a terrible situation just exactly for the dextromethorphan kind of thing. Unanticipated things happen and if there's still misleading labeling on some of the drugs, we're going to get ourselves in trouble. So, I wouldn't exclude anything. If it's not used in pregnancy, I would just make a statement that says that this drug which is for prosthetic hypertrophy is not used in pregnancy.

You asked about accelerated labeling. Are you really talking about acceleration in the sense that there would be a diversion of resources to get some things done quickly, or are you talking about changing the way that these things are ranked from eight years to seven years?

MS. KENNEDY: We're basically talking about moving them up. If you look at the older products, they would all fall at the end or in eight years or so. If there's some that that's not acceptable, then we would move them up so that the companies would have to have that labeling modified within a year or so.

DR. FRIEDMAN: But does the implementation plan need to be based on how long it has been since approval? Or could it be based on completely different criteria, such as frequency of use or category D or X or something else?

MS. KENNEDY: That's what we're asking your help on. There will be a basic plan in place that is based upon length of time on the market, but we can pull a certain limited number of products out of that scheme and move them up so that they would have to have their labeling revamped before they would have been required based upon the time that they're on the market.

DR. FRIEDMAN: Why does it need to be based on time on the market?

MS. KENNEDY: It's out of our control, that part of it. It has to do with what Sandy was talking about, about revamping the entire format of the labeling.

DR. KWEDER: Well, in addition, if you just think about the universe of all drugs, there are thousands of them. Some of them don't even have labels. When the FDA requirements for demonstrating efficacy came into being, some of those drugs were just grandfathered in as generally considered safe and effective, GRAS and GRAE. They don't have labels or they don't have labels in the way that we know them. So, just saying that all drugs have to do this is an impossible situation.

The agency has historically, whenever they've applied a new regulation to all drugs and biologics, for example, used this kind of an implementation schedule based on length on the market for a number of reasons. One is

that they're hard criteria. They're easy to measure. If you try to base an entire implementation plan on something like how often a drug is used in pregnancy -- let's just pick that -- then you get into the question of, well, how do we know how often a drug is used in pregnancy? Based on what data, whose source? And you get into this back and forth and quibbling. Oh, no, my drug is here, not here. No one ever uses our drug. Well, maybe they do, but not in our data source. Maybe in their data source. Well, they're wrong. And it's a no-win situation. We can do that sort of thing for a limited number of products, but to make that the criteria that applies to all products is really tough.

We've had some experience with trying to develop specific lists of products. We've done this for pediatric labeling. It's very difficult. It's extremely difficult. You always find products that someone has forgotten. You missed someone's favorite. You didn't put it high enough on the list and it's really very difficult. So, that's the reason that the agency almost always goes back to using time since approval as the benchmark and then overlaying on top of that an additional set of considerations that allows us to consider individual products on a case-by-case basis.

DR. GREENE: Ms. Chambers, you wanted to get in

on the conversation by phone?

MS. CHAMBERS: Yes. I don't know if Beth and Gideon would agree, but from the perspective of the teratogen information services, the two guidelines that Sandy and Dee set out seem to apply to the types of calls that we get, and I think it's probably consistent with what clinicians are concerned about.

From a public health perspective, we would like to see the labeling or the information that's available to pregnant women be updated for older products that treat chronic conditions that women of reproductive age are likely to have. Categories like antidepressants and other psychotherapeutic drugs, asthma drugs, and hypertensive agents might be three areas that there's probably a high volume of use among pregnant women, and it's many times a situation where the woman would like to or needs to continue to use the drug during pregnancy. So, from a public health perspective, those would be important categories to move to the top.

Now, those overlap I think with some category D products, which when you look at this, the category D product list doesn't make any sense at all because there are classifications of drugs on here. For instance, valproic acid in a variety of forms is on here, Mebaral, and I think chewable Tegretol tablets. But there are other

forms of anticonvulsants that aren't on the list. So, to just stick by a category D or X list probably doesn't make sense.

And there are probably many drugs on this list that are unlikely to ever be used by a pregnant woman. When you look at benzodiazepines, I think Klonopin is on here and Ativan by injection, but nothing else.

So, to judiciously go through the category D list and pick out those drugs that might likely be used by pregnant women and also add to that drugs that fit into that same category I think would do a lot to prioritize drugs that either might occur in an inadvertent exposure and raise anxiety because of the category D label or also might be chronic type use drugs that would fall into the public health concern area.

Then the thing that Jan brought up about category X, I think that's really important. There are few drugs that fall into that, but there are few drugs that fall into that category because there's any data to suggest that they're human teratogens. So, I think category X drugs should definitely be prioritized to the front of the line.

DR. GREENE: Dr. Wier?

DR. WIER: Like Dr. Koren, I got the impression from the slides that the ascendant criterion was appearing

to be based on preponderance of use, whether it be or unintentional. I was thinking to myself what would add the most value was those cases where the label is going to be most different. Looking at it that way, what we should focus on are cases where the current label information is perceived to be unclear or misleading potentially. Obviously, you can look at those labels and say, boy, I could do a better job than that, so those ought to be a target.

Another is where there is substantial new information. Obviously that will change the content of the label substantially. To a certain extent, those may not be the drugs with the greatest preponderance of use, but that may be where we have the most impact on the label.

I looked at one of the lists of most frequently prescribed drugs in pregnancy that were distributed ahead of the meeting. It was interesting to note that in one list over half of the top 20 drugs have substantial amounts of human data. For example, if you look at the Michigan Medicaid Project, over half of those drugs have something like 1,000 or more newborns with first trimester exposure recorded and some assessment of outcome. Over half of those drugs are old enough to have been studied in the Collaborative Perinatal Project.

So, I think to a certain extent, if you look at

the drugs with the greatest preponderance, you might miss the target again because there may be more knowledge in practice about those drugs through familiarity, and what we really should be thinking about is the ones with maybe a little bit less preponderance but more potential to change the label.

DR. GREENE: I'd like to hear from Dr. Kweder and the people at the FDA whether lack of clarity of the label is going to be an easier criterion to enforce than frequency of use.

(Laughter.)

DR. KWEDER: I think we're both sitting here thinking how are we going to do that.

I have to tell you I just had a discussion with one of my staff the other day about a label. It was a new label that I really liked. I thought it was great, and he thought it was the worst label he had ever read. It was absolutely awful. So, we do run into that. That's something that we have to contend with because we need to not be arbitrary.

I actually made a note to myself that these are some of the kinds of things that will take a lot of resources on our part to really sit and look at individual product labels and work with outside groups to get their impressions as well.

DR. GREENE: Dr. Koren?

DR. KOREN: I agree. I think we have now the advantage that there are about 50 organizations that are dealing with the public in explaining that information. So, I agree with you. I think the agency should work with the OTIS members that do this because we do it every day.

And I agree with Patrick that this is one way to go, areas that there will be an impact rather than just the numbers.

To add to what Tina said, the category D is misleading on another level. Many of them are anticancer drugs naturally, and there's no proof that in the third trimester they should not be used. Oftentimes women may actually put their lives at danger by not being treated for cancer because of misinformation. In the third trimester you cannot do fetal -- it can affect brain development, of course. But here is an example where this is very ambiguous. It affects very small numbers, but even as it is, it's ambiguous. So, one may want to deal with it, but these are very small numbers too. One needs to think whether it's worth it in your implementation, that is.

DR. GREENE: We need to take just one minute or more. It's about 11 o'clock, and on our program, this is the time when the hearing is open to comments from the public. Now, no one has registered, to the best of my

knowledge, to speak and requested an opportunity to speak before the committee. But there is an opportunity for members of the public to speak before the committee without notice, and this is your chance to speak now or forever hold your peace. If there is anyone who would like to speak, I'm also asked to remind them that they need to disclose any potential duality of interest or conflict of interest. Any public comments?

(No response.)

DR. GREENE: Then we can continue with our discussions then, please.

MS. CONOVER: Actually I have a question. Now, we've been talking about the issues of setting up registries. Is mandating registries, or however we're going to phrase that, linked to the new labeling process? In other words, sort of behind this is getting back to Pat's comment, which is if we have no new information and no human information, you can make someone change their label, but it won't be helpful; whereas, if you are not asking people to start to gather that human information until they have to do a new label, then that might give us a different group. Do you know what I mean? It's almost like we want to mandate that registry process through asking them to do a new label.

DR. KWEDER: If I understand what you're

asking, you're asking is there a way to somehow through the labeling rule process encourage registries to be conducted.

MS. CONOVER: Well, there is a whole group of drugs that we have human data on that are not currently put on the label. Then there are many drugs, like Zofran, that I would personally like to know human information on that there's not a registry, there's not information being gathered on. So, I'm wondering if I put Zofran at the top of my list and said I want a new label on Zofran, would this mandate them starting to gather that human information?

DR. KWEDER: At this point that's not a framework we're thinking about. One way to look at it from a different direction, any company that's in the process of collecting that kind of information is probably going to be the kind of company that would automatically be more motivated to change their label anyway. But the other way around really gets to the issue of how does one require a company to collect such data, and that's a much more difficult question and probably beyond the scope of today's discussion.

MS. KENNEDY: One thing that will help in this regard in the future, another proposed rule that's in the making is for postmarketing surveillance, and we're harmonizing things internationally. The companies will be

required to evaluate the positive and negative effects of drug use in pregnancy.

MS. CONOVER: On new drugs.

MS. KENNEDY: Across the board.

And then with our proposed rule, we will say, you shall take whatever information you have available and update your labeling or let us know why you're not doing it. So, they're all kind of tied together.

DR. GREENE: Dr. Wisner?

DR. WISNER: If I think about my field specifically, say, psychiatry, and follow up on the points about the impact, the labeling that I think would create a great impact are the labels that have to do with the drugs that we use to treat bipolar disorder like lithium and anticonvulsants. In fact, anticonvulsants are now used by psychiatrists as much or more than neurologists to treat this illness, and it's not an illness that we have other alternative treatments for.

The other issue is that I think in our field there have been a number of prominent reviews in well-read journals about use of antidepressants in pregnancy, and that presents at this point less of a problem because the literature has kind of picked up that information piece independent of the labeling.

So, when I was talking about category D drugs,

although it's very clear that some of the drugs I'm talking about belong in a number of different categories, it's those agents that I think would create the greatest impact as far as helping physicians work with women to make the best choices possible.

The other issue is we don't have alternative treatments. For depression, at least we have other modalities like psychotherapies and light therapy and other treatments, where we just don't for bipolar disorder.

The second area that I get a lot of calls about is smoking cessation from women who want to stop smoking in preparation for a pregnancy, but they are more or less actively trying to become pregnant anyway. So, questions about bupropion which is one of the agents or the patches also might make an impact and might be helpful in terms of weighing smoking and all its exposures versus these other anti-smoking agents.

DR. GREENE: Dr. Koren?

DR. KOREN: With the risk of being more specific, one condition which is not chronic, but it's pregnancy induced is nausea and vomiting in pregnancy. FDA does not have any approved drug on the market, although there is Bendectin which was never disapproved but was taken off the market. At the present time, American women take a course of different medications for this. Most of

them on the label say, don't take in pregnancy. So, there is a huge clash here between practice and what labels say, which is a huge medical/legal tension and many other tensions produced.

The rate of hospitalization of American women for morning sickness tripled after Bendectin was removed. In Canada when Bendectin in another name came back, the rates come down.

So, here's an example of a high impact, if you wish, that the group may want to consider as something that should be put forward. Although it's not life-threatening and it's not chronic, it may be throughout pregnancy.

The list of medications used by American women is about 15 or 20. We just had a paper published on that, and I can share that with you. But basically any antiemetic is used, and I believe that physicians and women and their families need more support on what's known.

For example, we know a lot about the antihistamines. There are even meta-analyses of them in pregnancy but none of them is in the product monograph.

DR. GREENE: Dr. Friedman.

DR. FRIEDMAN: The issue of their being information out in the literature that provides guidance to physicians that differs from the labels has been raised a couple of times this morning and is something that concerns

me. It seems to me that this doesn't provide a reason not to revise the labels. In fact, it provides a reason to revise the labels because when people get conflicting information from the literature, from reviews, from meta-analysis, from textbooks, and then they go and they read the FDA label and it says something different, it really can cause a great deal of anxiety both among patients and among physicians.

DR. GREENE: Dr. Andrews?

DR. ANDREWS: Really I have a couple of comments and really a question for clarification. In an overall framework, I would be inclined to give priority to something that translates to public health impact, which would include frequency of use and chronicity of use and also the extent to which information is available and that a substantial change in the label would make an impact.

That leads to the question about what these rules are likely to look like when published. I'm a very practical person and I like to have a sense of how these will be translated into action in terms of the negotiations that will occur between the agency and the sponsor because it's easy to assume that there's a substantial body of information that could be put into the label, but sometimes it becomes very difficult to translate that information into actual language in the label. So, I'd like to have

some confidence that we'll be able to actually make that happen before spending a lot of effort in trying to make it happen and end up with labels that are only marginally more informative than they are now.

DR. KWEDER: Actually I'd like you to expand on that. Can you just give us a hypothetical because I'm not sure everybody else at the table really follows what you're saying?

DR. ANDREWS: Well, I can imagine a scenario in which the medical reviewer at the Food and Drug Administration is looking at the gold standard of clinical trials and insisting that the only data that go into the pregnancy section of the label come from randomized, controlled clinical trials, which we know are not likely to happen. I can also imagine that companies tend to be very conservative in what goes into a label. So, the two forces might conspire to provide a label that's based on what's considered very, very solid information that doesn't look exactly like the practical information that we know is really needed for consultation and clinical decision making.

DR. GREENE: I'm not sure how that is going to really change from the current situation or how the new requirement is going to make that more difficult than it is at the moment.

DR. KWEDER: I don't think it will make it more difficult. I think Elizabeth is right. It will put all of this stuff right out on the table. We encounter this all the time. It's one of the reasons that under the current labeling system, there aren't too many category B's because the gold standard at the agency has historically been randomized, controlled clinical trials.

This is a really hard rule to write, and in addition to the rule, the agency is going to have to have a companion document, a guidance document, that will be used by the industry and our own reviewers that tackles some of these issues and really just lays it out there, that we are not likely to find randomized, controlled trials in this area of medicine and describes what constitutes reasonable data to consider.

That's very, very hard to do and on our part requires a culture change that won't happen overnight. So, I recognize that and that's one of the reasons why we want to hear from you about what are the kinds of things that you're concerned about, what are the kinds of products that you're concerned about so that we can take that back and try to incorporate those things and prevent just a stalemate and something that really isn't much better that what we already have.

DR. GREENE: Dr. Koren?

DR. KOREN: I think Elizabeth brought up the most crucial point, the methodological type of evidence and how this is solid. But let's not forget and the agency needs to discuss that too, that there have been advances in that too. In several New England papers just two months ago, face to face RCTs versus observational studies. And we have a paper, I believe the first to do it in pregnancy in an area where RCTs happen such as the antihypertensives. So, the area is moving. Even that area is moving in a way that the agency needs to know. It is not fair to say that there is no data in the observational studies and so on. It's just not true and oftentimes it's not even different as both the New England papers show and we show with the ADRs or antihypertensives in pregnancy.

I am fully aware and sensitive myself to the medical/legal situation of companies which, of course, needs to be addressed. So, even if a company shows all the data accumulated now, there may be a concern that that may be construed as if they support the use of that product, and that's where the tension is and that's something we cannot ignore. I know this is one of your biggest tasks. I don't think it affects so much the implementation because any model that you would come up with for a new labeling would need an implementation program.

Just to be more practical now, how are you

going to identify it? Maybe one way is to produce a master list and then to have organizations and academic and consumers and others rank them to get, as you say, the universe of response. Rather than just two agency people, one ivory tower, bald individual in a university, I would say try to get all of this and get a group of people to --

DR. KWEDER: We did do something a little bit different. Actually a couple of years ago, Marietta Anthony, who I think is in the audience, was with our Office or Women's Health and is now at Georgetown, sent letters to a number of organizations and individuals asking them how they would prioritize products, what products they thought were important, and if the label changed, how would they prioritize it, just to begin thinking about what the scope of our task was.

We decided not to share any of that with you, the responses we got, because they were all over the map. It depended on who you asked. Everybody had their pet peeve category of label. If you asked the pediatricians, you could really see that it was things where they saw the mothers. There were many lactation issues. It was all over the place, and it really wasn't all that helpful.

That's what made us realize the problem here is trying to create an exhaustive list. What we need is to define what are the criteria for products to be on any list.

DR. GREENE: Dr. Dattel?

DR. DATTEL: As usual, I have a little of a dissenting opinion. I had some thoughts prior to coming as well, and I agree very much with everything that has been said here. But in a more practical sense, you have to have as an organization to be able to defend why you're doing things in a certain way.

To be honest with you, in going through these list, for the things that there's a lot of controversy and for the things that are used in critically ill women, most of those patients are not being seen by the people who are generally prescribing these other drugs. So, they're being seen by specialists and they're being seen by people who actually know that you can use cancer drugs in the third trimester and that you can treat people with seizures. So, they probably to me would be less of a priority.

Actually what's more of a priority are all the other drugs that are being prescribed by every ambulatory care center, doc-in-the-box, whatever you want to talk about, family medicine people who don't know that you can use cytoxan for breast cancer in the third trimester because they're not going to take care of that patient. And we are and we know that.

So, I would say the best way to approach it would be to take the most commonly used exposures that

people have that are being prescribed by non-specialists who don't know any better necessarily about these esoteric issues and focus on those as making the largest impact. And that also allows you to defend your criteria for moving things up that have been on the market, like ampicillin, for eons and saying you've got to change its label because every family practitioner in the world is giving ampicillin for ear infections.

So, to me that makes more sense and allows you to have a defensible position, although I agree with everything that's been said here. Absolutely. I'm just thinking in a very practical sense. The people who need to know are the ones who are giving 14 percent of women antibiotics that are okay, and you shouldn't use Levaquin, which I'm standing in the middle of the intensive care unit telling interns not to do the other day. So, that's the type of thing and that's why they call me to see that person.

So, from my perspective, the generalized drugs that are most commonly used would be the ones that I would focus on, and you can triage them with some of these other issues. That's my two cents.

DR. GREENE: Ms. Chambers, did you have a comment?

MS. CHAMBERS: No, but I can give one.

(Laughter.)

MS. CHAMBERS: In listening to what you're saying, I think that it makes sense to think that the specialists who's treating a woman for a chronic condition with psychotherapeutic drugs or a medication for a seizure disorder would be knowledgeable about the medications or have access to reviews in the literature and not rely on the label. Yet, pregnant women I think who do read the label pay attention to that information independently of what their physicians are telling them.

So, I think it does have an impact on a woman's perspective on what's going on with her pregnancy, and to have it be inconsistent with what the neurologist hopefully is telling his or her patient or the psychiatrist is hopefully telling his or her patient I think is an issue and I think that those drugs should be prioritized at the top even though a family practitioner may not be the one who's prescribing them.

DR. GREENE: Dr. Holmes, did you have --

DR. HOLMES: No. I think really the comments everybody else already made cover it.

DR. GREENE: Dr. Wisner?

DR. WISNER: Thinking about this implementation process and thinking if I were on the receiving end and having to make up new labels for these agents, I would be

fairly anxious. The thought that came to mind is some kind of initial pilot project where perhaps some of the criteria that has been defined, a drug as an example of that criterion could be selected, like say a category X drug, and then develop a model for each of these criteria for a specific drug and then have perhaps another meeting to get feedback about that pilot data so that there are models that are developed and the initial problems in applying the new labeling are ironed out up front before the wider group of drugs needs to be accommodated to the new labeling.

DR. KWEDER: The rulemaking process actually does allow for some of that. Typically anything that's going to be as widely implemented as something like this requires that when you publish a rule, that it be a proposed rule to give companies time to do that, to try and apply the rule to their own situation and then give the agency feedback on whether or not they think they're going to be able to comply with this, what are the elements that will work, what are the elements that are problematic, and then give us comments back and allow us to modify the rule and the implementation plan. Oftentimes we will specifically seek comment on the implementation plan. So, that is built into this.

DR. WISNER: I guess what I'm wondering, Sandy, is whether there is almost a partnership between the agency

and the company so that the first drugs that are looked at are actually done jointly and a model that can be more widely applied is developed. That's kind of what I understood you to say.

DR. KWEDER: That's not exactly what I said, but I think one of the things that we often do in situations like this is we look for companies who are interested in doing this -- and there will be some who will be interested in doing this -- and try to work with them together, as we get closer to the end, to do some of that.

DR. GREENE: Dr. Koren?

DR. KOREN: I agree. I think you brought in an interesting point of view, but do remember -- at least in my experience -- many women, although seen by a specialist, say a psychiatrist who wants to put them on a medication, may not see them for a year or two. Oftentimes pregnancy happens in the meantime. So, I agree, as Tina said, the woman will read the label or will go to a family physician in areas where there are family physicians. So, I don't think it's fair to assume that all will be an informed group of specialists. There's a huge hiatus and black holes between when women see specialists.

DR. DATTEL: I agree with that. I'm just saying you have to have an implementation plan and you have to be able to defend why you're choosing certain criteria.

It would seem to me that if you had to prioritize, use the things that are most commonly used with some of these other issues taken as caveats. but you have to be able to defend -- I don't know who the companies are -- to somebody why you've had a drug that's been out for 22 years and now you have to change your label. And you say, well, this is one of the most commonly used drugs and everybody who has a commonly used drug is doing that. I don't envy the task in terms of the organizations that have to be worked with.

But I agree with that, and not everybody is equally informed and women do read the labels. I agree with all of those issues, but in terms of starting someplace, I think that's --

DR. GREENE: Dr. Wier?

DR. WIER: Since floating this suggestion of impact, the resonance seems to be a lack of comfort on how to be quantitative in assessing that. Perhaps that's one of the reasons that we tend to revert to preponderance of use because there's a number there. It's out there. You can grab it. So, to the extent that the agency has the time and funding available to do it, I think we should make some practical suggestions on how they could potentially have a semi-quantitative indication of the impact that could be gained with changing particular labels.

I think that that could be accomplished with

certain survey methods. To be quantitative about it, there could be information in organizations like OTIS because a certain number of their calls are coming because people are reading something saying this is not clear. So, I think there is quantitative information to be had there beyond the nature of surveys that may have been done in the past and people were just sort of openly saying, well, the whole thing is a mess and it wasn't really helping you rank out individual compounds. So, other sources of information, perhaps another survey design.

In that regard, I don't think we should go into it and say, well, we should weigh greater the clarity perception by experts versus general practitioners versus laypersons. They all have to be taken into account.

The other portion of the impact score may relate to the degree of new information. There too there are quantitative measures possible. You can make this based on the number of papers that have been published in the last 10 years on a particular drug related to safety in pregnancy. They can be both preclinical as well as clinical papers.

So, I think there is a way to become more quantitative in deriving the sort of impact factor that you could use in conjunction with the readily available quantitative numbers on preponderance of use.

MS. CONOVER: Dr. Friedman is not tooting his own horn, but TERIS, which is one of the databases we use, had to decide a long time ago what kind of data they were going to include in their agent summaries both on human and animal data and made some rules and sometimes they bend the rules, but obviously went through a process. So, there are examples of that already out there in terms of what kind of information was acceptable or reliable for use.

DR. FRIEDMAN: Unfortunately, it's not quantitative information. It's based on judgment.

I'm a little concerned about a complex process for prioritization that might slow down the day when the last of these agents is put in there because I think the bottom line is that every drug on the market needs to have information on safety, and I don't accept the proposition that there are any that don't require information on safety. So, if one goes from that point of view, then it's just a question of time. If we have a process that takes five years to prioritize, requires going out and getting additional data and figuring out how to do this, I think we're going to slow down the day that that last agent gets in there.

So, I would prefer a fairly simple process. It's going to be arbitrary. It's going to not include everyone's favorite drug at the top of the list, but a

fairly clear, simple process that could be implemented quickly without five years of review before it's put into place and a date at some point in the future when a pregnancy label exists on every drug that's on the market in the United States. This eight years plus. It's the "plus" that bothers me.

(Laughter.)

MS. CONOVER: Sort of kicking in the last OTIS question, when I made my list of things, kind of the bottom line here, the things I really wanted -- I think what Jan is saying is, of course, we all want them all right away because we've been dealing for years with questions where we didn't have very good answers.

So, of course, the points you've made about inadvertent exposures, well, we all suffer over inadvertent exposures where we want reassure the woman but we're not sure that we really can and there's not very good data there and how much is the risk really and she's considering whether to continue the pregnancy. And they're heartbreaking cases. Of course, for all of those drugs we want the answers right away.

Then I'm always being asked by family practitioners and obstetricians for a list of safe drugs, using the S word, "safe," but at least maybe first choice drugs would be a good way to say it because we deal in

shades of gray. It's a very hard list to derive. But I think a public health perspective would be very good to have, some choices of currently existing first line drugs and maybe some ones you want to add to it. So, I want that too.

Then the third group that we really, really, really struggle with are the category C's. Now that we've got D and X --

(Laughter.)

MS. CONOVER: But I think Bonnie is kind of aiming toward that too. When I look at the ones that I'm really interested in, there's an awful lot of category C's, and category C is a very complicated category to explain to people. They get the idea that B is better and D and X are not as good, and we would all quibble about which drugs ended up there or how they're described.

But C is this category which is amorphous where it's either there's not enough data or they're not sure about how to interpret the data or it doesn't agree or whatever. It's very difficult. If you asked me about the ones that I struggle with the most and I think are the most important -- and it is a big category of drugs -- it's the C's which are the ones that clinicians commonly want to use. They want reassurance that this is on the safe list, on the drugs of choice list. There are many good, new

drugs and not even so new. Many of them are 20 years old that are still in C. We still don't have enough data or they aren't being moved up because the label is not being updated or whatever. It's a very, very important group of drugs and probably one of the most frequent ones. If you looked at the numbers of exposures, many of the agents are fitting into the C category.

DR. GREENE: It's approaching 11:30 and we've had about an hour and a half of general discussion. I'd like to make sure that we have enough time before noon to address the specific questions that the FDA has posed and address them very specifically.

Before I do that, I want to just get one point of clarification on a question that was asked early in the session, but I'm not 100 percent clear on the answer myself, and that is the scope of these proposed regulations with respect to over-the-counter drugs, biologics, vaccines, et cetera.

DR. KWEDER: We expect this would apply to biologics or vaccines.

Let me see if I can clarify the over-the-counter. For products that have prescription versions, this would apply to the prescription version. The specific language or formatting of the label will not apply to over-the-counter labeling itself, what you see on your Tylenol

bottle. We would like to think that ultimately what information is applied to a prescription version of that is going to have to be translated somehow into the OTC version, and that's something we'd be sensitive to, but the rule itself will not apply to that because over-the-counter labeling is a different set of regulations.

The origins of product labeling, when we talk about it generally here, is that's for the prescriber, although we know that consumers/patients read it as well. Over-the-counter labeling is never for the prescriber. It's for the end user.

DR. GREENE: That actually addresses another point and that is that inevitably, when you have over-the-counter products, there isn't "the learned intermediary" to help the user understand the label. So, I would imagine then that you would anticipate different criteria for the labeling language?

DR. KWEDER: Oh, absolutely. We even regulate the size of the font.

DR. KOREN: With the risk of being beyond the scope of this, one of the rules that many OTIS members use is that during pregnancy a woman should not self-prescribe. You should have an intermediary because of a plethora of issues that you may not think about when you're not pregnant, such as the NSAIDs in third trimester versus

first and second.

So, just because you, Michael, brought it up, it may be something the agency should consider whether in a generic way labeling for pregnancy should include a language that will say something about don't self-prescribe in pregnancy. I don't know if you can be as strong. I know for me as a clinician it's easier to throw out these sentences, whereas you have many other domains to look into. But that may do a lot of good to bridge this lack of generic because if you're going to take aspirin, do talk to your health professional.

I don't see why this should be a problem to include it. Pregnancy is a special situation, and I don't think it's a bad idea for a woman not to self-prescribe and it may solve a lot of these issues. So, I know it's not directly on point, but it's in the context. It may close the bridge with the nonprescription section here.

DR. GREENE: Yes, one last comment.

DR. ANDREWS: I know that the agency faces the difficult issue of phasing in new things and dealing with new labeling versus existing old labeling. But I think one thing to consider is indication. For example, if we phase in the new rule based on frequency of use, one could end up with a very confusing situation for the patient and physician. For example, in antidepressants, if we selected

only the most frequently used antidepressants, and a patient was trying to compare the label between the new label which will contain significantly more information against a simpler, old label that just uses category B and C, they might draw the wrong conclusion about which would be the drug of choice. So, I guess I would support looking at all drugs within an indication when feasible.

DR. GREENE: So, if I could then direct the discussions toward the specific questions, let's start with question number 1, which is posed by the agency. In general, is an accelerated implementation plan for certain high priority products a worthwhile endeavor from a public health perspective?

I think it's fair to say from all of the conversation this morning, a simple one-word answer to that would be yes. Any discussion about that?

(No response.)

DR. GREENE: Let's move on then to question number 2. If so, what criteria should we use to identify or prioritize products? Here I'll just take a minute.

The agency has proposed two specific criteria, frequency of use and potential for inadvertent exposure, as criteria. Implicitly in the materials that they distributed, they also suggested that agents for which there is a suspected adverse impact upon pregnancy also be

moved into a priority status by listing, for example, drugs in category D or category X, as has been suggested. The implicit suggestion or recommendation there is that a criterion might also be drugs for which there is a suspected risk of harm.

Just to summarize a couple of other things that I heard this morning, the suggestion has been made that drugs that are used to treat conditions for which there are not obvious good alternatives might also be a criterion so that the indication for use and the available alternatives for use might be a consideration as a criterion.

Then the other idea that has been floated and discussed is drugs for which there are significant changes expected for the labels either because the existing label may not be entirely clear or the data on the existing label may not be up-to-date and consistent with the recently available data.

Are there other criteria that we can enunciate fairly clearly for the FDA? Jan?

DR. FRIEDMAN: I'm afraid that we're getting into the situation that Gideon mentioned at the beginning where you've got almost every drug in that high priority group, which really doesn't help you very much.

I wonder if there's a way that a carrot could be built into this in the context of what Beth said. It

would be very useful to clinicians if there were a list of drugs for which there is the most information with respect to use in pregnancy. If there could be some way that companies could be encouraged to submit new labels so that people knew that these were not drugs that were necessarily better, but at least drugs that there was more information on and had a clearer label, that that might be of some benefit to them.

It seems to me that there's a perversity in the way that labeling occurs now. Some could argue that it's of benefit not to have, say, a B on your drug because it might potentially open you up to litigation. If there was a way that we could change those incentives around so that companies were rewarded for getting a better label on their drug and a more up-to-date label on their drug and a continually updated label on their drug, it would be very valuable.

DR. KOREN: I'll first answer Jan and then I'll make my own suggestion for criteria.

Of course, you're talking now as a clinician. For most drugs, most companies do not want to label them as drugs of choice. So, we do it in various chapters, reviews because we are medically/legally in a very different place, and we are protected by what's the standard of practice, whereas companies are not. So, I understand why that may

not happen as part of the labeling process.

But going back to the criteria, I still think if I have to choose one sentence, it should be drugs where changing labeling will have the most impact on women now. Of course, I have heard several interpretations around the table, what will cause this. But for me, this means drugs for which there is much more information, for example. Then women and their physicians can be much more informed. Or drugs for which information is in the gray area, such as again the NSAIDs that at different times have different risks, women need to know about. The antidepressants -- and, of course, Kathy did a lot of that work -- where women now stop cold turkey because people tell them there is a risk even if there isn't, and they may endanger their life and certainly their quality of life. So, I'll go around what will have the major impact on women.

Of course, the point that was made, Michael, is that you need to have new information. If nothing happened, every normal person will come up still with the same labeling. But it's fair to say that the amount of information now published in the area of maternal/fetal toxicology, teratology is exponentially increasing. So, with the databases of Michigan, I don't think zero information is true for most drugs several years after they enter the market just because 70 percent of women do not

plan pregnancy. It's a matter of time that someone will write down the first 30 cases of olanzapine or just anything.

MS. CONOVER: See, we never give you a straight answer.

But I think we've also been playing around with the issue of medical conditions that are more common in pregnancy, even arguably depression, but certainly things like reflux, nausea and vomiting, certain kinds of infections, which I think you could give us a really great list of in terms of things that people dealing with men don't see nearly as often. So, it's those enhanced conditions. Nausea and vomiting is such a great example. It's not that other people don't have nausea and vomiting, but it's such an issue within pregnancy and so much more frequent in people who are pregnant.

DR. GREENE: Other thoughts.

DR. KWEDER: I can just comment on the list. Historically the agency hasn't put together those kinds of lists, if you're looking to the FDA to do it. One of the reasons is it involves making direct comparisons. That's not something, outside of the confines of an individual application, we have really the regulatory authority or mandate to do. Typically those sorts of things are done by other organizations. The NIH does it often with a Public

Health Service task force kind of thing. That might be the sort of thing that we could help facilitate, but you would probably never see an FDA list. That would just get us in a lot of trouble.

Interestingly, you may have seen such lists. Other countries do it differently, and particularly in Europe it's not uncommon for those kinds of things to come forth from the equivalents of FDA. But they also have a very different culture of what's acceptable to clinicians in practice. Their country's view of the role of the regulatory agency is a little bit different.

DR. GREENE: Other thoughts or comments?

DR. DATTEL: I was just going to say one thing. I think nobody here at the table wants to see the agency get bogged down in just looking at D's and X's that have absolutely nothing to do with women's health. So, rather than make sweeping generalizations, I think most commonly used, in conjunction with common conditions, or something, that would give you the basis that you would need to defend your position.

DR. GREENE: Finally, the third question is how would you suggest identifying specific products that meet these criteria? I think we've pretty much addressed that throughout the morning.

Are there other questions that you have for the

panel?

DR. KWEDER: I've heard a couple of suggestions. Actually Dee mentioned does OTIS keep a list of most common consults, drugs most commonly consulted for. That's one source. How else? Give us some other ideas. Who else tracks this sort of stuff? What other objective sources or not so objective sources are there?

DR. KOREN: You furnished us with several lists by several stakeholders that collect such data, but what's missing there is the problem, the women's health impact issue. And that's where the OTIS members and practicing obstetricians are probably at the top of my list. I have no question if I show my team now a list, they very easily, from 1 to 5 or any other analog we choose, will tell you where the problems are, either a lot of anxiety or a lot of confusion, a lot of misinformation.

That brings me back to maybe criteria are being set up and even a large list of potential drugs are coming in. I can see those who are the front-line, OB geneticists, OTIS members and the practicing OBG could identify high and low impact within them. It will be like any consensus. There will be standard deviation around it, but it's not, Sandy, what you had done before that you didn't want to share with us. I don't think you should ask these people to come with their lists, but rather let them

rank your list as to problem or impact. So, then there is no ambiguity.

DR. GREENE: The difference between the data that the teratogen information services may have and the information that you'll get from practicing physicians is practicing physicians will give you a rating on a visual analog scale, but there won't be much science necessarily behind it. I think that the teratogen information services will have much more quantitative information.

Other suggestions might be things that we already know about, like the Michigan Medicaid database. Many of the large HMOs now that provide prescription drug benefits also keep this kind of data. Many studies have come, for example, from Puget Sound, from Walnut Creek. The large HMOs that we know keep databases because they've published the results and the data from them.

DR. DATTEL: I think those are valuable but they have to be used with caution inasmuch as there are huge regional variations in drugs of choice. Having been to both coasts, what Walnut Creek might use is a lot different than may be used in the South.

DR. GREENE: The choices of drugs may be different, but the conditions for which they will be prescribing them should be similar.

DR. DATTEL: Right, those should be the same.

DR. KOREN: Again, I think we have already on the table enough of those lists, and the new list will not change a lot. I didn't have any surprise in these lists when I read them as someone who deals with this. I think it's more the complexity and where we will have an impact. Here I thought, Michael, your community of academic obstetricians will know. If a woman is with depression and she doesn't know if she should continue the drug or not and so on, your community will identify issues that are not resolved presently where the up-to-date information will be helpful.

So, I didn't mean so much another list. We have many of those, and they will not change much. Half of pregnancies are not planned, so you just get fecund women between 15 and 45. That's what you get. It's not surprising. I meant more the problems where the impact will be. MVP is a big one. Women don't know what to do. They get different messages from everyone and their sisters too. Everyone needs to say something, and it ends up that many of them don't take anything, for example.

MS. CONOVER: Which, Mike, I bet you deal with this all the time, when somebody calls you and says, how do you treat allergies in a pregnant woman and she's in her first trimester or her third? How do you treat reflux in a pregnant woman and she's in her first trimester or her

third? For me that's how a lot of the questions present because I run a provider hot line. I think she might have influenza. How do I treat her?

Those are the questions that lead you into as you start to think of, now, what medications do I feel confident about, which ones do I wish I could use but I wish I knew a lot more about them. And that's where we get into our questions we wish we knew the answer to, and the labels would help. More data would help too.

DR. KOREN: With the risk of repeating a lot of this, how do you treat something? It's something the companies will not be able to help. None of them will indicate anti-allergics, H1, for pregnancy. Very rarely. I don't think anyone has as yet, and I don't think we should expect them to do it. This is where the medical community should, but the safety is important.

MS. CONOVER: Gideon, I was just thinking of, for example, something like loratadine. That's the question behind the question of what is the risk of using loratadine in pregnancy. So, I guess I was trying to think of the background thought of how you were going to derive your list.

DR. GREENE: Some years ago I saw a cartoon of a physician awakened in the middle of the night and on the phone. He says, don't you have some tried and true family

remedy that you could try?

(Laughter.)

DR. GREENE: I think for such things as nausea and vomiting and allergies, that's always the first choice.

Other comments?

DR. KOREN: I had a professor in medical school who said, you learn for so many years, and then you go to fellowship. Then at 2 o'clock in the morning one day, a patient comes with something you don't have a clue. You close your eyes and think, what would my mom do?

(Laughter.)

DR. GREENE: Yes, please.

DR. WISNER: Can I ask a question that may be somewhat unrelated but it certainly comes up in these kinds of consultations? That is, whether any of these rules or regulations will have anything to do with the complementary and alternative therapies because we get many more calls about those kinds of products.

DR. KWEDER: I'll do the best I can. For the most part in the state of things as they are today, most of the products that would probably fall under what you're thinking of as alternative therapies or complementary therapies are considered dietary supplements. They are not drugs. They become a drug and are regulated as a drug when a company makes a specific claim to treat a disease or a

specific indication for relief of a particular symptom. So, the answer is that none of this will apply to most of those products because most companies are very careful not to make a specific claim in that area.

DR. GREENE: Dr. Kweder, do you want to make closing remarks?

DR. KWEDER: Yes. Actually your discussion has been very helpful. I actually have three pages of list items that mostly fall within the general list that you just summarized, and I think it gives us a good start. Actually getting down to the details is going to be a challenge, but it gives us a good start. It gives us something to work with.

What we'll do with this is we'll make a list and we'll do something like, now, what if we applied this? How many products would it mean we'd get in one year? What kind of a burden is that for us to deal with? What kind of burden is that for the industry as a whole? Then we'll start tweaking it from there and seeing if we can get to something that's reasonable.

But this is very, very helpful. I really want to thank you for taking the time to come early today and help us with this. When people want to know why does this stuff take so long, it's because we have to do this kind of stuff. This is really difficult and this is just the

beginning. The fun stuff is coming up with the big ideas. This is the stuff that's really agony. So, thank you very much.

(Whereupon, at 12:00 p.m., the subcommittee was adjourned.)