DR. WIEDERMAN: Yes.

MR. LEVIN: Yes, myasthenia.

DR. EDWARDS: Okay.

DR. LEGGETT: Can I say my two bits.

DR. EDWARDS: Yes.

DR. LEGGETT: I had already said to make a black box for myasthenia, but the reason I am abstaining is I don't know enough about labeling and all the FDA requirements to be competent to say anything about that. I would leave that up to the FDA.

DR. FOLLMAN: I would agree. I don't know what a black box really means and I don't worry about too many of them.

DR. EDWARDS: Let me go on if I could. Dr. Follman's comment is very germane and I think we are virtually all in that position if I could suggest that. But, again, we are just advising you from this particular perspective.

Could I see a show of hands for hepatotoxicity?

[Show of hands.]

MR. MARCO:[?] If you were going to do a label, would you want it?

DR. EDWARDS: Right.

MR. LEVIN: It is already in the warning. It is already bolded in the warning.

DR. EDWARDS: It is a bolded warning. So the question is would you be in favor of a black box addition to the current label which is a bolded warning for hepatotoxicity. I am just going to go right around and ask for a yes or no. Dr. Levin.

MR. LEVIN: Yes.

DR. EDWARDS: Dr. Wiederman.

DR. WIEDERMAN: Yes.

MR. MARCO: Are you saying for a black box?

DR. EDWARDS: Yes.

DR. EDWARDS: Dr. Smith.

DR. M. SMITH: Yes.

DR. KOSKI: No.

DR. NORDEN: Yes.

MR. MARCO: Yes.

DR. EDWARDS: No.

DR. FOLLMAN: No.

DR. GUTIERREZ: No.

DR. BRADLEY: No.

DR. LEGGETT: No.

DR. PROSCHAN: Now, I am confused. I would like to hear more what Dr. Follman said about exactly what the implications of that are because I don't really know exactly what that means either.

DR. EDWARDS: Can you help us with that, Dr. Cox?

DR. COX: If a black box is included, it is typically prominently displayed at the beginning of the label so the information is right there at the start. It also impacts upon advertising in that the black box is always included with advertising and various things that might be given out, just a pen or something like that. It always has to have a label affixed to it. Am I wrong about that? It always has to have a label affixed to it.

DR. MORRIS: No; there is no reminder advertising.

DR. COX: Okay.

DR. JENKINS: The black box potentially reserved for the most serious warnings that we have. So we have a definition in the regulations that it is for serious risk associated with the drug. But in lay terms, it is always reported in the media as the strongest warning FDA can put on a drug label and, as Dr. Cox said, it is actually in a box to draw your attention to it. It is at the very beginning of the package insert.

It does have implications for promotional activities because the box needs to travel with all the promotional materials. It generally means, for example, that things that are called reminder ads, where all you get is the name of the drug can't be provided unless you have the box there as well.

So, for example, you can't have a pen that has Ketek on it unless you somehow get the box on the pen as well. So that is some of the impacts it has on--it does not preclude, by the way, direct-to-consumer advertising because you can divulge the risk in the direct-to-consumer

advertising to provide fair balance. So that is just one clarification. It does not preclude DTC advertising.

DR. EDWARDS: Okay. Dr. Proschan, does that help?

DR. PROSCHAN: Yes. So I wouldn't put it for hepatic.

DR. EDWARDS: Okay. Thank you. Dr. Morris?

DR. MORRIS: Is the question--there is going to be a black box and the question is what do we put in it. The answer is everything. I would put all four risks in it.

DR. EDWARDS: Thank you.

DR. EDWARDS: Dr. Townsend.

DR. TOWNSEND: No.

DR. EDWARDS: Dr. Heckbert

DR. HECKBERT: I am going to vote yes for the hepatotoxicity but I have to qualify that by saying I really don't feel qualified to make this decision and I would like to know, when other drugs have things in black boxes, what is the level of

evidence for them. I would like to know that it is comparable here.

So I think probably the contraindication of the myasthenia gravis I am less concerned--I think that definitely should be in the black box but I am not quite so sure with hepatotoxicity. But I am voting yes.

DR. EDWARDS: Dr. Wong-Beringer. She has left? I'm sorry. Dr. Shapiro.

MS. SHAPIRO: I don't know.

DR. EDWARDS: I'm sorry?

MS. SHAPIRO: I don't know.

DR. EDWARDS: You don't know?

MS. SHAPIRO: Right. I am abstaining.

DR. EDWARDS: Okay. Thank you. Dr. Smith.

DR. J. SMITH: I vote no, but I am concerned for the same reason that was just stated a few seconds ago just in terms of being consistent and that is something that I am not sure about. So I do strongly agree that the myasthenia-gravis risk warrants such a black-box warning.

DR. EDWARDS: I think we are almost obliged to go around the room on the other two toxicities. I really don't see any other way out of it. So let's go with the visual issue.

Dr. Levin.

MR. LEVIN: Yes.

DR. WIEDERMAN: No.

DR. M. SMITH: I think yes.

DR. KOSKI: Yes.

DR. NORDEN: Yes.

MR. MARCO: Yes.

DR. EDWARDS: No.

DR. FOLLMAN: No.

DR. GUTIERREZ: No.

DR. BRADLEY: I am going to vote no but I also have another comment on the hepatic toxicity. Trovofloxacin, I believe, had a black box and the drug actually wasn't withdrawn from the market. But when you put the black box on it, the company, basically, didn't support its use anymore for whatever reasons. So the impact of a black box can be huge. Can I confirm that?

DR. COX: When the issue with hepatic toxicity came up with trovofloxacin, the indications became more limited. It started out with indications in the teens and I think it went down to five more serious indications or thereabouts. Also, the type of information included in the label talked about starting the drug on inpatients.

Yes; that did have an effect on use. But that was part of trying to get the risk and benefit to those situations where there was more benefit commensurate with the risk. But it did affect use.

DR. BRADLEY: And you didn't pull the drug off the market, though.

DR. COX: Correct. The drug was not withdrawn from the market by us at that point in time and then subsequently the drug is no longer marketed.

DR. EDWARDS: Dr. Leggett.

DR. LEGGETT: I am going to vote--

DR. MOYER: I think it would be helpful if one of the FDA does have Code of Federal Regulation

to read what a black-box warning is required for because there has to be a significant health risk associated with the black-box warning. There is a regulatory definition for such. That may be helpful, if we could ask for that.

DR. AVIGAN: I don't have a photographic memory but it does come across once in a while in a review. I can sort of give you at least some concepts.

One, in the regulation, is, for a serious and life-threatening event, if the information will help a patient recognize an event and modify the outcome because of the recognition. The other would have to do with the fact that it is a buyer-beware idea that, if you know that that was a risk, you might alter your decision to take the drug, again, for a serious and life-threatening condition, precluded for those.

So those are the kinds of caveats or criteria that are used in black box--the difficult is to determine where the burden of events are to go with that because it obviously, in real life,

there are gradations of risk that we deal with.

DR. JENKINS: I do need to clarify. The criteria that Dr. Avigan was just describing actually are the ones for medication guides, although there are clearly a lot of similarities between when the regulations describe the need for a box warning and when they describe the need for a medication guide. But I think the ones you are describing are actually the ones for when a medication guide can be required.

For the committee purposes, if you don't understand what I mean by medication guide, medication guide is a patient labeling. So is it labeling that is written in lay terms for the patient and is required by regulation to be handed out with every prescription dispensed at the pharmacy.

So it is a sheet of paper that the pharmacist is required by regulation to hand out with every prescription, both new prescriptions and refills, for a limited number of products, just to clarify if anyone has any questions.

DR. EDWARDS: Dr. Proschan.

DR. PROSCHAN: The fact that we don't really know what the requirements are--I hope we have a chance to change our vote after this one, too, because I really don't feel confident at all that my recommendation is--I just don't know what to say on this. I feel strongly that more should be done.

Now, exactly what more should be done, I don't know and I don't know whether it is really the right thing to do to put a black-box warning if it doesn't fit the definition that they use for black-box warnings.

DR. JENKINS: Hearing the sense of the committee earlier that you thought that at least some of the risks rise to the level that you would advise FDA consider a box, that is probably adequate information for us to go back and consider and decide what the specific language would be.

Believe me, committees have difficulty with this issue every time we ask it because you are not involved in writing labeling. You are not

completely aware of all the regulations. So you are struggling just like every other committee does that we ask this question.

We got the sense, I think, earlier, that you thought at least some of the risk rose to the level that you were recommending a box and I think that would actually be sufficient from our standpoint if you wanted to go from there.

DR. JOHANN-LIANG: Can I just add a couple of things? A couple of things to keep in mind also regarding--myasthenia gravis keeps coming up. If you recall, I think, in Dr. Wassel's presentation from OSC, he did discuss that, in the label, aside from the box, there is a Contraindications Section where you say, for a certain population, this drug should not be given. So that is something I didn't want you guys to forget about.

Lastly, about medication guide, just to follow up on Dr. Jenkins' remark, the company has discussed patient package inserts and how they have changed it over time which is good. But, again, patient package inserts, there is no requirement

for that to go to the patient.

Medication guide is the only that has a requirement that you must distribute with the drug to the patient. So that is something for you to think about as well because, remember, we are discussing communication to the prescriber, which is the labeling. But we also need to make sure that we have adequate discussion about how to communicate to the consumer since these adverse events are very right up in front which is what we are concerned about.

DR. EDWARDS: I need, now, to ask Dr. Cox and Dr. Jenkins--I think, on the basis of what you just said, Dr. Jenkins, we probably ought to stop voting on the black box at this point.

But we now have the issue of other kinds of modifications. Is what we have done regarding the black box enough of guidance regarding other kinds of modifications?

DR. JENKINS: I would like to hear your thoughts on medication guide. That, again, would be the vehicle to try to ensure that patient gets

information that is directed at them about the risk and benefits of the product, how to use it appropriately, what to look for, what to report to the doctor.

It could include, for example, if you get blurred vision, stop taking the drug, don't drive. So it is very patient-focused labeling and, as I said, it is required by regulation to be dispensed.

There have already been discussions between the agency and the sponsor about medication guides.

DR. MOYER: We can make it real easy if you would like. We are going to do it.

DR. JENKINS: Okay.

DR. EDWARDS: Dr. Jenkins, could you ask us a specific question about the medication guide that would help us. Would the question be, should there be increased warnings in the medication guide. I am just not exactly clear where--

DR. JENKINS: I think the company kind of took that question out of the realm because they just said that they agree that they will have a

medication guide. So it is kind of like the box. We will work on writing it and describing what should be in there.

I think we have already heard from you during the last couple of days there are issues about making people aware of the visual changes, stop the drug, don't drive, what to look for for hepatic symptoms, what to do if you get those. I mean, those are the types of things we put in medication guides in language that is appropriate for the average consumer.

So I don't think we have any specific questions about the medication guide beyond whether there should be one. But the company has agreed.

DR. MORRIS: I think you do. You just don't know it.

DR. JENKINS: We will have lots of questions when we start writing it.

DR. MORRIS: There is something more basic than that and that is there is no evidence these medication guides ever get to patients. I developed a medication-guide project when I was at

FDA. Even though FDA requires it, it is not clear how it is delivered.

What the company has offered up is actually something better than a medication guide. They have offered up packaging. The packaging, putting it in the packaging, is more important than calling it a medication guide.

If you want to call it a medication guide, fine. But making sure that it is in the package and that the package has information on the outer carton so the patient sees the information before they take the drug. That is important. Having a medication guide which may not be read until after the patient starts taking the drug, for these particular set of problems, is giving the information too late.

So I think I would very highly recommend a packaging solution. I don't care if you call it a medication guide or not, but as long as it is packaged in the product, that, I think, is a very important issue.

DR. MOYER: We agree. The 5-day is

already packaged to be able to do that. It is the larger pack that needs to be packaged that same way and that will be done.

MR. LEVIN: So you are going to unit-of-use packaging.

DR. MOYER: In some way, the packaging will be available so that it--

MR. LEVIN: Right. The only thing about a med guide, Lou, is that there is sort of a format that is prescribed. So I think it is valuable to make sure that the format meets some standard. For now, a med guide is about the best state of the art.

DR. MORRIS: Right. I think their current patient package insert is in that format. But there is a good reason to call it a medication guide in that, the same thing as a black box, there is a symbolic value to that, that it says there is something different about this drug.

The reason that a black box has value, because I think there are many, many drugs now that have black boxes so the signal value of black box

is lessened quite a bit as you suggested.

Medication guide is--only about 50 drugs that have medication guides. So the signal value is still there for medication guides to a greater extent. But that signal value is going to be used both by the company and by its competitors.

Its competitors are going to say, oh, look at that drug. So I do think there are going to be unintended consequences as well as the intended ones.

DR. EDWARDS: Dr. Cox.

DR. COX: I was wondering if we could get a little more discussion and maybe a vote with regards to the issue of a limited indication or a modified indication. There was some discussion about that earlier on, I think a discussion of second-line.

DR. EDWARDS: Perhaps I could ask for a show of hands of those individuals who would be inclined to add a second-line, add, this drug is a second-line indication for CAP.

DR. COX: Right; and exactly what the

wording would be we would have to figure out. But is it an alternate? In certain circumstances, would you essentially put it in that second-line position?

DR. EDWARDS: Let me see if a show of hands will work on that. How many people feel that language--oh; okay. Lt. Mosaddegh would prefer we go around. It is hard to keep track. I empathize completely.

Dr. Levin, let me start with you.

MR. LEVIN: I don't want to delay this because I know people are running to planes already, but I am just not clear on whether we are--how firm we are being with what that says. I have a little discomfort, from my perspective, being too proscriptive with what that says. But I think some indication that there may be reason to try other us first, something along that line without being too proscriptive.

DR. EDWARDS: The way you have just worded that, would that be satisfactory, Dr. Cox, some indication that this be a second-line agent?

DR. COX: Yes. I guess we would have to figure out the wording but I hear your general idea.

DR. EDWARDS: So general idea.

LT. MOSADDEGH: That was a yes, Dr. Levin?

DR. EDWARDS: Dr. Levin, was that a yes?

MR. LEVIN: Yes.

DR. EDWARDS: Dr. Wiederman.

DR. WIEDERMAN: Yes.

DR. EDWARDS: Dr. Smith.

DR. M. SMITH: I would agree; yes.

DR. KOSKI: Yes.

DR. EDWARDS: No.

DR. FOLLMAN: I will have to abstain. I am not a physician and I don't really know what my vote would mean.

DR. BRADLEY: I would say no. There are enough professional-society guidelines on CAP. Everyone has got guidelines on CAP. They are very explicit on which is first-line, which is second-line. Telithromycin already is second-line therapy so I don't see that there is the need for

the agency to actually put that it is second-line in the package labeling because that should be made--that decision should be made locally based on your prevalence of resistance organisms and ultimately clinical and microbiologic efficacy. And it may change with time.

DR. EDWARDS: Dr. Leggett.

DR. LEGGETT: I agree entirely with that statement.

DR. EDWARDS: Dr. Proschan.

DR. PROSCHAN: I am clueless on this. I have no--

DR. EDWARDS: Abstain. Dr. Morris.

DR. MORRIS: I would say no. I am comfortable that a black box will do that but I don't think I am comfortable with the information that says the comparative safety and efficacy to make it second-line.

DR. EDWARDS: Dr. Townsend.

DR. TOWNSEND: I wouldn't feel the need to limit it to second-line or third-line. I don't know if this is the place to bring this up. I

think it may be worthwhile to put in some wording about using telithromycin after another macrolide and the possibility for increased hepatotoxicity in that situation. So, anyway.

LT. MOSADDEGH: Is that a no, Dr. Townsend?

DR. TOWNSEND: A no.

DR. EDWARDS: Dr. Smith.

DR. J. SMITH: No, and I would agree with Dr. Townsend's last comment.

DR. KOSKI: Can I change my vote?

DR. EDWARDS: Absolutely.

DR. KOSKI: Okay.

LT. MOSADDEGH: That is a no, Dr. Koski?

DR. KOSKI: Yes.

DR. EDWARDS: Dr. Cox, where would you like to go next?

DR. COX: I think we are almost there. I am just wondering if we can just--we have heard some about DNE with regards to some ideas in other studies. I don't know if there is anything else that people want to say to that issue, and then,

No. 3, I think we have also heard some thoughts but we might want to hear a little bit more about exactly what people would want for ABS and ABECB if there was desire to further pursue that.

Question 3

DR. JENKINS: In particular, for No. 3, you have recommended that it not be indicated for ABS and acute exacerbations of chronic bronchitis. So if the company were to do the superiority studies that we heard recommended earlier and prove that this drug works in those two indications, is that enough to tip the benefit/risks in a favorable direction? If it is not, you can question why they would bother to do the studies.

DR. EDWARDS: Let me actually ask that question and we will go around. I am not going to rephrase it. The question is, just as Dr. Jenkins stated.

Dr. Smith.

DR. J. SMITH: Yes.

DR. EDWARDS: Dr. Townsend.

DR. TOWNSEND: Yes.

DR. EDWARDS: Dr. Morris.

DR. MORRIS: Yes.

DR. EDWARDS: Dr. Proschan.

DR. PROSCHAN: I am sort of on the fence on this one. I probably would say yes, but--I guess I will go yes.

DR. EDWARDS: Great. Dr. Leggett.

DR. LEGGETT: Yes, just like before.

DR. EDWARDS: Dr. Bradley.

DR. BRADLEY: Still yes.

DR. EDWARDS: Dr. Follman.

DR. FOLLMAN: I would say probably yes, but I think it would also depend on the magnitude of the benefit of the drug over the placebo. I can't just say, get a huge study and get a small p-value and there is no difference, really, no substantial difference that it would be good evidence.

DR. EDWARDS: My answer is, as a general concept, yes.

DR. EDWARDS: Dr. Koski.

DR. KOSKI: Yes.

DR. EDWARDS: Dr. Smith.

DR. M. SMITH: Yes.

DR. WIEDERMAN: Yes, but I would want to see the number-needed-to-treat calculations.

DR. EDWARDS: Dr. Levin.

MR. LEVIN: Yes, again qualified by what the evidence said.

DR. EDWARDS: Dr. Cox?

DR. COX: I think that helpful. I will turn it back to you but it seems like we have gotten through the major questions here, the major issues.

DR. EDWARDS: Okay. Actually, in the last portion of these questions, there is a tremendous amount of decision-making process and so forth that goes on. But I think, within the limits of our meeting today, this is about as far as we can get with it at this point.

Dr. Levin, you had a comment?

MR. LEVIN: I would just like to thank the chair for his job in organizing a very difficult and complex meeting.

[Applause.]

DR. EDWARDS: Thank you very much. I appreciate that. I would like to thank everyone involved with this meeting. This, again, was really an extremely difficult process for us all. I know everyone appreciates the difficulty. I appreciate the 13 pounds of reading material--I actually weighed it--that we have all been through, and the staff who supported this meeting.

I need to give special credit to Lt. Mosaddegh who has done a tremendous amount of work.

[Applause.]

And I also wanted to thank very much Alice Toigo who is our transcriber who has been working very hard for two days.

[Applause.]

Thank you, again, for all the presentations and all the deliberations and we are adjourned.

[Whereupon, at 5:15 p.m., the meeting was adjourned.]

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