efficacy for Ketek. In particular, how much should I weigh those recommendations of the panel? Should I just believe them? Or should I make my own decision?

DR. JOHANN-LIANG: You are talking about the FDA regulatory briefing slide that I was showing?

DR. FOLLMAN: Yes.

DR. JOHANN-LIANG: Regulatory briefings are held internally usually with senior upper management like Dr. Jenkins and Dr. Kweder. So perhaps I will defer to Dr. Jenkins as to what this is.

DR. EDWARDS: Dr. Jenkins?

DR. JENKINS: I can get us started on this. I tried to address some of this yesterday because, as part of the process of evolution of science and regulation, new products meet standards that are different from what was met by products years or decades ago.

An example, I think I mentioned yesterday, would be on the Cox-2 nonsteroidal side, it is

highly unlikely, if not totally unlikely, that we would approve another nonsteroidal agent today without a cardiovascular outcome study. But the old traditional NSAIDs don't have a cardiovascular outcome study. We have not attempted to try to make them do that because it brings up issues about our regulatory authority to do that. But they all got a black-box warning about the potential for that.

On this question, maybe a way you could think of looking at this is, keeping in mind what Dr. Cox presented, all the available antimicrobials that are approved for these indications were approved based on noninferiority studies.

So the level of evidence for all the products is equally suspect. If you suspect it for Ketek, it is equally suspect for all of them. If you conclude that the risk of Ketek is equal to the risk of all the other comparators, maybe that would be something you would decide not to concern yourself with at this meeting.

On the other hand, if you conclude that

the risk for Ketek looks worse than the risk of the comparators, you may think, in your mind, well, it looks worse and I am not so sure about the evidence that it actually works. So that may play into your decision as well. That would be one framework I could suggest you think about because, as Dr. Cox said, we are not here to readjudicate and go back and discuss what to do about all the antimicrobials who have this indication. That is the course of natural history of regulation.

As I said yesterday, we usually go back and look at those only if something arises to pull it out of the queue, so to speak. The reason we are here with Ketek is to ask you, does the safety profile for Ketek pull it out of the queue such that you think it is less safe than the other available therapies that make you think that we should do something different as far as how we regulate Ketek compared to the other available therapies.

Hopefully, that helps clarify it some.

DR. FOLLMAN: Yes; that is helpful.

DR. EDWARDS: Let me, though, ask--you are suggesting--you just emphasized the safety but, in our instructions, we have been advised to consider the efficacy in light of the newer discussions on noninferiority trials. Is that not correct?

DR. JENKINS: I thought I tried to touch on that as well. We certainly want you to be aware and consider, as you are going through your discussions, the uncertainty that exists about the benefit of Ketek and all the drugs that are approved for sinusitis and acute exacerbations of chronic bronchitis.

I was just trying to make the point, Ketek is not unique with regard to those concerns about what the benefit is. It is really your task to help us understand, given that information and considering what we know about the safety, does that rise to the level that you think Ketek should be treated differently, meaning do you think it shouldn't be available for one or more of these indications.

Maybe you will even want to give us some

advice at the end of the day about other drugs that you think we should go back and look at in this list. I think there were 12 and 18 drugs on the list.

DR. EDWARDS: John, before I go to you, if I could just ask Dr. Johann-Liang a question. I am reflecting on your slides with the colors. During your presentation, you made some comments that led me to come to the following conclusions which I would like you to help me with, whether they are valid or not.

There is a signal for hepatotoxicity with telithromycin. What I am not entirely clear about is whether that signal has actually occurred at a time in its introduction to clinical use earlier than the signal which has occurred with other comparable antibiotics.

I believe that you said that it has but I would appreciate your either affirming that or correcting me.

DR. JOHANN-LIANG: Okay. The other drugs that are currently--if we are looking at Warnings

and Precautions Section, those are usually safety issues that we have had some discussions about, some analysis on. Usually, everybody agrees that things go into the label. So, if we are talking about hepatotoxicity, the other antimicrobials of interest are really--and now I am expanding the comparison from what I had said on the talk which was pretty narrowed to what I discussed, drilling down.

I am now expanding because that seems to be the interest. Augmentin would be a drug of interest. It is labeled with issues with hepatic dysfunction. There are cases of hepatic failure. I know that there have been data-mining talks to show the level of score, et cetera.

The level of review that goes into looking at--and you have seen how the Ketek hepatotoxicity cases were reviewed. That level of review has not been done for Augmentin. So it would be hard for me to tell you exactly, let's put the numbers and let's compare it side-by-side.

Given that, Augmentin, as I said, has a

huge denominator history just because it has been in the market and it has been used so much. The understanding, the general understanding, of the liver issue with Augmentin, and hepatology experts could jump in if you want, is that if it is more of a--there is more a component of the cholestatic picture to Augmentin.

It is not considered generally that, after the first or second dose, that you would have such severe clinical deterioration. The other class that we consider in this comparison would be the other macrolides. Those macrolides are labeled also for hepatotoxicity and we have heard discussions about the comparison to clari on the epidemiological study that has been done.

It is of great interest to us. We would like to review that data ourselves and really try to understand what that all means.

However, again, that kind of analysis has not been done for clari. The only analysis that we have truly done where hands-on review of each of the individual cases was done is what Dr. Brinker

presented against the other fluoroquinolones.

Fluoroquinolones' hepatotoxicity is, I think people are aware, that there is a hypersensitivity component to the fluoroquinolones. So, if we had to say what is the clinical manifestation comparison of these drugs, Ketek behaves most closely to other fluoroquinolones in its hepatotoxicity.

What are the comparative numbers? I think Dr. Avigan just talked about that 23 to 6 between moxifloxacin and Ketek for the regular reporting rate.

We have not looked at moxi in the analysis that Dr. Graham had done which accounts for person time. As I said, the only other antibiotic which is a fluoroquinolone that that type of comparison was done is trovofloxacin.

So that is kind of the clinical picture if that is what you are asking, Dr. Edwards, of where Ketek is in regards to sort of the clinical manifestation of the rapid and sudden onset of acute liver failure.

I hope that is helpful.

DR. EDWARDS: I was more asking whether the signal, which has occurred with Ketek, has occurred earlier in its clinical introduction than it has with the other drugs that are used for the indication for community-acquired pneumonia, if we can get a sense for that.

So, again, the question is there is a signal. There is a signal for other drugs as well. Is the Ketek signal occurring earlier than it has for the other drugs? Can we tell that?

DR. JOHANN-LIANG: Our general sense is yes, that it is, that is it most comparable, probably, to the hypersensitivity-type of hepatotoxicity that we are seeing with quinolones.

DR. DAL PAN: I think you are asking how soon after marketing--

DR. EDWARDS: That's correct.

DR. DAL PAN: That is the question you are asking.

DR. EDWARDS: That is the question.

DR. DAL PAN: Do you know the answer to

that?

DR. COX: Allen may be able to talk more, but Trovan, which had a number of indications and had fairly quick market uptake after it was approved, the signal there appeared soon after marketing. Mark, do you want to add a little more?

DR. AVIGAN: I was just going to say yesterday I introduced or mentioned the iceberg concept of signals. As you recall, the initial liver signal for Ketek was actually seen in the clinical trials before it was approved.

There were two cases and one in particular that Finnish gentleman where he peaked his ALT at 30 times the upper limit of normal, had a mild hyperbilirubinemia and there was eosinophilia infiltration in the biopsy and circulating eosinophils with no other causality that could be assigned other than Ketek.

So the most precise answer is that the signal was actually seen in the clinical trial.

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

DR. BRADLEY: I would just like to go back to Dr. Jenkins' comment a little earlier on the evolution of how we view efficacy because I think yesterday, when I asked the question and he had an outstanding response that actually covered both current and past issues, I have been trying to put that in the context of the discussion today.

There is clearly a difference in how we view efficacy for rapidly spontaneously resolving infections. Three months ago, the agency first evaluated publicly with the committee sinusitis with one of the fluoroquinolones and the bar was raised three months ago to say, in order to properly evaluate efficacy, we need a superiority trial.

I think we were all together pretty much at that time. Once one makes that decision that, in order to evaluate efficacy, you need a superiority trial, then there is no way you can't go back and look at all of the other drugs that are on the market for sinusitis.

The field has evolved, as you pointed out,

and, to grandfather in drugs is to say toxicities of drugs, of older drugs that are already approved, need to be evaluated differently and a toxicity for a drug which shows no efficacy is acceptable whereas now you need to show that you are actually putting together an appropriate benefit and risk because going forward we know that the benefit is there.

That inconsistency, I have a difficult time accepting. So I think where, three months ago, the genie was out of the bottle, the decision that, in order to evaluate the efficacy, we have a new standard. I don't know how we will get there but evaluating drugs for sinusitis and acute exacerbations of chronic bronchitis and otitis media, in view of what we know now, seems to be inevitable.

In our trying to assess a risk/benefit, we need to know what the benefit is. Whether one says, okay, 24 months from now or 36 months from now, everyone needs to come back to us, or the NIH needs to provide money or Congress needs to provide

money, but we need to all have a level playing field and every drug out there for sinusitis needs to demonstrate efficacy so we can judge for each drug that we treat sinusitis with that the risks justify the benefits.

So what I am looking at, as you ask me whether telithromycin is worth the risks or worth the benefits, I don't see that these risks are too disproportional for other drugs that are out there for sinusitis and acute exacerbations of chronic bronchitis.

But then is the risk worth it? I can't answer that question because, in view of where we are now, we can't answer that question. You have asked a question we can't answer.

So, back to you, Dr. Jenkins.

DR. JENKINS: Welcome to working at FDA. Is there a question there?

DR. BRADLEY: The question is is there any way the agency can, instead of grandfathering in these things, go back to the way the Kefauver-Harris Amendment was done and say, we now

have a new standard everyone. This is the standard. Every drug marketed for sinusitis needs to meet the standard and you need to meet it by such-and-such a date.

DR. JENKINS: We could certainly explore the options on how we would proceed with that type of a process. Clearly, the time that we have the most ability to get the data that we want and expect is before approval. That is the reason we have the most leverage. After drugs are on the market, it gets much more complicated in assessing what regulatory authority we have to require the studies, who we are requiring the studies of.

For example, Ketek, it would be pretty clear who you would be requiring the studies of. What about ampicillin? Who would we be requiring conduct the studies of ampicillin. There are probably tens, if not hundreds, of generic manufacturers of ampicillin.

You mentioned Congress and you mentioned NIH. You start getting into issues about who is actually going to do those studies, who is going to

fund the studies for the older antibiotics. So it becomes very complicated to accomplish.

DR. BRADLEY: The NIH is funded and the study section meets next week on generic antibiotics for treatment of community-acquired MRSA. So there is a way.

There are also, I was made aware, package label changes that there is an asterisk that can be put on groups for drugs for specific indications to say, the data collected in noninferiority trials may not prove efficacy, or just something generic like that.

DR. JENKINS: We definitely hear your concern about a fair level playing field for all the antimicrobials that have the indication and we will take that back and put on our thinking caps about what approaches there might be to get the level of evidence that we would like to have today for all of those products.

But I can assure you it will be a very complex endeavor and maybe similar to me trying to climb Dinali.

DR. BRADLEY: You could do it.

DR. EDWARDS: Thank you. Dr. Proschan.

DR. PROSCHAN: I think that noninferiority trials have been criticized and I don't like them for other reasons that what have been brought up today. I think some of the criticisms today are a little unfair. In fact, Dr. Liang's--one of the slides, I think is just wrong, basically, and that is the one that showed the line going through and all those trials.

The implication was that, if you had done a noninferiority trial that ruled out .10 and you had that other confidence interval for the test versus the control, that those two interventions overlap, that that would not be evidence that there was a difference between the test and placebo. That is just not true at all.

If you had gotten that result, then, if you had done a superiority trial of the test versus the placebo, it would have come out highly significant. So I think that is just not--I think there has been a false impression of the fact that

noninferiority trials are somehow so much less reliable.

Also, the reproducibility issue got brought up and the implication there was that a superiority trial is more reproducible. Again, that is just not correct. If you do a superiority trial and you do it at alpha equals 0.05, and let's suppose you reach that p-value, p equals 0.05. There is a 50 percent chance that, if you repeated that trial, it would not come out significant the first time.

So I think there is a false impression about how much better superiority trials are. Having said that, I still don't like noninferiority trials for, as I said, for other reasons because things that would hurt you in a superiority trial are actually benefitting you in a noninferiority trial, namely if you switched to the opposite drug, that is going to bring the two rates closer together. So you are actually, in a sense, being rewarded for something that is bad.

That is the reason that people like to do

per-protocol analyses in noninferiority trials. The problem with that is that is not a randomized comparison anymore.

So I think there are problems with noninferiority trials but I think the problems that have been brought up today have been somewhat exaggerated. The situation is not quite as bad as what was presented, I think.

DR. JOHANN-LIANG: I would like to respond to that. Let me backtrack. So the last point you made about--I wasn't trying to say superiority trials are just better in general. The only thing is that it is our legal requirement to say, when you are providing substantial evidence of efficacy, you need to show that taking the drug helps you over just not taking anything at all or a sugar pill.

So, in noninferiority trials, because there is no concurrent negative control, we are not assured that that is actually happening. That is the only point. Whereas, in a placebo-controlled trial, of course, trials vary. Placebo-controlled

trials vary from one trial to another.

That is what that graph is trying to show. But at least there, in that test condition, taking the drug by whatever measure of efficacy you have, shows that it helped the patient over not doing anything at all. So that is the only point.

Regarding what you are talking about, reproducible and reliable, I am not talking about noninferiority trials. I am talking about the placebo-controlled trials that you would assess to figure out what the margin is.

You need consistent and reliable sort of falling out of the placebo-controlled body of evidence to be able to say, okay, we have an historical margin that we can use as sort of the historical concurrent control for your noninferiority trials.

So I think that that point--thank you for asking again so I can clarify.

DR. EDWARDS: Dr. Shapiro.

MS. SHAPIRO: I am not troubled by the notion that there may be a better way to assess

benefit. I am not commenting on whether noninferiority trials are okay or not because I am not qualified to do that.

But if that were the sense, I don't have a problem imposing something else at this point and not going back and redoing all the approvals that we did in the past aside from impracticality concerns. I kind of like the approach that Dr. Jenkins has thrown out about, well, if there are problems going forward, we would.

The analogy is in clinical practice, in standard of care, and malpractices cases. We always see standard of care as determined by judges improved. So there is a famous case about the glaucoma test. For years and years and years with certain signs and symptoms, even though it was available, it wasn't done. So doctors who would be sued would say, well, my colleague isn't doing it. Standard of care doesn't require me to do it.

Then a court said, well, they may not be but we are going to now, going forward, require this because it is the right thing to do. They

didn't go back and round up all the doctors who had gotten off scott free who didn't do it when it was available. But, going forward, this is how medicine, research, drug development, gets better.

So I don't have a problem with that.

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

DR. M. SMITH: I am a lowly community doctor in many ways. Hearing the discussion sort of makes my head spin. But I kind of want to bring back our charge and that is to try to make a decision amongst--because we could argue forever.

One of my concerns in hearing all this discussion is I think myself and several other people on the committee get to see what actual practice of antibiotics is. When you see what happens once a drug is released, I think our charge, really, is much more thinking of the people who are not going to read the package insert and the drug is going to be used in people who don't really need the drug.

When the evidence here--I guess this is evidence--talks about noninferiority, and you are

talking about relatively--and I don't want to negate people's symptoms--that these are relatively benign diseases except for community-acquired pneumonia. You are talking about giving a drug that, from the evidence that I hear, does sound to me like there is early evidence of significant hepatotoxicity.

When I think about using this drug, I would put this in a category where it would be my third tier or fourth tier. In my own mind, I would put a black-box warning on it that this is an alternative when I have nothing else.

So if we are going to vote, and I think we should try to push everybody to do that in a reasonable time, I would say that this is a drug that we need but this would not be something I would reach for. And this would be something I would discourage people from using.

DR. EDWARDS: I would like to hear Dr. Leggett comment on that, on your comments.

DR. LEGGETT: I concur, in a sense, with what she said. I have yet to use Ketek for exactly

the reasons that I had heard about in prior committee meetings.

Doctors don't read those letters that get sent to us. We get five a day. So either it is a black box that makes the pharmacist anxious to give the drug out or nothing else is going to be effective if the goal in continued use of the drug is to limit it to where it is actually needed.

Those are sort of the comments that I would say. On the other hand, I am not convinced from the data yet that the hepatotoxicity is out of the range of the stuff I have seen with other antibiotics, especially Augmentin and the fluoroquinolones, even though they aren't.

MR. LEVIN: Would you clarify that? In terms of the rapidity of onset, is there anything unique that you see you think is going on between older drugs and this drug in your experience?

DR. LEGGETT: My experience is that sort of statement is as good as the surgeon's research experience. I have seen a case. I have seen a series.

DR. EDWARDS: Dr. Norden, you wanted to follow up on those comments.

DR. NORDEN: I did. I wanted to follow up particularly on Dr. Smith's comments which I really agree with probably more forcefully than Jim. I think it is good that we are dividing up the areas. I would just, for purposes of trying to clarify my position, without being a hepatologist, I am reasonably convinced that there is significant liver toxicity with this drug.

I was particularly taken with the DILIN study and the methodology of doing it. I can't say whether it is more than with other agents but it does seem to me to be very rapid.

So if you look at the three indications and you start with that as a premise, there is some toxicity apart from the loss of consciousness which I think is another issue.

Community-acquired pneumonia, I thought Dan Musher gave a lovely talk. I think that it is a disease, you can make a diagnosis reasonably clearly. It is not just based on symptoms. We do

have resistant infections, resistant pneumococci. I think that Ketek offers an alternative. I wouldn't necessarily be my first choice but I think it ought to be preserved for that.

The other two diseases, AECB and sinusitis, Dr. Sethi also gave a lovely talk but the people that are being treated for acute exacerbations of chronic bronchitis in the real world are not the kind of patients that he is describing who are very sick. These are mild to moderate at best that are being done in clinical trials and that is what we have the data for for Ketek.

So, for me, for both of those two, sinusitis and AECB, the risk of the drug seems to me to make it not appropriate to keep on using it for those. That is probably the way I am going to vote unless I hear something different that convinces me differently.

DR. EDWARDS: Just to add to those comments. There is a study which has been done by a third-party payer which indicates that

approaching half of antibiotic prescriptions in the U.S. are done over the phone rather than the patient being seen by the physician.

The actual proportion is quite astounding from this study. I haven't been able to critically review that study but it is available for that critical review. It adds to the concept of exactly how the drug is used is not necessarily going to result in a very careful selection of exactly the right patients with the indications that we are concerned with today, especially related to sinusitis and bronchitis.

Dr. Proschan, you had another comment.

DR. PROSCHAN: It seems to me the comparison that is most relevant, I think--I agree completely that it would be great to see whether any of these drugs are better than the placebo. Here is the problem. A patient comes in to the doctor--I mean, nobody is going to get this drug without seeing a doctor; right? It is a prescription drug--oh; it is not true?

DR. EDWARDS: Absolutely not.

DR. PROSCHAN: Without a doctor's approval; okay. Sorry. So the doctor that either sees the patient or talks to the patient or whatever, that doctor is not going to prescribe a placebo. That is just not going to happen. So the question is, are you better off prescribing this drug or having the doctor choose a different drug.

So, in a sense, the most relevant comparison is between drugs. I think it would be great to find out whether all these drugs are better than placebo but, at this point, I don't think you want to take all of them off the market. So I think it is very hard to single Ketek out so I think the relevant comparisons between Ketek and other drugs that are available right now.

DR. EDWARDS: Dr. Bradley.

DR. BRADLEY: I just want to give a perspective on how we use drugs in medical practice. The FDA has presented data from a sponsor on the drug and an indication, organisms, and the FDA will or will not approve the drug for those indications.

The FDA, and this is my understanding and please correct me if I am wrong, isn't in the business of recommending medical practice to the physicians in the United States but they clearly frame the use of drugs based on the information that is presented to them and the recommendations, actually, that go out to physicians for use of the drugs come from organizations like the Infectious Disease Society, the American Thoracic Society, the American Academy of Pediatrics, the American Academy of Emergency Physicians, any number of professional groups.

So putting limits on the use of the drug, not having this drug be the first drug that you use if you have got a particular illness, falls on professional organizations which should limit. Actually, Dr. Powers showed a few recommendations where it said this drug should not be used.

So the FDA reviews the data that is presented to them and then how the drug is used tends to be molded by peers who then are supposed to be able to influence practice on a local level.

DR. EDWARDS: Dr. Levin.

MR. LEVIN: Two things. One on the issue which has been discussed around the table of sort of how do we deal with the grandfathering issue and sort of a view that we have to--our responsibility is to sort of equitably treat all products in the class, or in the classes or the family.

That is not the way I see it. I don't think that is our responsibility. If there is a problem between industry and the agency as to what the guidelines are, what the ground rules are, I think it is for them to resolve that.

Our charge is somewhat different. I think the example of the coxibs is somewhat instructive in that there was an action taken against two Cox-2 drugs despite the fact that everybody recognized that there may be C.V. problems with all of the Cox-1 and the Cox-2 spectrum of drugs. But that didn't negate having to take an action based on what we knew.

When you are talking about the public interest and the public health, I think it is

simply sort of avoiding the responsibility that we have to say, well, because we haven't done this level of investigation of older products and we can't say that they are any safer or any more efficacious, our hands are tied and we can't act now.

We owe it to the public to tell them what we know about this drug at this time and to act accordingly. So I think that is what should guide us.

Now, to bear my soul on this where I am troubled and need help is the argument has been made that this drug has some unique benefit in terms of the resistance issues. So I would like to be better informed than I am at the moment as to what evidence we have in clinical practice that that is true.

DR. NORDEN: I will try and respond to that, and others may be better able to including some of the people who spoke before, not from the panel. But most of it is anecdotal. It is as you heard. Patients who have an organism that is

resistant who are being treated with the drug to which the organism is resistant and who don't do well, and that is the anecdotal--someone else did present some data showing a comparison, that patients who were treated with a drug to which the bug was sensitive did do better than patients who had a resistant organism.

Dr. Wiederman, can you help?

DR. WIEDERMAN: I was just going to bring up--it has been presented but maybe it needs to be restated or emphasized, pneumococcal disease is decreasing in this country, although my friend Dr. Musher has almost seemed to blame pediatricians for quinolone resistance before we are even using it.

But it remains to be seen whether another pneumococcal serotype will emerge in the numbers that will increase pneumococcal disease but, right now, not only in children where it has been dramatic but even in adults, as we saw on those slides, there is less pneumococcal disease.

I don't know how to predict what is going to happen. It takes someone smarter than I. So I

think we have to keep that in perspective, too, when we are talking about resistant pneumococcal disease. How many people are going to be affected? How many people are going to be helped? How many people are going to be harmed, whatever decision we make?

DR. EDWARDS: Dr. Hilton.

DR. HILTON: So far, we have largely been talking about comparative success rates in terms of points in time, like at 17 to 21 days, so say 85 percent success rate in both groups.

But I was looking back at a slide shown by Dr. Ferguson. She was evaluating patients with ABS and comparing placebo with penicillin and amoxicillin. Basically, the median response rates, so the median time to response, was 10 days in the placebo group and was 5 days in the others.

So, really, what success means for an effective drug in this setting is your symptoms diminish in 5 days instead of in 10 days. So I am asking myself, am I willing to take on these risks for 5 days of symptom relief. Am I willing to wait

5 more days and feel kind of crummy or--it seems that the adverse events are hitting people very much at random. There are 22-year-olds with no prior history of anything.

So, especially in the ABS and chronic bronchitis, for myself, I would not take that risk.

DR. EDWARDS: Thank you. Dr. Heckbert.

DR. HECKBERT: Thank you. I would like to make a few comments about the safety data as a member of the Drug Safety Committee. It seems to me that what we have with all the presentations that we have heard today and yesterday actually does give a fairly, to me as an epidemiologist, remarkably consistent picture of the risks.

From the preclinical studies, we had a signal about possible hepatotoxicity and visual adverse effects. We had early reports from overseas about exacerbation of myasthenia gravis. Then the system that is put in place to tell us about very rare adverse effects, which is the AERS system, that system did its job. It actually--in the data-mining analysis, it showed us exactly

those three adverse effects plus the loss-of-consciousness adverse effect.

We saw some reporting rates which are calculated both per million prescriptions and per million or per ten million person years. So I think the AERS system showed us some clear signals of adverse reactions. There is no doubt in my mind about that.

I think what is more difficult to decide is is this greater than for other antibiotics or is this greater than for other drugs. As an epidemiologist, the idea of using person years in the denominator is perfectly natural to me and makes all the sense in the world. It is exactly the way I would have done the analysis if I had been asked.

If those are the numbers you are looking at, then telithromycin has a considerably higher reporting rate for hepatotoxicity than trovofloxacin and triglidozone, both of which are off the market for hepatotoxicity.

So I think, in view of those facts and the

issues that Dr. Smith described so well that we see how this drug is being used in the community and we also know that doctors don't read labels and patients don't read labels.

I think, in the interest of public health, we need to consider that we have a drug with some serious safety problems here and that we need to take these issues seriously.

DR. EDWARDS: Thank you. Dr. Cox.

DR. COX: I just wanted to follow up on Dr. Bradley's comment and then just make a couple of other comments about some of what we have heard.

The first issue with regards to the label, what is in the label describes how the product gets used in that fashion, can be safely and effectively used. We do hope that that information does influence clinical practice. The practice of medicine is something we don't regulate and certainly professional guidelines are written and described, different recommendations from professional societies as to how they recommend people should use drugs.

But the label, we think, has a role for finding information to inform those that are out there making those decisions in their practices.

The other issue with regard to resistance, with community-acquired pneumonia, there is wording for multi-drug resistant Streptococcus pneumoniae. We had discussion about this previously. It is not something where they have shown superiority but what we have done is looked at data from strains that are resistant to commonly used drugs to treat Streptococcus pneumoniae in the respiratory tract and they have shown evidence much like we would add an organism to the label or within an indication, that the drug is performing similarly in those groups of patients who have resistance organisms as to those that have susceptible organisms.

We are also looking for a good body of evidence that it works well and if there is enough information to know that the drug works well in Streptococcus pneumoniae, so a comment on the issue of the resistance issue.

Then one other thing that I just wanted to

comment on that we have heard some about is the issue of second-line therapy. That is something that we do, sometimes do. The tricky thing is wording that correctly so that that doesn't leave the impression that the drug is more effective and that is why you should hold on to it.

If, in fact, it is concerns about toxicity that would lead one to put the drug in the situation where you wouldn't jump to it as the first agent, describing that and carefully wording it appropriately so that message is communicated can sometimes be challenging.

DR. EDWARDS: Dr. Proschan.

DR. PROSCHAN: To me, the big safety issue, I think, is not liver because I don't think the evidence has been all that convincing that this drug is worse than other drugs, other antibiotics, in terms of liver.

But what bothers me a lot is actually the blurred vision, the fact that a patient could have an accident while driving a car, because I certainly, as a patient, never read those labels.

First of all, they are too small a print. I probably couldn't read it even if I tried. And, if I did read it, I would say to myself, of course, they have to say that. If that happens in any of a million people, they will have to put that in a little thing.

I would never think, oh, wait a minute. One out of 100 people gets this? Of course, if I take an antibiotic, I am never going to think that I am going to have blurred vision. That, to me, is the biggest safety issue. It is not the hepatic because I really don't think the evidence was that strong to show that this is different from other antibiotics.

DR. EDWARDS: Thank you. Dr. Townsend.

DR. TOWNSEND: Actually, I have a couple of questions about efficacy for the sponsor. I am trying to sort of decide how much telithromycin sort of adds to what we already have here and how much we can use the data that we have to assess its efficacy.

So one question I have which is kind of

unfair but I am going to ask it anyway. Clearly there are problems with Study 3014 mostly associated with improper conduct at the sites. I am just wondering if there is any overlap between the sites that were conducting the previous studies that we actually have some efficacy data on with the sites that were associated with 3014.

Again, it is unfair, but if a lot of the sites that were associated with the previous data were sites that were associated with 3014 with all the problems that were there, I would be a little bit worried about trusting the data coming from those sites.

The second question I have is, again, trying to decide if telithromycin adds significantly to our current armamentarium for trying to decide if the risk is worth the benefit, if it had a significant benefit other antibiotics don't have, going back to what Dr. Smith was saying, it would be worthwhile taking the risk.

One of the considerations would be is it really effective, more effective, against resistant

drugs than the current drugs are.

There was a study that has been conducted, or it still may be ongoing, 4003, to look at the drug-resistant Streptococcus pneumoniae but I don't know if we have any data on that. Again, if we had something to tell us that telithromycin is so much better than other drugs for these drug-resistant pneumococci, that would be a point in their favor.

DR. EDWARDS: Mark Moyer, would you care to respond to that question about the sites.

DR. MOYER: Regarding the sites, no; they were not. That was a usual-care study in which community physicians that are not typically engaged in Phase III clinical trials participated and, in our Phase III trials, they were completely different physicians that typically do participate in Phase III trials and knowing how to correctly conduct those.

The other one, I would ask Bruno Leroy to come forward to address the other question that you have regarding 4033, was it?

DR. LEROY: I don't think that 473 was

intended to look for superiority in resistance. We have performed two Phase IV studies with an intent of superiority. I can show you those data if you are interested.

DR. MOYER: Those results have not been submitted to the FDA at this point and we would need to ask permission if we are going to show results such as this because they have not had any submission of this at all.

DR. COX: It is okay to show those results. We also need to note that they haven't been submitted to us. We haven't had a chance to review them yet.

DR. LEROY: We performed one study to try and address the problem of performing, conducting, a superiority trial in pneumonia. Slide on.

[Slide.]

This was an open trial comparing telithromycin versus what was the standard of care in a country of high-level resistance which is one of the designs that we can think of. It was comparing open-label parallel-group comparative.

It was conducted in Greece. You recognize those countries with high-level resistance. Clinical efficacy at test of cure was the primary endpoint.

We had some precise calculation looking for a difference of at least 10 percent delta.

[Slide.]

These were the results. They happened to be significant but it was not a 10 percent difference although it was significant. There were limitations in these trials to conclude on the superiority but the significance was not reached in a true, complete ITT analysis when we put back all the patients. It was--I don't know if we have this value in the next slide.

No; we don't. We can put back the former slide and then go to adverse events.

These were the results. The significance was around 7 percent. The other limitation is that you cannot extrapolate the standard of care of one country to the other countries. The last limitation was that it was stopped after the third--it took two winters to recruit the patients

and it was stopped before the third winter just before having reached the number of patients that was initially planned in the proposal, not very far away but--so, next slide.

[Slide.]

So here what we can see about the drug really is its profile. This is a drug that looks to be really effective on S. pneumo. It seems to be no discussion from the data, even if there are limitations. Consistently, it is effective against S. pneumo.

What it didn't show here is it didn't show anything on S. pneumo resistance. First, it is difficult to find discordant treatments so we were unable to show anything on S. pneumo resistance in this trial.

So, on the one hand, interesting data. On the other hand, we cannot show, I would say, a compelling information. That would be one study.

[Slide.]

Another trial that was trying to address in an acute exacerbation of chronic bronchitis,

this was a different type of approach. It was trying to show exposing a large population--we were trying to develop a model, sort of an epidemiological model, of, when you expose to telithromycin in a certain disease where you can have infection and colonization by S. pneumoniae, what do you end up having further down the road and you compare three treatment groups.

So we have performed, and it was completely hypothetical superiority trial comparing telithromycin versus azithromycin versus cefuroxime axetil. This is 1.4,;1;1 ratio. The initial sample size of approximately 5,000 patients based on the hypothesis of 10 percent carriage of S. pneumo and 50 percent less carriage in the telithromycin group.

We were looking at what we called PERSp which is penicillin and/or azithromycin-resistant S. pneumo, Streptococcus pneumoniae. So it is a mixed bag of both just to see if it was different.

[Slide.]

So the primary endpoint was to demonstrate

the superiority of telithromycin in decreasing the carriage rate of PERSp at test-of-cure visit over azithromycin and/or cefuroxime axetil.

[Slide.]

This is what was the population included, safety population, 3,900 ITT, 3,800 and astringent SPmTT population that patients with evaluable sputum at conclusion and at Visit 3 or Visit 2 in case of failure treated by an antibiotic.

[Slide.]

So this study was positive. Is showed positivity of superiority versus azithromycin. So this is at the test-of-cure, 12 percent versus 28 percent azithromycin, not positive versus cefuroxime axetil, in this study. But, again, it is a mixed bag here.

We need to adjust this test, in fact, because there was an imbalance at entry of PERSp across treatment groups. So this one is a positive test adjusted and the initial test was also adjusted.

[Slide.]

The other endpoints were for some of them positive. The clinical success rate overall in the ITT population versus AZ. So it is limited improvement but it was significant. It was the overall population. In the patient having this PERSp strain at entry, it was significant. This is at the end of treatment. We looked also at an earlier endpoint.

All this discussion now made us look at the earlier endpoint. The clinical and bacteriological success at test of cure in the patient with Strep pneumoniae at V1 shows a trend for efficacy versus azithromycin, same thing. It doesn't reach the significance of 0.25 in this study.

DR. COX: I just want to state again, we haven't had a chance to review those.

DR. LEROY: I'm sorry.

DR. MOYER: Actually, these results have just been compiled and those have been submitted. So that is why we don't want to go any further because we want the FDA to have the fair

opportunity to review those results.

DR. EDWARDS: Thank you very much. At this time, we are going to take a break. I would like to return at 3:45 and we will begin our voting at that time.

[Break.]

DR. EDWARDS: If there are no pressing further questions, I would like to go ahead now and begin the voting procedure.

Dr. Smith, please go ahead.

DR. J. SMITH: Thank you. I just want to make one comment about the visual changes on a comment that was made earlier about that being concerning. There are many other medications that are associated with vision blurring, accommodative changes. They are not commonly antibiotics.

So there are many medications that you are aware of, decongestants, other medications. So the issue there is educating both prescribers who may be nurse practitioners and people who might be using this that that is the potential side effect of a drug of an antibiotic which gets to this other

issue of education being an important factor, whether the hepatotoxicity has a higher slope so that it is earlier and what that means compared to other antibiotics.

If you don't know about something, it can be more dangerous because you are not aware of the risk. So this is a new drug, a newer drug. So one of the important things about things that get in the community, as Dr. Smith said, is people need to be aware of these things so that they can mitigate risk.

So education of both the prescribers and people that might be using this again with all the issues that people don't read these things, how are we doing to do that--that is a separate issue--I think is critical to impacting safety.

You can't really take education away from safety because if you don't know about it, there is potential risk. So I just want to make sure that people are aware that there are many other medications that cause ocular symptoms.

I am not saying that the dimming is

related to accommodation, and certainly that should be investigated further.

DR. EDWARDS: Thank you very much.

We are now going to begin the voting procedure. What I am going to do is go in the order which we have received from the FDA; that is, community-acquired pneumonia and then acute exacerbations of chronic bronchitis and then sinusitis.

Again, I would like each of the members to give their vote and then to explain the reason they have voted.

Question 1

Community Acquired Pneumonia

We are going to start with pneumonia with Dr. Levin and go around the table this way. We are going to come back in the second voting in the opposite direction and the third voting that way.

You are actually seated intentionally somewhat mixed so that we are not just going to be hearing what the safety people have to say the beginning and then what the anti-infective people

say in that sort of a sequence. So there should be a diversity in our voting.

Again, after we have heard everyone's rationale, there is going to be an opportunity to change your vote. I would suggest that changing one's vote is not necessarily a sign of weakness.

Are we ready. Let me read the question again. "Based on your discussion of whether or not Ketek's benefits outweigh its risks, do the available data support the continued marketing of any of the following indications. Please vote separately for each indication."

The first indication will be community-acquired pneumonia. Dr. Levin.

MR. LEVIN: My vote is no and my reasons are that I have not yet heard compelling evidence of what I think is the most compelling argument and that is the issue of--the importance of this drug relative to the issue of resistance.

DR. EDWARDS: Any other comments you would like to make?

MR. LEVIN: No.

DR. EDWARDS: Dr. Wiederman.

DR. WIEDERMAN: My vote is yes. I am certainly troubled by the safety data and I am troubled by noninferiority trials generally. But I think that is less of a concern with a condition like community-acquired pneumonia. So I lean towards the benefits outweighing the risks for this indication.

DR. EDWARDS: Dr. Smith.

DR. M. SMITH: My vote is yes but I would stipulate a little addendum on that and would say I would prefer to have a black-box warning on it.

DR. EDWARDS: I am sorry, Dr. Smith, but your reason for yes.

DR. M. SMITH: My reason for yes is that I think it looks at least not inferior. I can't say that it is better. By the study designs, I think it is probably equivalent to everything else we use for community-acquired pneumonia but I am worried about the toxicities more than anything else.

DR. EDWARDS: Thank you. Dr. Koski.

DR. KOSKI: My vote was yes. I did that

because I thought that this is a significant infection. I think that one needs sometimes a spectrum of drugs when you have a patient that is not responding.

DR. EDWARDS: Dr. Norden.

DR. NORDEN: My vote is yes for some of the reasons I gave before. I think that there is efficacy in pneumonia, at least as much as in any of the other agents that have been used. I do think that, despite the difficulty proving that resistance is successfully treated, I think there is enough anecdotal data and enough clinical experience to make me believe that it is useful for that.

I agree with Dr. Smith, by the way. I don't know if we are supposed to be putting that in now, but I think there should be a black-box warning also for several things.

DR. EDWARDS: Dr. Marco.

MR. MARCO: I say no. I am very concerned about the risks and I think the risks outweigh the benefits. If you asked me, on a multiple-choice

question, would it be hepatic events, visual loss, loss of consciousness, exacerbation of myasthenia gravis, then I would probably have to say e), all the above. I can't choose one.

So I have to say no. I could see, if this does go yes--I don't know how it is going to go--that I would really want to either see a black box or I would want to almost see it prescribed through something like a registry similar how thalidomide is now prescribed for oral apthus ulcers to where it would have to be under a very controlled setting. But still no.

DR. EDWARDS: Thank you. I vote yes. I am concerned about this safety data. I think we have somewhat limited capability of analyzing it from what we have seen. I am also concerned about the noninferiority-trial design but, again, less so with this particular indication.

The issue with having a drug like this available for those instances of resistance is important to me and I am anticipating that we will see future resistance problems arise for which this

drug may be of benefit.

Dr. Follman.

DR. FOLLMAN: I am going to vote yes on this and I would like to explain my reasoning a little bit. First of all, in terms of the risks, I thought about the liver risk and, to me, I guess the fact that the rate of acute liver failure was 23 per 10 million compared to 58 for a drug that had been withdrawn from the market. I also expect that rate of 23 million is somewhat based on inflating reporting.

It didn't seem so out of line from the other drugs that are on the market. The two large epidemiologic studies that the sponsor provided were really very reassuring to me because they showed that the overall risk was similar for the other antibiotics.

The data mining added little from my point of view. I think that is better for identifying signals you don't know about rather than to try and quantify a risk that is not huge.

The study 3014, you know, I don't want to

get into, like, who did what when, basically. It is a dataset that we don't have. The drug was put on the market for whatever reason and now we have a lot of experience based on its exposure and population.

In terms of the other risks, I am more concerned, really, about myasthenia gravis because, you know, Dr. Koski's calculation of about a risk of 1 in 25 if you have myasthenia gravis, or death, hospitalization, serious medical problem, that kind of caught my eye. Also, I was concerned about the fact that 7 of, I think, 33 cases were in those who didn't know they had myasthenia gravis.

So if we let it out there, it is a small number, 70,000 people, but, still, for those people who have it, this is not a good drug. I just hope somehow, through the communication of whatever, it is not prescribed to those people.

In terms of the benefit, I was torn about whether to think the bar is a superiority or a nonequivalent study. I guess, for this indication, I am viewing it more as a noninferiority study. So

I don't really buy that it works for multi-drug-resistant pneumonia because I haven't seen compelling evidence of that. So that is just a supposition. Some of my colleagues think that maybe it is good enough to get it approved or to keep it labeled for this indication.

I don't really know but I will accept that the benefit outweighs the risk for this indication.

DR. EDWARDS: Dr. Gutierrez.

DR. GUTIERREZ: I vote yes and the reasons I vote yes is tempered by my recognition that we have a real need for new antibiotics that can cover multi-drug-resistant organisms. It is at least not inferior to the other antibiotics that we use to treat community-acquired pneumonia and it does have a theoretic potential for benefit in multi-drug resistant Strep pneumoniae even though I am not totally convinced that that is proven at this point.

I do want to just say a couple of things. First is there have been comments that maybe this should be a second-line or third-line agent. I do

agree with that but I do worry that, as a second- or a third-line agent, it will be used after another macrolide. I think that we really need to sort out the issues of using sequential macrolides. So that would be my concern.

Then my last concern is that, in terms of how physicians are educated, I think the education has to be very broad. It can't be only to certain groups--for example, the myasthenia groups--because I think the people that do prescribe this drug are community physicians. They are pulmonologists. They are allergy immunologists and they may be prescribing for longer periods of time than are recommended.

So those are my comments.

DR. EDWARDS: Thank you. Dr. Bradley.

DR. BRADLEY: I vote yes. I agree with Dr. Edwards and Dr. Gutierrez that the in vitro activity of this drug is unique and particularly unique among the macrolides. The lack of clinical microbiologic efficacy in multiple-drug-resistant Strep pneumo is, I think, more a function of study

design and difficulty in getting appropriate patients enrolled and evaluated accurately.

For many other antibiotics in vitro, activity predicts clinical efficacy and even in many of the package labels which, I believe, actually are quite excellent just as a parenthetical comment.

So, two years ago, when companies were coming for label changes to allow them to market their drugs for erythro-resistant and then penicillin-resistant and multiple-drug-resistant, we discussed the fact that all you need to do is look in vitro at what is susceptible and that giving a drug all of these new claims actually was misleading.

Some of that came up in our discussion that it is not better than other drugs which are active in vitro against the same organism. So I wouldn't change the package label with respect to multiple-drug resistance unless you took everyone's multiple-drug resistance claims away which I believe, actually, would be a more fair thing to

do.

With respect to toxicity, I very much appreciate Dr. Brinker's analysis. When he mentioned that they are keeping an eye on this acute liver-failure rate and, if it jumps from 23 per 10 million to 58 per 10 million, that they would do the same thing that they did with trovofloxacin. I thought that was excellent and I very much appreciate him keeping an eye on acute liver-failure rates.

Thank you.

DR. EDWARDS: Dr. Leggett.

DR. LEGGETT: John, were you just trying to be invited back with that labeling stuff? For this kind of meeting, I don't think I would want to be necessarily.

I vote yes. My comments about a second or third line, those were my personal prescribing habits. I don't hardly ever use a new drug until after it has been on the market for six or 12 months or I have had experience.

I assumed several things about efficacy.

I assumed clarithro was as effective as other treatment as was suggested. I don't think we need to withdraw its approval for community-acquired pneumonia because we have already, at the last meeting, recommended that it was efficacious where we had much more data than we were able to go through here.

I think one could make an argument for consistency going forward for the FDA as much for their own ability to get things done as for anything else. I was persuaded by the going-forward legal example given during the talks.

In terms of toxicity, I am not impressed with the uniqueness of the hepatotoxicity for the following reasons. The DDRE example about having not met the bar, I agree with. If all drugs such as antibiotics are given for five days, which is the practice now for community-acquired pneumonia, or seven, then using person-time analysis doesn't make any sense. It is superfluous because everybody has got the same time. So I didn't really buy that switch in the New England Journal

article.

Then the comment was made by the hepatologist that a drug hepatotoxicity can mimic any other type of hepatotoxicity. Well, then, the vice-versa is true that all the other types of hepatotoxicity can possibly mimic telithromycin or at least some of the time. So I wasn't convinced that all of these episodes are clearly telithromycin.

I am not particularly worried about the blurred vision because we have already had 60,000 cases in the United States given the 6 million prescriptions and I haven't heard a lot about things going on.

Then, in terms of the loss-of-consciousness issue, it was noted here that it was very heterogenous. I don't know what to make about a very heterogenous toxicity that could have many, many causes all of which, in terms of those particular reasons, are much lower than is the aggregate. So I think it probably just needs to be studied more.

The toxicity that worried me personally the most is the myasthenia gravis. I don't think I am qualified to tell the FDA what to do about labeling or moving up and down or those sorts of things because we aren't supposed to do that, I don't think. But I would sort of consider doing something about limiting the amount of time that people are exposed to ketolides plus macrolides.

We have already done that in the past for limiting the time to linazolid just in terms of hopefully trying to be proactively--trying to help people.

DR. EDWARDS: Dr. Hilton.

DR. HILTON: I will vote in favor cautiously and hope that, in two years, we don't meet again about this. But I think that a lot of really important questions have been raised like drug interactions and duration of exposure. I do think that, if you don't take some risks, you don't make any advances.

So, in this case, I am going to vote in favor of taking a risk and count on FDA staying on

top of it and guarding the public.

DR. EDWARDS: Dr. Proschan.

DR. PROSCHAN: I would vote yes also. As I said, I am not convinced that, in terms of liver toxicity, that that is really out of line compared to other antibiotics. I definitely disagree with the per-person-year analysis. For example, if one drug you have to take for a year and another drug you have to take for only one day, then the per-year event rate is not what is relevant if I only have to take it for one day.

So I definitely disagree with that analysis which is the one that showed the biggest difference. So I am not convinced about the liver toxicity.

I am convinced about the myasthenia gravis and I am not sure exactly what to do about that because I think strengthening the label is not going to have that much of an effect. I heard people say that the Dear Doctor letters are not read by doctors anyway. So maybe what you have to do is serve something like a subpoena so it looks

like they are being sued and then, inside, it would say, "Do not give this to a patient with myasthenia gravis." Now, I am not sure exactly to do about that but I do believe that one.

To me, the one that there is the strongest incontrovertible evidence for the eye problems, that I think everyone agrees that there is that side effect. I guess people, though, with pneumonia are probably not going to be doing a lot of driving. So I am willing to live with that.

So, based on all those reasons, I would vote yes.

DR. EDWARDS: Thank you.

DR. MORRIS: Are you sure you don't want Ed McMahon to deliver it personally?

I would vote yes as well. I think the physicians on the panel have come up with a lot of reasons about the need for another drug in this area. Clearly, for this disease, there is a need.

In terms of safety, I agree with FDA that you do have this rapid-onset problem. One of the things that the sponsor offered up was a packaging

solution. Of all the offers, that was the one that appeals to me in terms of being able to intercept the patient in a way that they will see it, at least.

We will get into this I am sure in terms of the risk management. I would think, along with a black box, having a design package and an insert in it to further explain it would be an interesting, probably under-utilized, remedy but I would like to see some discussion of that.

DR. TOWNSEND: I would, with trepidation, as with other panel members, also vote yes. I think the efficacy data is adequate to assure me that this drug is at least as good as what we are already using for treating pneumonia.

The safety data is concerning. I am still unsure about whether or not the risk for hepatotoxicity is significantly greater than for other drugs in the class which is the toxicity that worries me most.

I think we can at least make efforts to obviate the risks with the other toxicities,

warnings about myasthenia and warnings about driving, et cetera, for the vision and loss-of-consciousness problems. The hepatotoxicity, I am not sure that we can do a whole heck of a lot if it is really a significantly increased risk. That worries me.

But I think I am willing to risk the lives of the American public and see what happens over the next couple of years. As Dr. Hilton says, I hope we are not here discussing this again in a couple of years.

DR. EDWARDS: Thank you. Dr. Heckbert.

DR. HECKBERT: I found the data on the safety problems reasonably compelling. I think if the hepatotoxicity were the only consideration or the only problem that had surfaced and appeared to be valid, I would have a harder decision. But I would vote no. The reason is because we have not only the hepatotoxicity but the other problems that the other panels have discussed so well. I think, given the whole picture, that the benefits, even for the community-acquired pneumonia indication, do

not outweigh the risks.

As I mentioned, I found the data from AERS which is not perfect, it has many problems that have been well-discussed, but I did find it compelling and I have to say that the epidemiologic studies that were presented by the sponsor, although I think they were very well done and of high quality, they were not big enough to give--they were underpowered to give us a clear statement on whether one agent has a higher risk than another.

DR. EDWARDS: Thank you. Dr. Wong-Beringer.

DR. WONG-BERINGER: Thank you. I would say, for the community-acquired pneumonia indication, I would vote yes. My reason for that is that I think we need a broader option, oral treatment option, for community-acquired pneumonia, particularly in the cases where there is multi-drug-resistant pneumococci involved, not that it is proven to be effective based on the studies or any data shown. But I think there is that

potential and we do need a broader array of oral-treatment options and also to reduce an over-reliance on the fluoroquinolones which now are overly used and have created quite a bit of problems in the resistance arena not only in gram-positive but mainly in the gram-negative bacteria.

I am concerned and I need to acknowledge my concerns for the risk involved with this with the toxicities. I would like to see, in some way, perhaps, that the label can reflect maybe a third or fourth tier of where this drug fits, to be mindful of its toxicities, not so much as in an efficacy standpoint, so either in the form of a black box or whatnot.

I am concerned that the mechanism that currently exists in terms of getting this information out to prescribers and patients, it sounds like nothing really works that well, the Dear Doctor letter or whatnot.

I would like to put on the table as a suggestion perhaps to explore other ways such as

partnering with the pharmacy professional societies as well. I think, specifically, the Society of Infectious Disease Pharmacists and also the pharmacy at the point of dispensing can also do a whole lot with patient education as well.

Thank you.

DR. EDWARDS: Thank you. Dr. Shapiro.

MS. SHAPIRO: I am going to vote yes provided there are conditions that we will get to it looks like from the likely vote tally here. If we can go back to previous questions and change our vote if we don't have those conditions, that is what I am going to do.

But, in light of what my medical colleagues have taught me and particularly given the non-self-resolving and serious nature of this indication, that is my vote.

DR. EDWARDS: Dr. Smith.

DR. J. SMITH: I vote yes with the caveats, that I see that the drug is comparably effective based on noninferiority trials to other things that we are using. I am concerned about the

overall safety profile and how we might educate everyone better about that and how we will look at that in the future. But I think, at this point, for community-acquired pneumonia, the benefits outweigh the risks.

DR. EDWARDS: Thank you. Could I have the final tally. It is yeses 16 and no's 3 at this point.

Now, having heard all the rationale, at this point I am going to ask if anyone would like to change their vote. At this point, Dr. Cox, by the comments that were made, I think now is the time we should explore labeling issues. Several mentions were made of the black-box warning.

Would you like us to take a tally on that issue or how would you like us to convey information regarding the black box.

DR. COX: I think it would be reasonable to go through and get folks' thoughts on that. We can take a tally. It is certainly your prerogative. The other thing, too, is we heard some folks talking about modified indication or

limits to the indication. It would be interesting to hear more about that and perhaps that would be another area where you might it might be helpful just to hear a tally.

DR. EDWARDS: Okay.

DR. JENKINS: It would be nice for reference if maybe you could follow the questions in Question 2 for CAP because they go through any changes to the indication and they go through any product labeling changes. They go through risk-management strategies. So it would be nice if you could categorize them into those so we can keep the records pretty straight.

DR. EDWARDS: Okay. Regarding the black-box warning, could I see a show of hands of those individuals who are firmly advocating a black box.

[Show of hands.]

DR. LEGGETT: Is this for everything?

DR. EDWARDS: No; this is just for pneumonia.

DR. LEGGETT: I mean, which A.E. You

could have a black box for myasthenia but not for others.

DR. EDWARDS: Okay. So this gets pretty complicated.

DR. LEGGETT: Ed, I don't know that we are going to be help you before tomorrow about 6:00 p.m., if we do that.

DR. COX: It does get complicated because it gets into the issues--we are hearing that it is important to communicate the safety information. I think what we are seeing from some of the hands that were up around the room that there is a level of concern here, so we should consider as we think about labeling safety information for the product.

DR. JENKINS: Dr. Edwards, it might be simpler if you finish the indications because, for example, black-box warning will be on the label for whatever is in the indications. If you decide or recommend that one or more of the indications be removed, then you are not really talking about a box for that indication.

So it might be good for you to know what

the sense of the committee is for what the indications might be your recommendations and then you could describe, given those recommendations on indications, what you would propose for modifying those indications for first, second, third line, whatever status, boxes, medication guides, et cetera, knowing what the package would be

DR. EDWARDS: Actually, I think that is a very good suggestion, Dr. Jenkins. Can I get a sense from the group about that? Shall we go on to the other? Great.

Acute Exacerbations of Chronic Bronchitis

DR. EDWARDS: We are now going to go to the bronchitis indication. Again, if you would please state your rationale. Dr. Smith, we will begin with you.

DR. J. SMITH: For AECB, I vote no, that I don't believe that the benefits outweigh the risks because this is a different type of condition. It is more commonly self-limited and I think that I need to know more about the risks to balance with benefit in this particular clinical indication

which is different.

DR. EDWARDS: Dr. Shapiro.

MS. SHAPIRO: I vote the same way for the same reason.

DR. EDWARDS: Dr. Wong-Beringer.

DR. WONG-BERINGER: I also vote the same way with the same reasons.

DR. EDWARDS: Dr. Heckbert.

DR. HECKBERT; I vote no because I already voted no for pneumonia. The reasons are even more compelling here.

DR. EDWARDS: Dr. Townsend.

DR. TOWNSEND: I also vote no. Again, I think I am saying what everybody else is saying or intimating. But I don't think there is compelling evidence that the drug is any better than placebo in the treatment of exacerbation of chronic bronchitis. I had a discussion with Dr. Powers about this and the phrase, putting the O ring back on the space shuttle, came up,

I think that is fairly apt. I think to put an indication for the treatment of chronic

bronchitis for a disease we don't even know any antibiotic is necessary is at least not beneficial and potentially harmful.

DR. EDWARDS: Thank you. Dr. Morris?

DR. MORRIS: I vote no as well, but I guess my reasons go back to the--well, I guess what Dr. Townsend said. I am just not convinced that the drug is efficacious given the clinical trials and given the issues of placebo response rates in this particular disease.

I think this is maybe one of the instances where I guess there is going to be some kind of change in inferiority and superiority trials. They just didn't make it through the hoop fast enough.

DR. EDWARDS: Dr. Proschan.

DR. PROSCHAN: This one I don't know enough about the disease, really, to know how often this resolves on its own. I plan to vote no for the ABS and I am sort of on the fence here because I don't know, relative to pneumonia, pneumonia is very serious. I don't know where this fits.

I take it from all the comments that this

is somewhere between the other two and exactly how far between it, I don't know. So I am sort of on the fence but I would say I probably would vote no and, again, for me, the concern is not liver but all the visual side effects and possible loss of consciousness. So I would vote no overall.

DR. EDWARDS: Thank you. Dr. Hilton.

DR. GUTIERREZ: I vote no. I think the risks outweigh the benefits.

DR. EDWARDS: Dr. Leggett.

DR. LEGGETT: I am going to play devil's advocate. I am going to vote yes. You can't record a qualified yes so I am just going to keep it as a yes. The reason is that I am assuming the same efficacy as all the other drugs that are not on the market and I am assuming the fact that we had already approved it. It is unfair to single out a single drug company because we have shifted the playing grounds.

But my caveats are I would love to have the company do, if they have not already started, and it appears that they have, superiority trials

and they do mandatory event reporting for some reassessment if that is possible from your regulatory standpoint.

I would also like to add, in terms of the toxicity, remember that these are still hypotheses on the part of the FDA.

DR. EDWARDS: Thank you. Dr. Bradley.

DR. BRADLEY: Starting this out with repeating my previous observation that, with these sorts of diseases, with AECB and bacterial sinusitis, that superiority trials need to be done before we can assess efficacy and then, going back to Dr. Jenkins' comments yesterday morning, that, at this point in time, we look at all of the older drugs.

Until they can be re-studied and brought up to snuff, we should look at them as they were approved based on our previous understanding. So I thought I was going to be the first one voting yes, but it looks like I will be the second one to vote yes. But I am going to put a sunset clause on my yes and, in 24 months, if I don't see data for

superiority, then it would automatically revert to a no.

DR. EDWARDS: I am not sure that is legal, Dr. Bradley. Dr. Gutierrez.

DR. GUTIERREZ: I think, just given the nature of this entity and in comparison to community-acquired pneumonia, I am going to vote no just because I don't think that we quite have enough understanding of the risks associated with it. I guess I am not as optimistic as John is that we are going to see a lot of information.

So, I think until we do see more information or have a better understanding of the risks, I vote no.

DR. EDWARDS: Dr. Follman.

DR. FOLLMAN: I am going to vote no on this based on the comments other people have had and made. I think the risk exceeds benefit.

DR. EDWARDS: I am going to vote no, also. I must say this was an agonizing decision for me. However, I am very aware of all of the issues that have been brought up regarding the noninferiority

trials and believe that we have learned a great deal about that trial design.

So the vote is consistent with a notion that we don't have a clear vision of the efficacy in this particular indication across the board.

I do believe there is certainly a subset of patients with bronchitis who would benefit by this drug. Again, I don't know exactly what the benefit would be related to the resistance issue. But I do anticipate increasing resistance problems in the future.

However, I don't think we can define that subset at the present time and I don't think that that subset would necessarily be the only group of people with bronchitis who would get this drug.

The decision is also in concert with the Kefauver-Harris Amendment stating that efficacy must be demonstrated for approval of a drug. In that context, the toxicity issue is really pretty much irrelevant. However, I did take the toxicity issue into consideration, again thinking about that subgroup of patients who might benefit by this

drug.

I am concerned about the toxicities and I am concerned about the possibility that the level of toxicities we see right now may herald an increasing prevalence that may occur in the future.

I would just like to add that I think this decision is consistent with the decisions that were made at the last advisory board last September. I believe this committee has difficulty--well, let me put it this way--is challenged to be consistent for the reason that we do not have a written updated guidance in this area.

I do believe that the fact that we don't have guidance is really impacting three different groups here. One is industry. The other is the FDA, as we have seen that there has even been some controversy within the FDA. The third is this group. It is difficult for us to come to these decisions without some sort of guidance that we can use to maintain a consistency and a rationale of thought.

So those are my reasons for a no vote on

this indication.

Dr. Marco.

MR. MARCO: Again, I will vote no. Similar to Dr. Heckbert, this was an easier vote than my previous vote because the scales--in that original vote I thought that the risks slightly outweighed the benefits. Now the scales are tipping and I am sure you will be able to guess what my next vote will be.

DR. NORDEN: I am going to vote no. I think the risks outweigh the benefits.

DR. EDWARDS: Dr. Koski?

DR. KOSKI: I would agree with that, so, no.

DR. EDWARDS: Dr. Smith.

DR. M. SMITH: I am going to vote no as well more so because I don't know that anybody is going to benefit at this point from this drug for this particular indication.

DR. EDWARDS: Dr. Wiederman.

DR. WIEDERMAN: I vote no. Nothing substantial to add to the discussion.

DR. EDWARDS: Dr. Levin.

MR. LEVIN: I vote no for all the reasons that have been well-articulated around the table.

DR. EDWARDS: Having listened to the rationales, are there any voters who would like to change their vote? Okay. That is 17 no's and 2 yeses.

Acute Bacterial Sinusitis

We will move on, then, to the sinusitis indication. Dr. Levin, let me start with you.

MR. LEVIN: Again, I vote no and, again, for the reasons that I believe the risks outweigh the benefits.

DR. EDWARDS: Dr. Wiederman.

DR. WIEDERMAN: I vote no also for similar reasons although, at least with this condition, I have, as a pediatrician, a little better handle, personal experience, with similar disorders. But, no.

DR. EDWARDS: Dr. Smith.

DR. M. SMITH: I vote no for all of the above.

DR. KOSKI: No, self-limiting disease and too much toxicity.

DR. EDWARDS: Dr. Norden.

DR. NORDEN: I vote no, same reasons.

DR. EDWARDS: Dr. Marco, we know how you vote.

MR. MARCO: No. Right on. Right on.

DR. EDWARDS: My vote is also no for the reasons that I stated regarding the bronchitis indication. Dr. Follman.

DR. FOLLMAN: I vote no for the reasons that have been given.

DR. EDWARDS: Dr. Gutierrez.

DR. GUTIERREZ: I vote no for the previously stated reasons.

DR. EDWARDS: Dr. Bradley.

DR. BRADLEY: Well, I am going to vote yes again. The reason has to do with the fact that, as we look at the graphs that were shown by a couple of people today on delta creep and original studies compared to placebo, and then subsequent studies compared to those drugs, compared to those drugs,

everyone is focusing on how the lower limit of the delta eventually can cross zero and the drug can be no better than placebo.

While I absolutely recognize that, there is also the potential that the delta creep doesn't go down but stays the same or goes up. I find no inherent reason in the pharmacokinetics or the in vitro activity of this drug that it shouldn't work as well as the original drugs that were studied for sinusitis.

The company showed noninferiority based on this clinical-trial design that was shared with the FDA so that they followed the rules as best they could.

So, as I did last time, I will vote yes with the qualification that, with this as with all the other sinus-approved drugs, go back into some sort of clinical trial to document their efficacy over placebo. So I am going to vote yes again.

DR. EDWARDS: Dr. Leggett.

DR. LEGGETT: Birds of a feather. I am going to vote yes. Despite my comment about

pollyanna, taking the entire collection of kids or adults in one clinical trial and then saying that antibiotics don't work does not get you to the subgroup, subsection, of where somebody has had rhinosinusitis for a week and then gets worse.

The drug has activity and I think there is a place for it. I wouldn't throw antibiotics at anybody. Whenever I would go to work after telling my wife not to give our kids antibiotics for otitis, of course, she called the pediatric and they were immediately on antibiotics within 24 hours. So I know how that works.

But I think that there is a place for it. However, given the pollyanna reference, I would very much like the company to try to get a superiority trial.

DR. EDWARDS: Dr. Hilton.

DR. HILTON: I vote no because I think the risks outweigh the benefits. I hope the company will focus its money on CAP, instead.

DR. EDWARDS: Dr. Proschan, we know how you are going to vote, also.

DR. PROSCHAN: Right; you do. I just wanted to add one other thing which is that, when I take medicine, I often take it and forget that I have taken it. So I have to ask my wife, did I take that, or not. Sometimes, she knows the answer. Sometimes she doesn't.

So I think it is not unlikely that there are other people like me who are going to end up taking twice as much as they are supposed to because they can't remember that they took it. Then we saw some of the smaller studies that showed much worse blurring, much more frequent, or many more people with the blurring on twice the dose.

So I think this is the condition that resolves the most by itself. So I would vote no.

DR. EDWARDS: Dr. Morris.

DR. MORRIS: I vote no as well, but I do have a concern and that is that I think many of us are voting no because we don't think that the drug has really proven its effectiveness. I think that, for these conditions, we probably have similar caveats or concerns that other drugs may not have

been proven to be efficacious.

I think, as a committee, we would send a signal to IRBs that we have concerns about the efficacy for many drugs because, unless IRBs believe that there are ethical reasons to use a placebo, getting these placebo-controlled trials done is going to be a real problem.

So I do think, even though I think part of my vote would be, as long as we also make a general statement about other drugs and the need for placebo-controlled trials and the ethics of placebo-controlled trials because we doubt the--we don't have good evidence of efficacy for any drug.

DR. EDWARDS: Dr. Townsend.

DR. TOWNSEND: I vote no for the reasons everybody else has already stated. I won't elaborate on those, but just as an editorial comment, I think it was Dr. Bradley said, the genie is out of the bottle, and actually it has been out since September, as far as looking more rigorously at trial design and holding new trials to higher standards.

The question of whether or not this is going to go retroactively back in effect drugs that are currently indicated. I think that it is practical to think that all those drugs will be reviewed. But, frankly, nothing would please me more than if we went back and looked at all the drugs that currently have indications for sinusitis and chronic bronchitis and found out whether or not they actually are any better than placebo. I suspect most of them aren't because I think that most of these infections, as has been discussed already, probably don't need antibiotics.

So, if that is the end result of these discussions, I think we have done a very good job here today.

DR. EDWARDS: Dr. Heckbert.

DR. HECKBERT: Yes. I agree with Dr. Townsend's remarks and I am also concerned about safety, as you know, so I would vote no.

DR. EDWARDS: Dr. Wong-Beringer.

DR. WONG-BERINGER: I would also agree with Dr. Townsend's remark and my vote is no.

DR. EDWARDS: Dr. Shapiro.

MS. SHAPIRO: No for all of the above.

DR. EDWARDS: Dr. Smith.

DR. J. SMITH: No for all of the reasons already stated.

DR. EDWARDS: Having heard the rationales, would anyone like to change their vote? Then the tally on that is 17 no's and 2 yeses.

Now we will return to the questions as we have had them submitted to us.

Question 2

DR. EDWARDS: "If continued marketing is recommended for any of the indications, should any of the indications for which continued marketing is recommended be modified or limited."

That returns us to the issue of the black-box warning for the CAP. Dr. Cox.

DR. COX: One other thing, here, too, thinking about this, maybe we have heard some discussion about second-line therapy, third-line therapy, those sorts of boards that would--because of reasons of toxicity. So that maybe something

that we could include under the discussion of the a) part of the question here. And then the question with regards to the black box, that could also be considered under b), too, with regards to the product labeling and such.

DR. EDWARDS: Is there further discussion about the black-box issue?

DR. COX: We certainly could handle it and then do the modification of the indication.

DR. EDWARDS: Dr. Wiederman.

DR. WIEDERMAN: I am generally in favor of that. But I am also thinking today a black box may get someone's attention more than a Dear Doctor letter. But, as these become more common, it is going to be the Dear Doctor letter of tomorrow. So we also have to do some out-of-the-box unintended thinking to, like Dr. Wong-Beringer had mentioned, some other ways to get at this to really inform the public and the medical profession.

DR. EDWARDS: Yes, Dr. Koski.

DR. KOSKI: I must admit, I do not want patients in the community with myasthenia gravis

receiving this drug because they will not be monitored in the way that they should be. Although we do think that most of this happens over the first couple of doses, the point is that I could honestly see some circumstances where a myasthenic may have more difficulties further into their clinical course and then have a reaction when they get another dose of the drug, maybe 3 to 4 days out.

So I would actually prefer myasthenics not to receive this drug in the community. I don't have any reservations about them receiving it in the hospital setting, although it is an oral drug, mainly because they will be monitored and, quite frankly, when we are worried about vital capacities and what not, these patients are monitored on an hourly basis. So we can see trends actually as they develop.

I think the other thing which I found very interesting when I was sort of reviewing this data was a lot of the visual circumstances which we have been presented some information that high doses, at

least, are associated with some difficulty with accommodation. That certainly would produce visual blurring for a period of time.

I think the timing is very interesting, particularly related to the myasthenia gravis. I really wonder if some of this isn't related to, for instance, a difficulty with acetylcholine and the way it is either released or handled in the synapse in both the neuromuscular junction and possibly with the parasympathetic fibers that are involved and use acetylcholine, obviously, as a transmitter in the accommodation reaction.

So, in terms of the black box, and I don't know how extensive we want to do it, I really think that the myasthenia has to be very clearly stated. I think that that will significantly reduce some of the side effects.

Sure, we are not going to pick up the ones that have not been adequately diagnosed, but then, that also needs to be an educational issue. Pharmacy, I think, is a very good way to go at that.

DR. EDWARDS: Dr. Morris.

DR. MORRIS: Just some clarification from FDA. If this drug is relabeled, will it be in the new format?

DR. JENKINS: I think so. I am hearing from my expert that it needs to be an efficacy supplement that triggers the new labeling format, although the company could voluntarily choose to--

DR. MOYER: We have already--

DR. MORRIS: So the thing that is nice about the new format is it does have a section about recent labeling changes. One of the things that I would think, because there will be a new label and that may even be part of a black box, that the company, in all its promotional material, would need to prominently display the recent label change.

So I think that one way of communicating to doctors is to make sure that, because it is going to be reformatted in new label information, that the fair balance within all the promotional material would have to prominently display this new

information that we say.

So I think that we might be lucky in the sense of being able to communicate to doctors in a much more complete way because--just by FDA enforcing that part of the label.

DR. JENKINS: Could I ask the sponsor--I heard you make some comment about whether you were developing a PLR format. If you could go to the microphone and just clarify what that comment was. For those of you who are not clear what we are talking about, we are talking about the new format for labeling, the Physicians Labeling Rule.

DR. MOYER: Yes; we are developing that earlier than what the requirement is for the guideline and regulation. So we are developing the new Physicians Labeling Rule format of the package insert.

DR. JENKINS: I would just like to alert the committee that our review of a label that comes in in the new Physicians Labeling format is much more complicated than our review of a label that comes in in the old format that has been changed.

So you might well see changes in the old format in advance of seeing this converted to the new format because if we try to convert this to the PLR format, it would delay getting the changes done because there is a lot of work that goes into developing the Highlights Section, redoing some of the work. So just to alert you that that may be the course of events.

DR. MORRIS: Regardless of the format, I guess one recommendation I would have is that FDA makes sure that it considers the label changes that are going to be made especially anything including the black box as essential information for the fair-balance section of promotion. I think DDMAC has that prerogative and that we would highly endorse that.

DR. JOHANN-LIANG: I just wanted to add about the new labeling, there have been several situations recently where we, from the Office of Surveillance and Epidemiology, would recommend that labeling sort of be elevated due to certain reasons, especially to a box.

We are encountered with this response. The new labeling will take effect which will highlight these issues so, therefore, we will wait until the new label goes into effect which is fine. I mean, we like the new label. We wanted to go there but there is this--just like Dr. Jenkins was pointing out, we are encountering that there is a time delay. If the committee feels that there is substantial risk here, then you need to consider that in your recommendations.

DR. EDWARDS: Dr. Shapiro, did you have a comment?

MS. SHAPIRO: I don't know if there is anything to do with this, but I was quite disturbed with your statistic about 50 percent of antibiotics being prescribed over the phone. If this is falling into that category, there are two levels of concern.

One is the doctor may not have important historical information about this patient like that they have myasthenia gravis and the patient may not hear all the side effects that he or she needs to

be on the alert about.

It was said earlier today, well, why wouldn't somebody who has blurred vision stop taking that drug. They may very well not know, unless told, that the drug is responsible for that. So they may continue to take their risk.

So I am concerned about that lack of doctor/patient physical interaction. I don't know if that is something that we could require.

DR. M. SMITH: May I just make a comment toward that?

DR. EDWARDS: Yes.

DR. M. SMITH: Most of the time, I think most physicians are referring to patients that they are already established in their practice that they might not have them in the office. This is somebody you think you know very well and so you are doing this over the telephone.

But there are occasions where I know physicians who prescribe antibiotics for a patient they don't know very well. So it can be across the board. It can be very complicated.

DR. EDWARDS: I just want to make a comment. I don't know that we are in a position to critically analyze that study at this point in time but it does raise an important issue about the usage of antibiotics.

MS. SHAPIRO: And risk communication which is what we are on now; right? That is the topic we are on now.

DR. EDWARDS: I was just going to see--Dr. Cox, did you want to make a comment?

DR. COX: I was just going to say it sounds like we are dealing with a couple of things here at once, which is fine. But, yes, Dr. Edwards?

DR. EDWARDS: I was going to try something to see if I could expedite the discussion a bit. What I wanted to do was poll the panel and see how many people were in favor of a black box of any kind and then we could look at--probably the best thing to do would be to look at just the hepatotoxicity, myasthenia gravis and the visual issues.

Then we could ask for anyone's propensity towards using a modification of the label such as a second-line drug or something like that and get a feeling for the group inclination in that regard.

Does that sound all right with you? That might get us right down to just a few odds and ends that we have to take care of very quickly.

DR. COX: Yes. That sounds like it will be helpful.

DR. EDWARDS: Could I see, by hands--yes?

DR. HECKBERT: Sorry. Are we assuming we are doing this just for community-acquired pneumonia?

DR. EDWARDS: Yes. Could I see a show of hands for a black box of any kind on the label.

[Show of hands.]

DR. EDWARDS: Sohail, I am going to have you--this vote is changing as the moments go on. 13?

LT. MOSADDEGH: Dr. Smith, your hand was up?

DR. J. SMITH: Yes.

LT. MOSADDEGH: Okay. Dr. Smith. Dr. Shapiro, 2. Heckbert, 3. Townsend, 4. Dr. Morris? You are either in or out. Dr. Morris, yes?

DR. MORRIS: All right.

LT. MOSADDEGH: Dr. Proschan, yes. Dr. Leggett?

DR. LEGGETT: I am going to say something afterwards.

LT. MOSADDEGH: Yes?

DR. LEGGETT: I am not going to say yes. I am going to say something different.

DR. EDWARDS: Dr. Bradley?

DR. BRADLEY: Yes.

LT. MOSADDEGH: Dr. Gutierrez, 8. Dr. Follman?

DR. FOLLMAN: No.

DR. EDWARDS: Myasthenia.

MR. MARCO: Yes.

DR. NORDEN: Yes.

DR. KOSKI: Yes.

DR. M. SMITH: Yes.