But it is entirely plausible that there could be a substantial number of pregnancies in however many women were lost-to-follow-up.

So I think it is really critical for FDA to make sure that that information is available. If the number lost-to-follow-up is substantial, then that is a big operational problem.

I realize how difficult it can be to do follow up for women who have no ongoing obligation to the program but it is really an essential piece of information to have to understand whether the program is likely accomplishing its aims.

With regard to the proposed changes, I wasn't able to--I just couldn't find in the materials we were given what the explanation is removing the HIPAA checkbox from patient registration, so I can't form an opinion about whether I think that is an acceptable change or not.

So, if it is an easy explanation or if you can just point me to something in the materials we were given, I would appreciate it.

DR. KING: That is Appendix IV from the Roche document, in case you were trying to find it. It says, "Remove HIPAA checkbox from patient registration." That is not part of my question. I am just saying, if you can't find it--

DR. PLATT: Well, I found it. I just don't know what it means.

DR. KING: It just means remove it, but I am not sure why.

DR. WALKER: We will ask Roche to address that question. Covance?

MR. SHAMP: Jim Shamp, Covance. Currently, the registration for a patient does include a checkbox that the prescriber has obtained a HIPAA form for that patient. As you have heard today, this program does not fall under jurisdiction for HIPAA so we are removing that checkbox from the registration.

DR. PLATT: So that will re-raise the questions about the privacy issues. If this program is not covered under HIPAA, then it seems to me there is more work to do to understand what

the privacy-protections really are.

DR. WALKER: Yes; we agree with that.

DR. KING: I had the review, the Appendix IV, printing out the 45 pages and, at the very end, was what I was really looking for which was what were incremental changes that may improve the patient or the physician or the healthcare providers who actually get into the computer and get out. Trying to do some of this can be quite difficult and, as proposed by this item here, it actually does make incremental improvements.

But relative to whether or not I agree with the changes, having gone through this battle a couple of times about this, it is much less rancorous this time and I would congratulate the FDA and the other members here and industry for making this discussion of how can we achieve the Holy Grail, can we stop pregnancy.

I am reminded of the Harvard Rule, under defined conditions, the organism will do as it damn well pleases. It seems to me that the issue brought here is that when people don't understand

or comprehend, then nothing happens good, or sometimes it happens great because, if you order something and don't send back for your refund, the business gets to keep your $30.

So I think that we need to address the issue of comprehension. I think we also have to do the equal part of that, is who is telling the people what verbally and in presentations and handwritings.

So, in dealing with this in my own issue of teaching for a long time, you really do have to do pre- and post tests and that is appropriate to me. I think that, in many ways, this is a very positive thing because there are a number of conditions where you tell people, don't smoke, don't drink, don't whatever, and yet here we have industry-financed proposal to study a very specific situation with a very specific combination of patients.

My concern is actually not do I agree with these changes. It is what do you do with those people left out of the system. In our experience

in a children's hospital, how do you manage the exposure to these isotretinoins. How do you deal with people who are on Medicaid? If they are locked out of the system, how are you going to deal with it not only in terms of complications but who is going to pay.

So my last question and comment really is how is this system, iPLEDGE, going to deal with the other people who are dealing with giving isotretinoin for non-acne and those who don't pay. So I make a plea that you keep it safe but you also expand your thought about who is in the system.

DR. CRAWFORD: Thank you. My comments are, one, I think, as a committee, a joint committee, we should be very clear about what we are being asked to comment on with respect to proposed changes. The first FDA presentation on Slide 22 this morning were three major changes. When I looked at the industry presentation, the sponsors, on Slide 28, it was those same three plus a fourth one.

When I look at Appendix IV--I was looking over Dr. King's shoulder--it is a much longer list. So I am not totally clear as to which specific changes we are being asked to comment on. So I would appreciate it if we could, perhaps, show a slide that says the exact changes that we should be considering once the vote is taken.

That is my first comment. The second one, this is just a quick--

DR. BIGBY: Hold on one second. Do you want to address this?

DR. WALKER: Certainly. The specific comments are on the three changes that were inducted to Dr. Diglisic's slides. The other changes, if you have comments on those, we are interested in hearing that. As you have already mentioned about the HIPAA, obviously that is something we will pay attention to and work towards a resolution with all the stakeholders.

DR. PLATT: But we are not being asked to vote on that?

DR. WALKER: No.

DR. PLATT: So, could we have that slide up?

DR. WALKER: Certainly. It would be Slide 23.

[Slide.]

DR. PLATT: Thank you.

DR. CRAWFORD: The next point is just a very quick one. I did hear--in the open public forum, it was stated about possible in-patient prescribing. I wanted to ask is there in-patient ordering and dispensing of isotretinoin and, if so, comment on how that works within the program.

While someone is coming up to answer this, my third comment only is just that I don't totally agree that there was a slide at the ready for any questions we posed because I remember quite a few answers of saying, well, we have that data; we just don't have it available today. I think that data should be presented to FDA by the sponsors before the final decisions are made as to whether or not to make these changes.

DR. WALKER: Can I make a comment there?

One reason for the meeting today was to put the information in the public domain and to get your initial impressions. As we move forward, obviously, you have raised some excellent questions in that data will be obtained and analyzed.

Hopefully, we can move forward with some of these changes without that depth of data. That could certainly be considered in the next meeting as information accrues. But I think we would be very interested in being able to work with the program with some of these changes in mind because, as we have heard today, some of these changes may actually increase compliance.

DR. CRAWFORD: Would someone please comment as to whether or not it is dispensed in in-patient setting, isotretinoin, and, if so, how does this work with the iPLEDGE Program?

MR. SHAMP: Jim Shamp, Covance. All patients that are prescribed isotretinoin must follow the same requirements as you have seen today. There is nothing in iPLEDGE that does prevent an in-patient from receiving, provided that

the prescriber and patient both follow those requirements.

DR. GROSS: Last but not least, I agree with the three changes. I do have a comment. Much as others have reflected, to me, this is a great public-health experiment between the FDA, the manufacturers, prescribers, patients and the pharmacists.

The experiment implemented a system to aid patients in the course of their treatment to avoid a personal tragedy. Given the presumed accuracy of the data, it is 99.9 percent safe and effective with a 0.1 percent failure rate. And we have to remember there is no alternative treatment available.

So, given the imperfectability of system design, patients, prescribers and pharmacists, the results, I think, are remarkable. But this is an iterative process and we need to continue to pursue perfection even though we may never reach it.

DR. BIGBY: So I think we can vote with a show of hands. The first question, then, is a yes

or no vote on whether the proposed changes are acceptable. All those who vote yes please raise your hand.

[Show of hands.]

LCDR MOSADDEGH: If we could go around and have everyone who has their hand raised, please say their name into the record and say yes afterwards and I will log it in.

DR. SCHMIDT: Jimmy Schmidt, yes.

DR. DAY: Ruth Day, yes

DR. MITCHELL: Allen Mitchell, yes.

DR. NELSON: Lewis Nelson, yes.

DR. SKINNER: Robert Skinner, yes.

DR. SAWADA: Kathy Sawada, yes, but with the and/or.

DR. BIGBY: Michael Bigby, yes.

DR. LESAR: Timothy Lesar, yes.

DR. HENNESSY: Sean Hennessy, yes.

DR. THIERS: Bruce Thiers, yes.

DR. KRESEL: Peter Kresel, yes.

MS. GRIFFITH: Gail Griffith, yes.

DR. KRAMER: Judith Kramer, yes.

DR. DRAKE: Lynn Drake, yes.

DR. WHITMORE: Beth Whitmore, yes.

DR. PLATT: Richard Platt, yes.

DR. KING: Lloyd King, yes.

DR. CRAWFORD: Stephanie Crawford, yes.

DR. GROSS: Peter Gross, yes.

DR. BIGBY: Are there "no" voters? Would you please raise your hand.

LCDR MOSADDEGH: If I could just--the industry representative, I appreciate the vote, but we will have to exclude his vote. Thank you.

DR. KRESEL: I'm sorry. But it always goes down for the record.

DR. BIGBY: If there are any "no" voters, please raise your hand.

I think we can go on to discuss the second question; discuss approaches to enhancing voluntary participation in the pregnancy registry within the iPLEDGE Program. Does anybody need clarification of what is being asked here?

DR. WALKER: I think the second question is about root-cause analysis. There it is. Right.

DR. BIGBY: The last shall be first. Peter, do you want to comment?

DR. GROSS: I think I commented previously that I think this should be dealt with up front in the beginning and the consent should be obtained at that point.

DR. CRAWFORD: I don't have a comment right now.

DR. KING: I think it is going to be a matter of education from my perspective and it is like Cool Hand Luke said, we have a failure to communicate here. I think if you are part of the tragedy, you have to share what happens to you with other people. I think voluntary participation almost needs a chat-room or something like that although that violates HIPAA-type things.

But I think that we need to work on this because, if I were in the midst of something like this with my daughter, I am not sure I would tell her to make it public or do all this. So I think we have a ways to go and to work on communication is the only way to do it.

DR. PLATT: I think Peter Gross's notion of at least starting the conversation at the time prescribing bears more thought. To what extend individuals can actually be required to consent in advance is not so clear to me, either required or whether it is a good idea to do that. But I do think that it is probably the best opportunity to try to start the process.

DR. WHITMORE: Mention was made about it being somewhat intrusive. I don't see it as being intrusive. I see it as being part of their treatment. I think what could be considered is, instead of voluntary, mandatory. I think it would be of interest to know how many women are actually at risk for pregnancy because we don't know that. We don't know how many people did not use contraception, did not take their birth-control pills every single day.

DR. DRAKE: I think that Dr. Gross is onto something; begin the conversation early. I must admit that mandatory makes me uncomfortable because it is still a woman's right to privacy. So

voluntary, I always think, is better, if you get a voluntary cooperation.

But I honestly believe that, fundamentally, if you decrease the volume, the volume of paperwork that these people have to understand and the linguistics probably really does impact this. I think you are going to address that and I would urge a very careful look at that.

DR. KRAMER: I think I may need some clarification because the question is posed as voluntary participation in the pregnancy registry. Then I heard Dr. Walker mention that she thought it was the root-cause analysis.

DR. WALKER: I can clarify that. I was bringing attention to the fact that Question 1 was up on the screen. It wasn't to change the question. That is the correct question there.

DR. KRAMER: I guess I am confused about the distinction between just the registry, that there has been a pregnancy, and then this very long form that was included in our review materials from the sponsors that is Appendix II, Root Cause

Analysis Questionnaire. Are we talking about that document--because I have a very hard time understanding how you could fill out this document up front when it is asking questions like, if your vaginal ring slipped out in the month before you became pregnant, how often did this occur.

DR. WALKER: The Root Cause Analysis document is a subset of the pregnancy registry. So we are interested in your thoughts on any of the items in the pregnancy registry.

DR. KRAMER: Okay. My comment about the discussion you can have up front is that I would think that somebody's view of what they would share in the hypothetical instance up front might be quite different, just as people's view of what they wanted and of life-care changes when they get closer to that decision. So it might be worth exploring, but I think it will be difficult.

Specifically, my comments on this questionnaire is that it clearly has some problems, not only in the way the questions are phrased but there is a pejorative--I mean, I was stunned when I

was reading through this and it was asking all these questions about failure of birth-control methods. Right after those questions, there was a question about, what is the highest level of education that you completed.

If that is not implying that you are stupid because you got pregnant, I don't know what else it is doing. So I think this really needs a careful review and clearly could be shorted to get out the most important information that we need to interpret what has happened here to improve compliance.

MS. GRIFFITH: I would just echo what Dr. Kramer suggested. I thought it was punitive in some aspects and intimidating and I would really like to see the language revised.

I would also ask, and perhaps we could--this is a larger notion in scope and may be difficult but it would be interesting to find out what precluded voluntary participation, if we could do some back-end research on that.

DR. KWEDER: May I just clarify that, as

we have looked at these kinds of registries before, we have been--it has become quite clear that we cannot make it mandatory.

DR. KRESEL: A couple of comments. First of all, I agree with everybody who has alluded to the fact that less data from more people is probably a better way to go. But, having said that, for those who haven't looked at this process over the years, I would like to point out the fact that we probably have information on more women as a percent than we have ever had before. It really has gone up dramatically.

So you may find these data to be inadequate but these are better than that which we have been able to obtain in the past.

DR. THIERS: I don't have anything to add above what has been said already.

DR. HENNESSY: No additional comments.

DR. LESAR: No.

DR. BIGBY: Actually, the one comment I have is that there were allusions made to what happens when there is inactivity of a registered

patient. I have had a few inactive patients and I never got notified of anything. So I think that that part needs some work.

DR. SAWADA: I certainly believe that we should start at the very beginning to kind of bring this into our conversation. It seems like all my isotretinoin visits these days are circled around with pregnant women, these issues, rather than asking them how they are doing on the medication.

I think that, certainly, it is time to revisit educating the prescribers and having, perhaps, Covance sponsor statewide voluntary, people who are already enrolled in the program, just refresher courses.

Regarding the 30-day follow up, we certainly should try to be, perhaps, a little bit more rigid about getting people back because I would agree with Dr. Bigby, I have had a few of those on my computer screen, lost-to-follow-up and I haven't received any letters or notification.

Some of those things, too, that you ask in lost-to-follow-up are hard to answer, like the

exact date of their last dose. Some people don't remember. So that kind of forces us to invent a number or a date.

But, again, educating those of us who are prescribing it, re-educating us, just reminding us and also, perhaps, emphasizing participation in the pregnancy program at the outset.

DR. SKINNER: I think, obviously, it has got to be up front and some explanation of why it is important to get on a registry. Certainly, being pregnant on Accutane or isotretinoin is not a good time and it is probably not the time to introduce, how about being on a registry now. So I think it is obviously got to be up front.

DR. NELSON: I looked briefly through the book that was given out and I don't find anything that says what to expect if you are expecting, so to speak. There is nothing that says that you might be asked, or you will be asked, to enroll in a registry and fill out an RCA and what not.

I think that putting this up front, whether the doc sits and speaks with the patient or

at least, when they read the book, they have that information available to them would be a good thing. I commented earlier about the carrot and the stick kind of approach. I think, as this is relooked at, perhaps the mind-set that could be taken is what would I feel like if I was a woman who just realized I was pregnant while on this very dangerous drug and what would I want to hear.

Do I want to be sat in a room with 100 sheets of paper and told, you have to answer these questions or, perhaps, is there a better way to entice people to participate. I think some of Dr. Kramer's comments are relevant there as well.

DR. MITCHELL: Given the hour, let me try to consolidate my comments. At this point, we really, I think it is clear, have no idea whether iPLEDGE is an improvement over the past systems. We would like to believe it is and there is certainly every reason to believe it is.

But the key outcome, which is going to allow us to make that judgment, is the pregnancy rate, the rate per 1000 women, the rate per 1000

courses. We don't know that. We don't even know how many courses have been completed and then, therefore, eligible for inclusion into that denominator.

So, in terms of what has to be done now, and I will separate that from what some general points, is clearly attention has to be focused on identifying all pregnancies. I think there is evidence that this program has devoted huge and very effective attention to the mechanics up until the point of pregnancy but it doesn't seem to have had the same kind of rigor following the completion of therapy.

So what has to be identified in my view is the number of completed courses and whether, among those completed courses, follow up was completed with one or two of the required pregnancy tests and whether it wasn't so we know what proportion of eligible women are actually followed for the occurrence of pregnancy. Otherwise, we are not much better than a voluntary survey.

Once the pregnancy rate is identified per

1000 completed courses, we need to evaluate those pregnancies, obviously, call it a root-cause analysis. There have been ways of doing this using the same kind of approach for years before it had that name.

I think, here, people have commented on the intimidating nature of the questionnaire and some of the problems with the questionnaire with which I fully agree. But I think what hasn't come up in the discussion is acknowledging that a woman who becomes pregnant has failed the program, quote, unquote. She is bad, in her view, and, perhaps, in the doctor's view.

This is not a feather in the cap of the prescribing physician. So I think we have to take into account that there is not only guilt on the part of the woman and a physician but there may actually be considerable reluctance and embarrassment about coming forward.

We have learned about overcoming this approach the way the airline industry has been--there has been lots of recent research

here--to destigmatize the bad outcome. I think tremendous attention needs to be placed in that area.

I am not convinced that the follow up of pregnant women is done as sensitively as it might be and I would also argue that another major principle is that there is inherently an assumption that all the women who were in the program are as intent on avoiding pregnancy as the FDA and the sponsors would like them to be.

In reality, we identified in years past, and it is well known, that some women consider an abortion to be a reasonable form of contraception. Some women are willing to take the risks even though they are fully informed.

So I don't think we can assume that all women who become pregnant didn't want to become pregnant or at least were not willing to take that risk. I think questions in the root-cause analysis have to be designed very sensitively, such as how concerned were you about becoming pregnant while taking isotretinoin. I think we will be surprised

to find that the pregnant women were not all that concerned all the time.

Did you think you were unlikely to become pregnant? I mean, these are questions that deal both with motivation and attitude rather than knowledge. I think the data, as they have in the past, continue to show, for those women that are identified as pregnant, that they are pretty much well-educated about the issue to the extent that their responses reflect what they really know.

So I would definitely include that. In terms of points to consider, I think the principle has been often stated but not always followed--I am speaking from my own experience--that I think a critical evaluation of a program is better done by an independent party than by the sponsors of the program.

I think some of these tough questions that the committee is asking today would likely have been asked by an independent evaluator.

I think that the bottom line is that this is a risk-management and not a risk-elimination

program. If anyone really thought we would get to zero pregnancies, I don't think anyone would have approved any program. It is just not possible recognizing that we are dealing with human behavior and it is imperfect.

I just did some quick math. Among the women that were identified in the study, roughly 40,000 were using the pill and condom as their primary and secondary method of contraception. If women failed to use the condom, you would expect roughly 400 to 800 pregnancies among that cohort, a 1 or 2 percent failure rate. That is assuming really good use of the method.

The condom, together with the pill, will reduce it to close to zero, but it only takes, as most of us know, one time to become pregnant. So I think we need to be really careful short of absolute sterilization, there are going to be pregnancies.

The question is how many and how many are acceptable. I don't think we have ever really dealt with that last question.

DR. DAY: I think a thorough review for cognitive accessibility and all the materials, not only to the patient but to the providers and especially those where they interact. It is not just language. I am not just saying make it eighth-grade level. That is not what I am saying.

But you have to think about what the multiple interpretations are of each of the statements, whether there is another interpretation other than that which we intend.

You have to consider the logical complexity of each statement. There are embeddings within embeddings. We also have to take into account the kind of accusative tone that comes in at various points that other people have raised.

So we are ultimately interested in behavior. We can't get to behavior without going through cognition. I am talking about the cognition not only for the patients but the designee or the prescriber who is going to interact with them.

If you are faced with a

root-cause-analysis form and it is hard to get through--I don't even know how you translate that into a spoken version when you are talking to them on a phone--then it is going to be a little harder to get motivated to do it.

So we have to make everything more cognitively accessible and usable for everyone. That is the major thing that I would like to say at this point.

DR. SCHMIDT: I want to say that I have lived these things. I have had people get pregnant--not with this iPLEDGE, but I have people get pregnant on Accutane and I have had people get pregnant after they are off Accutane.

One of the things I think we need to do is the education of the physicians, themselves, and when people enter the program to bring up some of these things so that they can be cognizant of this pregnancy registry first-off.

Usually, what I do is I tell the patients--I say, listen, if you get pregnant, you and I are both going to have to move to Paraguay.

And then the other thing that I have really got a problem with is, even the 2005 meeting and this meeting, there are so many pregnancies that they are just lost-to-follow-up. Boy, let me tell you something. In my office, if somebody calls up and says, "I'm pregnant," on Accutane, whooo, all hell breaks loose. I go over and live with them practically to see what happens.

I have had people actually get pregnant one day after they were on Accutane. It was a 16-year-old who got lost-to-follow-up and even Hoffman-LaRoche, everybody, tried to find her and would couldn't.

The only follow up I got was three years, or four years, later her father came in a patient. Obviously, I wasn't going to tell him what happened, but I said, "How is your grandchild?" And he pulls out a picture and he says, "Man, this kid is like Einstein." I went, "Oh, great." So I know that there hadn't been a problem.

So, to me, I really feel like these lost-to-follow-up, duh. What is going on with

these guys. It is a disaster.

So those are my comments.

DR. BIGBY: The last question; are there additional recommendations for the future to enhance the risk-management functions of the iPLEDGE Program. Given the hour, and the fact that I would like to end this meeting somewhere near on time, I am not going to go around the room. But, if somebody has additional statements they would like to make that they haven't already made, please do so.

DR. SKINNER: I just wanted to make one statement and follow up Covance on that. I really think that that question, "told to avoid pregnancy," should be a wrong answer if you say no because I think that really goes to the whole crux of this program. If you, for whatever reason and go through this and say, I was not told to avoid pregnancy, I think that ought to be a no and you have to go back and find out what was wrong there.

So, when they answer that question, it should be yes.

DR. DAY: I think that the many questions that have come from the committee today should have been in the report. I would like to strongly recommend that future reports include all the data about these issues. The slides were already there. We shouldn't have to ask for them to come up. We should have that information in our briefing package and in your report to the FDA before any meeting like this, and it should be a regular part of the report.

DR. CRAWFORD: Hi. Without elaboration, just to make sure it is part of the record for this No. 3, as I was taking notes as people were saying, I have five very quick points for No. 3 that we were just asked.

I would like to reiterate the need for review and approved translations of the patient educational material in additional languages. I am not comfortable that the call centers that can get different translations--I know that means it is going to non-standardized.

Two, obviously, there is the need for more

stringent review an accountability of the privacy standard. There is extensive review of all reported data on embryonic and other pregnancy exposures be they reported to iPLEDGE or from other sources. Four, better tracking of those patients who have, obviously, lost-to-follow-up in the iPLEDGE Program. Last, review and revision of the survey items.

DR. GROSS: Root-cause analysis, by its nature, is a retrospective approach. My suggestion is you try the prospective approach, failure mode and effects analysis, and see if any suggestions come up that might guide an improved root-cause analysis.

Number 2, I think we should study the best way to get information from the woman who becomes pregnant whether it is a written survey or a face-to-face interview or some other mechanism.

Last, if we want this stuff sent to us, can we just put our name on it and somebody will send us the package. I know that has been done at other meetings.

LCDR MOSADDEGH: Mail the iPLEDGE packages?

DR. GROSS: Yes.

LCDR MOSADDEGH: Yes. Just leave your name on there and leave a note for me that you want them mailed to you and I will take care of it.

DR. BIGBY: Susan, are we all right?

DR. WALKER: Yes. I would like to thank the committee extensively for the very informative and interesting and helpful comments that you have provided to us today. We will look forward to addressing these issues.

DR. BIGBY: Thank you all very much.

[Whereupon, at 12:33 p.m., the meeting was adjourned.]

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