of the study design and an agreement over how the study should be conducted.

In the case of sinusitis, there is also a document -- a points to consider document that was issued in 1998 which describes the body of evidence that is required for demonstration of efficacy of an antibiotic in this setting, and that is the existing guidelines today. There have been no published changes.

There may be ICH guidelines that describe the preference of superior studies, but within the context of anti-infectives, there s a very clear and established paradigm that we have undertaken to follow.

The second point I d like to make is I would respectfully disagree that the decision taken here is not without consequence to other sponsors. We believe there are other sponsors who ve conducted sinusitis trials, those also of non-inferiority design, and they, too, presumably would be impacted by a decision taken here.

The third comment I would make is the FDA do

have an opportunity, if they wish to change the goal posts, when a sponsor comes for an end of Phase II meeting and is embarking upon a Phase III trial program, to outline a different expectation that indeed placebo controlled trials are required and indeed help the sponsor in the design of those.

So there is an obvious inflection point to make a decision to change the rules and to change the guidelines.

The final point I d like to make is I understand entirely the difficulty of grappling with what is the magnitude of the treatment effect for all antibiotics in the setting of sinusitis.

But I would submit to you, though that s a question we clearly need to answer, but that a non-inferiority trial, where the delta that we show in the confidence intervals and the response -- and by the way, the per-protocol analysis is the primary endpoint for our trials, not the ITT population -- that we demonstrated that the delta of the trials measuring the per-protocol, and in most instances, the ITT, was actually under 10%, so

that we can reasonably expect that our drug was not inferior to the comparators.

It s another question, how big the therapeutic effect is of those comparators. But I respectfully submit that s a different question to whether we can demonstrate in non-inferiority studies our equivalence to other agents in this indication, and this is the current guideline. Thank you.

DR. EDWARDS: Okay. Thank you. All right. The -- okay, I have no one on deck. What I believe I d like to do now is unless there is an overwhelming feeling one way or the other, we re not going to take a vote at this moment on the efficacy unrelated to the safety issue.

I m not sure how we can convey other information to you all regarding the consensus of the panel centered on efficacy evaluation, and I m open to any suggestions that you might have.

What I think I d like to do -- let me continue, and then I ll come to you -- is we want to have plenty of time to preserve for discussion of safety issues this afternoon.

I m contemplating taking a 15-minute break at this moment and then moving on into the safety issue with follow-up of any other discussion we might have on efficacy preceding the safety issue, but I need to have enough time for our safety evaluation.

I m sorry? Well, we re going to -- we re planning to end at 5:00, Carol, and we ve been and hour and a half, and I think people are going to need to take a break, a 15-minute break.

Dr. Townsend, did you have another -- I m sorry.

DR. WIEDERMANN: Bud Wiedermann.

DR. EDWARDS: Did you have another comment?

DR. WIEDERMANN: Well, I was just going to -- I had written down a possible question to see if it would help the FDA in their question, or maybe you in your question, to try to separate out just the efficacy data. If safety were not a concern, should gemifloxacin be approved for the five-day treatment of patients with acute bacterial sinusitis?

I guess that wording would allow each committee member to decide what they think about the non-inferiority controversy, and give some sense of where the group lies in that.

DR. EDWARDS: I m sorry, I --

DR. WIEDERMANN: But if you don t want to do a separate efficacy straw man pull (phonetic), then that s fine, too.

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

DR. TOWNSEND: I ll try to make this short. A couple people on the panel have made the comment -- and this goes -- alludes to something Dr. Temple said a few minutes ago -- that -- so regardless of what the clinical trials have shown, that in vitro data are convincing enough that they feel comfortable that this drug would be efficacious for the treatment of acute bacterial sinusitis.

I just want to say I m pretty uncomfortable with that approach. If all we need are in vitro data, there s really not much point in doing clinical trials, at least for efficacy. We can

just say it s good enough. That s my point.

DR. EDWARDS: Okay. I d like to resume at 2:10. Oh, I m sorry, we ll make it 2:15. Oh, I m sorry, 3:15. I m on the wrong time zone.

(Off the record 2:55 p.m.)

(On the record 3:15 p.m.)

DR. EDWARDS: We re going to go and resume, then. Again, I just wanted to mention that this meeting is scheduled to go to 5:00, and I do not have plans to end it before 5:00, but I have plans to not end it after 5:00, and I really feel that this is such an important meeting that we shouldn t be trying to rush through it, truncate the discussions, and terminate early for the convenience of a minority of individuals.

So 5:00, we re going to be finished, but I m not anticipating being finished before that, unless things really start flowing in a different way than they have so far.

All right. I am now going to do something that is a hybrid of the vote, and I -- what I wanted to do is go around to each of the voting

members and ask them to give a succinct answer to a question, but the answer does not have to be yes or no. The question is, I would like you to comment on the evidence that efficacy has been demonstrated for acute bacterial sinusitis in a five-day treatment regimen, based on the data that has been presented.

So I want a comment on -- let me word it this way. Do you feel that efficacy has been demonstrated based on the data that has been presented for a five-day treatment of ASB (sic) with gemifloxacin?

If I could just have the answers succinct. It doesn t have to be a long answer, and again, it doesn t have to be a yes or no answer. So, Jackie, you get the privilege of going first.

DR. GARDNER: No.

DR. EDWARDS: No? Any further discussion?

DR. GARDNER: It s difficult for me to consider it in the absence of a -- the safety data, but if it s standing out as -- however it s being evaluated and presented to us, I would have to say

that the answer is not to my satisfaction.

DR. EDWARDS: Okay. Again, this is not a safety consideration, just the efficacy. Marian?

DR. GUTIERREZ: I believe that based on the standard by which this study was done and by which other studies of antimicrobials have been done, that yes, it appears to be effective. Can there be better ways of looking at this information? I think that s also a yes, but my answer is yes, as it stands.

DR. EDWARDS: Rich?

DR. FROTHINGHAM: Yes.

DR. EDWARDS: John?

DR. BRADLEY: By the new FDA criteria, which look at the delta, with current data, knowing that this -- that the current delta may actually make this drug no better than placebo, the answer would be no. Based on the old criteria, though, it would be yes.

DR. EDWARDS: My answer would be virtually identical to John s, based on the non-inferiority trial consideration issues which have been so

extensively reviewed over the last several years. Carol?

DR. KAUFFMAN: I actually don t think the data are strong enough. In my heart of hearts, I thought it was going to be good coming in, but the more I thought about it and went through it, I d have to say no.

DR. EDWARDS: Yes?

DR. TUNKEL: My answer is yes.

DR. TOWNSEND: No.

DR. HILTON: No.

DR. PORETZ: Yes.

DR. BIGBY: With the caveat that I don t treat patients with bacterial sinusitis, but I do look at a lot of evidence, I would say no.

DR. WONG-BERINGER: No, by the evolved standard.

DR. EDWARDS: Peter?

DR. GROSS: I would give a similar yes and no. Yes, based on the old standards; no, based on the new. And I would want to know whether the company definitely was not told, when they got into the

Phase III studies, that the rules had changed.

DR. EDWARDS: Yes?

DR. WIEDERMANN: No.

DR. EDWARDS: Sohail, could we have a -- hopefully, you recorded that. So we just --

DR. MOSADDEGH: Yours (inaudible) question mark, you both went both ways, but we have one -- four yeses.

DR. EDWARDS: Okay, four yeses.

DR. MOSADDEGH: Was yours a no or a yes?

DR. EDWARDS: No.

DR. MOSADDEGH: No? Okay. Ten nos.

DR. EDWARDS: And 10 nos. Do we have any further discussion about the comments we all just made? If not, I d like to turn the discussion now into the committee s feelings about the efficacy data -- I m sorry, the safety data. Now, we have a different topic.

Rich, would you like to start off?

DR. FROTHINGHAM: Yes, thank you. I have a few comments that I ve sort of typed up here, sort of summarizing my feelings about the safety. I came

in this very skeptical and was particularly noting that 82% of the AERS database reports were related to rash. What really impressed me, though, was the straightforward acknowledgment by the sponsor that the rates of rash with this drug are higher than the comparators, and I never heard any equivocation about that statement. That helped me a lot.

I also was very impressed with the 344 study, particularly the FDA presentation of it, where the same worst-case scenarios pictures were presented, and they weren t very bad. So I was left with the conclusion that, one, the skin adverse effect is much more common for gemifloxacin than for the comparators; however, this adverse effect appears to be balanced by an overall good safety profile in other areas.

For a quinolone to be addressed under modern standards, it seems to be holding up under a lot of other areas that are troublesome for quinolones in general. I found the results of 344 to be reassuring regarding the mild nature of the rashes overall and the complete reversibility of those.

So my conclusion there was that I was happy with the risk-benefit profile, something of a surprise to myself. However, I did want to say that whether or not this indication is approved by the committee as a whole -- I mean, by the FDA, after the advice of the committee as a whole -- that the package inserts should be modified radically.

The sponsor indicated that the current patient information section -- which, if you want to look at it, is in sponsor booklet Appendix 2, Pages 30 to 32, the very end of your sponsor booklet. The sponsor indicated that this patient information section emphasizes rash as an adverse effect, and this is certainly not the case.

Under Who should not take Factive, for example, rash is listed third, and it is not bolded. Secondly, under What are the possible side effects of Factive, rash is discussed in the third sentence and again, is not bolded. Under Serious side effects, QT intervals, CNS problems, tendon problems, and phototoxicity are listed,

which don t seem to be big issues for this drug, but rash is not described at all under Serious adverse side effects.

I really think this should be rewritten, and although I find the safety profile to be acceptable, there should be an extreme emphasis on rash, a statement of rash is the big deal here, stop the drug if you get a rash, educate your patients about rash.

Similarly, the main text of the PI does not provide a complete discussion of the rash adverse event, or emphasize it. Rash does not appear in warnings, whereas these other adverse effects that don t appear to be a problem are, so it s a totally flipped-around package insert. It should appear under warnings, and that discussion should be bolded.

The PI should, again, and the package inserts could clearly indicate that rash is more common for gemifloxacin than for comparators. That statement which we heard so clearly today is not stated in the package insert. It should emphasize patient

education on this topic, especially on the stop the drug if you have a rash message, and all of this should be bolded.

If that happens, I m pretty happy with the safety profile overall. I just want to see the emphasis on rash clearly demonstrated in the package insert in the education process and in the detailing to physicians.

So those would be my comments, and I guess I m jumping the gun here in giving my yes answer to the question that was up on our screen there.

DR. EDWARDS: Yes, Jackie?

DR. GARDNER: I don t agree that the data seemed to show a good safety profile, regardless of the severity of the rash.

The incidence of it or the prevalence of it is sufficient and also, of the condition, by the sponsor s estimate, five to 20 million cases of acute bacterial sinusitis annually, this suggests that at maximum, with widespread advertising of the product, as there would be, I expect, for this indication, that there would be tremendous exposure

in the -- particularly in the age -- and we might expect particularly in the age groups in which rash is most prevalent.

I think that the seriousness of the rashes is one issue, but also, the consequences of having a rash, we should not ignore. As Dr. Gutierrez mentioned, the -- what are rash signals, in terms of interventions, and the implications of that; the fact that it s more prevalent in women, without an explanation for that; and then just in general, a promotional effort for what may be inappropriate therapy in a number of cases, in light of a resistance developing.

I don t feel the safety profile is a good one.

DR. EDWARDS: Carol? Yes, Carol Kauffman?

DR. KAUFFMAN: So I m concerned, actually, in terms of the disconnect between the study done in healthy women and the rashes which were described as being pretty inconsequential -- and certainly, the pictures we saw, most of them weren t too bad, although some were bad macular papular rashes -- and then the AERS data, where it looks like, in

fact, they may be more severe.

Now, realizing the AERS data are flawed, but if anything, they re flawed toward people not reporting things, and so -- go around the room and ask how many times you sent in a MedWatch, I m sure we ve seen lots of complications and haven t bothered to do a MedWatch because we re so busy doing other things. So I suspect it may be even more prevalent out there in the real world when it s used, and I keep thinking can the company do something to make doctors use this correctly so the risk is decreased, and I m concerned about that, seeing how quinolones are used in the real world, not at all like we do in academics and certainly not like we do at the VA, where we pretty much restrict them in many ways.

So I don t think you can control what regular docs do. I think the treatment will be given for longer period of time than indicated, and I think the rash is going to be a significant problem, so I m concerned.

DR. EDWARDS: Did you have -- yes, Joan?

DR. HILTON: I m also pretty concerned about

the rash. Whereas it s been presented as being a relatively mild problem, the idea that the duration is two weeks on average, having -- the thought of having such a rash for two weeks, to me, is pretty scary and awful, and I certainly would -- if I had it, would never take that drug a second time. And I -- anyway, I ll stop there.

DR. EDWARDS: Did -- an average of two weeks? I m not sure that I know where -- okay, thank you. Yes, Dr. Poretz?

DR. PORETZ: I agree with everyone about the rash. I think that s going to be the major limiting factor. I think it s going to be -- as the drug gets marketed, you re going to see in absolute numbers a significant increase in rash. Some may be worse than others.

It will lead to going back to the doctor or the nurse practitioner or the P.A. who are prescribing the drug, and I think they will be -- in addition, to be -- overusing the drug, and I think it will allow people to be labeled as being allergic to all quinolones, as commonly happens

now. When someone s on one quinolone, they just said they can t take any quinolones, so when they may need a quinolone, they won t have access to it.

I think the cost of health care will increasingly increase because of the rash. That s my major problem.

DR. EDWARDS: Dr. Bradley, it s now time for you to ask Dr. Bigby the question that I deferred.

DR. BRADLEY: Well, I forgot all the details of my question, and that s probably good, but the essence was we had reassurance by Dr. Shear in 2003 with the data we had, your reluctance, and has the new data that s accumulated made you feel more comfortable about the safety?

DR. BIGBY: Actually, one of the things I did was I went back and looked at the transcript from 2003, because I wasn t sure that I actually agreed with you that I was so reluctant at the time. So this is what I said when we were asked to vote about it before, and that was that I think that the drug will have a high rate of producing rashes -- I think they re predominately minor in type -- but

that it shouldn t preclude being marketed. I thought it should have a warning about high rates of rashes, particularly in pre-menopausal women.

I certainly have heard nothing at this meeting that would make me more reassured about the safety of the drug, and, in fact, probably the opposite is true.

DR. EDWARDS: Other comments about safety, in general? Peter?

DR. GROSS: Yes, I think -- I guess you have to wait until you review their revised application, but there probably should be some warning in there about not taking the drug for longer than five days. I know a number of ENT physicians in our area often recommend long courses of antibiotics, and repeated courses for sinusitis, and that should not be done with Factive.

DR. EDWARDS: Other comments? John?

DR. BRADLEY: This came up a little earlier. Dr. Ferguson had mentioned that she probably wouldn t use this drug as first-line therapy for acute bacterial sinusitis. In the package

labeling, I m wondering if there s a way to reflect the fact that, given the higher rash risk profile, if -- assuming the drug were approved, that there could be some way just to suggest that this would be second-line therapy.

I guess that would be more a question to the Agency.

DR. COX: Yes, I mean, with --

DR. EDWARDS: Yes, Ed?

DR. COX: I m sorry. With labeling, one can recommend particular patient groups or if there are particular risk-benefit considerations that would make it more appropriate for one -- use in one group than another, then certainly, your comments on that would be helpful.

DR. EDWARDS: Dr. Tunkel?

DR. TUNKEL: Yes, just a question, a follow-up to something the sponsor mentioned. You had mentioned a fixed-dose pack? So in other words, would that mean that if anyone ordered gemifloxacin, they couldn t order more than five doses?

DR. PATOU: A physician clearly has the ability to write a prescription for any length of therapy. What we looked at in 2003, proposed to the committee at that time, was that a fixed-dose pack would lead to a better compliance.

What we ve shown in our risk -- our drug utilization study is that that s the case. It is likely that people prescribed the drug for longer periods of time will end up incurring a second co-pay for an additional course of therapy, because a course of therapy is defined as a single fixed pack of drug.

The other point I wanted to just sort of mention, if I may, related to that is that the FDA are reviewing a five-day treatment claim for community acquired pneumonia, and at the moment, we have a sort of duality of use of the drug, in terms of -- in the marketplace, in terms of five and seven-day durations of therapy.

We think that by -- if -- I mean, the FDA are reviewing this currently, but there is the potential here that we could move the whole

franchise to a five-day course for all indications, make it much simpler for the physician, reduce the consequence of a higher rate of rash with longer courses of therapy, and create a considerable impediment, if you will, to those sustained durations of therapy.

What we ve seen already in our sinusitis patients in that risk minimization study is they are not getting longer durations of therapies or more refills. So we actually have, even though it s sort of off-label, but we have that usage data showing there isn t prolonged therapy with this agent in that setting. Thank you.

DR. EDWARDS: Marian, would you comment on the rash issue, or on safety in general?

DR. GUTIERREZ: Okay. I think I agree with a lot of the other comments that have already been made, and an earlier comment that I made. One of the things that I am concerned about, I realize that all of us in this room are very well-educated about this product, but I know that when these products enter into the community to people who

aren t as familiar with all of the issues around them, I don t know that rash will be a huge concern on their radar screen.

I guess I m just -- I think that Dr. Ferguson had mentioned that she counsels her patients about what type of antibiotic they would like to be on and the duration, etc., and I wish all physicians could do that and could explain the risks and benefits of all antibiotics, but I know that even with a lot of education, that that, in the real world, just doesn t happen very often, and that s my concern.

DR. EDWARDS: Dr. Wiedermann?

DR. WIEDERMANN: I don t think I have anything new to add. I think in terms of serious cutaneous reactions, it s going to take it looks like years of post-marketing to get a handle on that. It s just these are uncommon events and even if they re happening at increased frequency, it takes time to know that information.

So I think I m stuck, like I was saying before, that in terms of minor side effects, drug

rashes are more problematic than other drug side effects, because I think they re more likely to precipitate a lot of tests and treatments that, in themselves, can cause even more problems. So that s my primary concern with what appear to be minor cutaneous side effects of this drug.

DR. EDWARDS: Rich, please?

DR. FROTHINGHAM: Oh, thank you. Several people have mentioned the issue of labeling a patient as quinolone allergic based on this rash, and that would ve been my logic, too. I mean, I think I would label such a patient in that fashion and not use the drug unless I had to.

We do have some conflicting data from that, though, from the sponsor s booklet, from the observational data and the patterns of use study, which is Appendix 1, and I should mention this is an ongoing study, so it s not completed. But on Page 10 of Appendix 1, they do provide us with some data on what happened to the people who got rashes with gemi.

They noted in that study that there were 4,763

patients who did not have a rash with gemi and of that group, 18% received another quinolone afterwards. Then they go on and talk about what happened to those patients. But that s 18% of those who had a rash with gemi, 147 patients, 21 of them received another quinolone, or 14%.

So 18% to 14%. The P value was 0.23. There s no difference in the subsequent use of quinolones in the patients who had a gemifloxacin rash. I m not sure that represents good practice, but it may represent real world, what people actually do in the real world.

DR. EDWARDS: Are there other comments regarding the safety issue, either related to rash or other safety concerns or issues? Okay. Dr. Albrecht, now, we could engage in other discussions that would be of advantage to you all in your final deliberations.

DR. ALBRECHT: Before we do that, I just wonder if we could actually get a count on the safety discussion, or did we get definitive enough answers?

DR. EDWARDS: Would you like us to a similar thing which we did with the efficacy issue?

DR. ALBRECHT: I think that would be useful.

DR. EDWARDS: Okay. So again -- yes, Dr. Bibgy?

DR. BIGBY: In that regard, I mean, you already have 10 votes about efficacy. Maybe we should just ask the original question and just go around and give an answer to the original question. That might --

DR. ALBRECHT: That would be fine.

DR. BIGBY: Yes.

DR. ALBRECHT: And then maybe afterwards, if there are some remaining questions.

DR. EDWARDS: So should we -- is it your preference, then, that we do the vote now related to the questions that you submitted to us in advance?

DR. ALBRECHT: Why don t we go ahead and move to that, if the committee --

DR. EDWARDS: Okay. Sohail, do you have a projection of the question specifically? Okay. So

we will -- would you like us to entertain the second component of that question if we go through each of the panel members which is, if no, what other information would be required?

DR. ALBRECHT: We would. I don t know if you want to do them in sequence or contiguously.

DR. EDWARDS: Okay. I think maybe what we ll do is we ll do them individually.

DR. ALBRECHT: Okay.

DR. EDWARDS: So we ll start at the other end, Dr. Wiedermann, this time. This is the question, and at this point, we need a yes or no vote.

DR. WIEDERMANN: No.

DR. EDWARDS: Dr. Wong?

DR. WONG-BERINGER: No.

DR. BIGBY: No.

DR. HILTON: No.

DR. TOWNSEND: No.

DR. TUNKEL: Yes.

DR. KAUFFMAN: No.

DR. EDWARDS: No.

DR. BRADLEY: By the new criteria, if it s not

effective, safety is not an issue, so I would have to vote no.

PARTICIPANT: And then by the old criteria?

DR. BRADLEY: By the old criteria, I would say yes, with qualifications for the patients that would receive it. I think older men with sinus disease would be a perfect population.

But if efficacy, as we re designing it now, is the way we re going to move forward, and that s for the better of -- for better patient care, better outcomes, less drug exposure, all those reasons. Then if the drug s not effective, hasn t been demonstrated to be effective, then safety is irrelevant.

DR. FROTHINGHAM: My answer would be yes, with some strong caveats to do with the patient information, package insert and programs to educate physicians, and I will discuss those caveats the next time we come around, because I think that relates to the second and third questions. So in any case, it s a yes with conditions.

DR. GUTIERREZ: My answer is no.

DR. GARDNER: No.

DR. EDWARDS: So that was two yeses, I believe?

PARTICIPANT: Two yeses, 12 nos.

DR. EDWARDS: Twelve nos?

DR. ALBRECHT: So perhaps at this point, the yeses could talk about caveats as in the second corollary, and the nos could also address that.

DR. EDWARDS: So Dr. -- let s see. Jackie, I guess we ll start with you on this.

DR. GARDNER: I was a no.

DR. ALBRECHT: Sohail, could you advance the slide? So this would be the question to address by those who voted yes to the first question. Then there s a second question for those who voted no.

DR. EDWARDS: Okay, right. Okay. So Rich, I believe you had several comments.

DR. FROTHINGHAM: Yes, I have quite a few comments about where I think this -- the use of this drug should go forward. First of all, based on the comparisons in the sponsor s booklet and also, in the FDA information about the estimates of

gemifloxacin utilization, it appears that the majority of courses of therapy were provided by samples to physicians offices.

This is a particularly concerning pattern of distribution of a drug, because it often means that individual providers who don t know much about the drug choose it because it s on the shelf and just distribute it.

So because this drug has a unique adverse effect profile, although I think it s an acceptably safe drug, I think that a specific program needs to go forward that would educate providers and in my mind, sampling should probably be suspended for this drug unless it is accompanied with some type of formal education of physicians that this is a unique and unusual adverse effect with this drug.

That could come in the form of the printed material that was provided by the sponsor of the drug, something that, for example, a physician would sign indicating, Yes, I m aware that this drug has a unique adverse effect profile which is different from other quinolones, and that I will

advise my patients accordingly, and that I understand five days is the limit on the duration of therapy that is safe for this indication.

We have examples of those programs for other drugs which have unusual safety profiles, and in general, I m generally speaking uncomfortable with physician sampling for any drug that has an unusual adverse event profile. Personal experience in seeing people who received samples of other drugs which had unusual side effects, which (inaudible) presented for, I think review of the AERS database will find a lot of those examples, as well.

So that would be my first recommendation, in terms of risk management, that the sponsor should initiate such a program. The literature should clearly state that this is an unusual effect of this drug, should clearly state five days is the limit for this indication, should clearly identify these are the risk groups and yes, I understand in receiving these samples, I m going to communicate that to my patients.

And then the second and third recommendations

for a risk management mechanism would simply be the modifications that I mentioned before for the patient information section and the PI.

I guess the main disconnect that I m seeing here is the disconnect between what we received today, which was a very frank and clear description, gemifloxacin has a greater risk of rash, and what s in the package insert, advertising, and patient information sections which is, yes, there s a rash, but nothing to suggest that it s an unusual rate.

So I think if we bridge that gap, that would be a way to promote this drug and use this drug safely.

DR. EDWARDS: Yes?

DR. TUNKEL: The other reason I voted yes, and I ll just add to that, is I m very concerned that we have a drug that has already been concerned by the FDA, and is being used by physicians for this indication with really no understanding about what the side effects may be.

I m more worried, if we don t approve it, that

we re going to have a drug out there where there will still be no further education of physicians, it will be used inappropriately, patients will not be monitored, and I m more worried that not approving the drug may have more of a negative outcome.

I mean, in 2003, based on what I ve heard, I might ve voted no, actually, but I think at this point that we have the approved drug, those are my reasons, in addition to what Rich has recommended, that I voted yes.

DR. FROTHINGHAM: If I might just clarify, these recommendations would apply regardless of the sinusitis indication, so I would consider these to be appropriate things for the FDA and the sponsor to consider going forward, even with just community acquired pneumonia and bronchitis, in which case it would be five or seven days, but it would be -- the education program needs to be there whenever samples are distributed for any drug that has an unusual safety profile.

DR. EDWARDS: Okay. Then for those who voted

no, what other information would be required? We ll start with you, Dr. Wiedermann.

DR. WIEDERMANN: I think for efficacy, we re now talking about superiority studies, and I think particularly to have some bacteriologic data with that, especially for multiply drug resistant streptococcus pneumoniae, would be helpful.

As best I can tell for -- in terms of safety issues, again, to get a handle on the more serious cutaneous reactions, obviously, that s going to be monitored in any clinical study, but it s really going to take post-marketing surveillance of that, which the company is already doing.

So I think the more information on that, the better. I m not sure I want them to do more hurdles in terms of some better study to figure out how many patients were labeled allergic, for example, and not just get a guess estimate, how many were labeled allergic to the quinolone class, things like that.

But as I say, I think that would be nice, but it s difficult to get that data. It might be too

steep a hurdle based on -- when we re talking about relatively minor cutaneous reactions.

DR. EDWARDS: Thank you. Dr. Wong?

DR. WONG-BERINGER: I would echo the same points that Dr. Wiedermann had mentioned, but I would also, considering a particular niche where I see -- considering that there are other floroquinolones out there, like moxifloxacin, for example, that could be used in a drug-resistant pneumococci -- perhaps to look at a niche where looking at floroquinolone resistant strains in that particular subset and see how gemi performs in a clinical experience setting.

I would also add that from the safety side, what I m not comfortable with or satisfactory with the data is looking at floroquinolone experienced patient population, not the healthy volunteers, but in that enriched population, to see what kind of rash incidence are we seeing?

Because we know floroquinolones, it s already so widespread prescribed out there. It s hard to not find someone who s been exposed to

floroquinolone, and in that setting, does it then accelerate or amplify this risk of rash in those populations?

DR. EDWARDS: Thank you. Yes, Dr. Bigby?

DR. BIGBY: I don t think I m going to make a comment about the efficacy arm, but in terms of safety, post-marketing surveys are only as good as the rigor with which the adverse reactions are sought.

You read a lot of post-marketing surveillance surveys where the incidence of side effects is extremely low, way below what is actually occurring in clinical practice, and I think it s because if you don t look for things, you don t find them, even though you keep track of the denominator. So I think the post-marketing surveillance arm of whatever they do should include sort of really active looking in the numerator part of the equation.

DR. EDWARDS: Thank you. Dr. Poretz?

DR. PORETZ: Not much to add, except to continue post-marketing attempts to find out fi anything new or different is going to happen. Our experience with quinolones over the last several

years, I guess there are more that have been removed from the market than ended in the market. God knows what s going to happen in the future. I just think we need to continue to prospectively follow potential either rash or any other side effects with this drug.

DR. EDWARDS: Thank you. Joan?

DR. HILTON: Okay. I d like to get back to -- I promised to give you the data on duration of rash. It s Page 73, and I did misquote that. I said it was about two weeks duration, and the text says five days, so --

DR. EDWARDS: Thank you.

DR. HILTON: All right. Getting to the question of what future studies I think need to be done, I think that if the sponsor really does have confidence in the efficacy of this drug, then a placebo controlled trial will show that, and there would be a black and white case made for the risk-benefit profile in that case.

So I d like to see them go ahead and do that, if they re confident that they have a good product.

DR. EDWARDS: Thank you. Dr. Townsend?

DR. TOWNSEND: In addition to a placebo controlled trial, along the lines of what Dr. Wong was saying, I think it would be interesting to do a trial, as we were discussing earlier, of treatment failure with this drug, as a comparator with a control agent.

DR. EDWARDS: Thank you. Dr. -- oh, yes, I m sorry. Dr. Kauffman?

DR. KAUFFMAN: I don t know that I had more to add, other than I would agree that doing the placebo controlled study at five days with microbiology data will prove the point. I think that nothing short of that is going to be effective, in terms of coming back and getting the FDA to approve the drug.

Otherwise, I guess post-marketing, I just don t know how good it is. I think we miss a whole lot of things, unless some disaster happens later on, like the trovafloxacin business, but that was many millions of patients later when it was finally found.

So I don t know how good it is, but it s worth trying, I suppose.

DR. EDWARDS: Thank you. For me, a decision in the future would be a risk-benefit equation analysis again. In that context, a superiority trial would be very helpful for establishing benefit. The continued following of the FORCE trial to completion, in addition to an effort to modify the proposed epidemiology trial, would seem meritorious. Those would be highly desirable for my reevaluation in the future.

DR. BRADLEY: I think just (phonetic) start off with the efficacy trial, a placebo controlled superiority trial, as requested by the FDA. I m actually pretty confident that the drug would work, but I want to make a plea that the communication between the FDA and the sponsor be better.

This entire 150-page briefing book from the sponsor suggests that they re using the old standards, and there s not any clue that they re considering a superiority trial. So somehow, either they didn t believe you or you didn t

communicate it to them or something, but if -- given the science, if that was really clear, then we wouldn t all be sitting here today.

So what would need to be done is the new superiority trial based on the new guidelines, which we d love to see.

DR. EDWARDS: Yes, Marian?

DR. GUTIERREZ: I would agree that I would like to encourage the sponsor to consider an efficacy superiority trial. I do believe this drug works, I thought, it s probably effective, and I made my decision based on the risk-benefit ratio, which I was not in favor of.

I also agree with your comment about how I think that this drug is a drug that would have a place in treatment failures and complicated infections. So I would encourage pursuing that avenue.

DR. GARDNER: I would agree about the treatment failures. That was the first note I made to myself when I began to read the documents, that it would be very helpful to know if it were clinically

effective in failures, because that would give it its own -- then we could really speak to that.

So if that can progress, that would be extremely helpful, but I think we re going to have a lot to do to get past this safety issue and continuing to monitor that and actively monitor it, which I think was suggested is going to be critical, or if we come back here in another three years and the data are the same about the rash, we ll -- I ll probably vote the same way, in the absence of fabulous efficacy data in resistant folks or failures.

DR. EDWARDS: I believe we have addressed the issue regarding risk management issues already in the discussions, Dr. Albrecht, unless you want additional suggestions in that area.

DR. ALBRECHT: I think I heard Dr. Frothingham s suggestion. I didn t know if maybe other members on the committee might want to talk about either risk management issues or labeling issues for the product, as well.

DR. EDWARDS: Regardless of their voting, I

presume?

DR. ALBRECHT: Regardless of how they voted, based on the information they heard today, just in general, whether there are any suggestions regarding risk management programs or additional labeling that they believe may be warranted.

DR. EDWARDS: Okay. Would anyone care to address those issues, risk management, with additional comments? Yes, Jackie?

DR. GARDNER: Well, on the assumption that you would proceed, then, I think the suggestion of the dose packaging -- limited dose packing would be extremely helpful.

I think the suggestion of not sampling, under the circumstances, would be critical to risk management, and targeted patient information or med guides or whatever kinds of things we re using now to alert people to -- just in general, as well as specifically -- to proper use of antibiotics to reduce resistance development, and not insisting from your physician that you get a second course because your condition isn t cleared up and so on

would all be helpful.

So patient communication, not sampling, and targeted packaging.

DR. EDWARDS: Any other comments?

DR. TOWNSEND: Just --

DR. EDWARDS: Yes, Dr. Townsend?

DR. TOWNSEND: I just had a question, basically, about suspending sampling. What authority does the FDA have to do that, and could it be suspended for all antibiotics?

DR. TEMPLE: I don t think we have authority to ban it. I think we could probably agree with the sponsor that for certain things, it wasn t a good idea, but that would be totally voluntary. We d need to check with chief counsel to get a more definitive answer, but I don t think we have that authority.

DR. FROTHINGHAM: There is precedent, in the case of trovafloxacin, where the indication was that it needed to be started in hospital, so -- which effectively eliminated sampling. So, I mean, I think in some cases of safety issues, the FDA

has, in fact, defacto abandoned sampling, if not du jour.

DR. ALBRECHT: May I follow up on that? You re correct. With trovafloxacin, that floroquinolone was available in oral and IV formulation. It was approved for a record number of indications, ranging from sinusitis, pneumonia, ABCB, through very serious indications, and actually, after the hepatotoxicity was discovered, the Agency and company re-labeled the product, removing some of those indications.

Again, this was a voluntary act on the part of the company, and it is in that context that it was limited. So this echos what Dr. Temple said. If the company is willing to change some of these approached, it can be done. But that was done in the context of re-labeling an indication such as sinusitis, ABCB, uncomplicated (phonetic) UTI were actually removed by the application from the labeling.

DR. EDWARDS: Dr. Temple?

DR. TEMPLE: Well, I probably should have

waited more before I spoke. There have been cases where we thought that only certain conditions -- certain conditions were necessary before a drug could be given out, like for clozapine, you have to get your white count done, and implicit in that is that you d be -- couldn t hand out a sample, because they wouldn t have gotten their white count done.

So there may be risk management programs that really would preclude it.

DR. EDWARDS: Yes?

DR. TUNKEL: Just for clarification, too -- I m sort of new to this -- what about changing the package insert? So will that happen automatically? Now, there will be a warning, use of this drug for more than five days may be associated with rash ? When a patient gets their prescription, will they get a little printout label say Use of this drug for more than five days may be associated with a rash. We want you to be aware of it ?

I mean, what do you have the sponsor do at this point?

DR. ALBRECHT: There are a number of mechanisms and approaches that we can use. The labeling of a product is actually a product of negotiation between the FDA and what FDA believes should be in the labeling, and then what the company believes is actually an accurate and complete reflection of the information.

So any labeling recommendations, either that you ve made that we would like to discuss with the company or, in fact, post-marketing information, as Dr. Mosholder presented, if that information is not in the product labeling, either the company will -- can or will submit it as a change -- known as a change is being effected supplement. Or we, as we identify these, may request that they update the labeling to include that.

Then as we learn more information about a product, we actually do periodically and routinely -- and we have done this on a couple of occasions for the floroquinolone product -- send out what are known as supplement request letters to these companies and ask them to either add additional

information, if we know such, or ask them to analyze certain signals that we may see in the post-marketing database.

As far as information that is required to be given to a patient, the mechanism available is known as a med guide. That is reserved for selected scenarios and situations, usually for toxicities, I believe, that are associated with serious outcome; hospitalization, mortality, etc.

I don t believe it s used for adverse events that are simply frequent and may not be classified as serious.

DR. EDWARDS: Yes, Dr. Wong?

DR. WONG-BERINGER: Thank you. I would also suggest that perhaps there might be a mechanism where we could request that the patient, the target population, the women less than 40 or post-menopausal on hormonal replacement therapy, to sign an acknowledgment that they ve received counseling from their physician regarding the risk of rash in those patients, and to limit duration to five days.

And along with that, to have a phone number that perhaps the sponsor could be managing for the patients to call in if they do develop a rash, and that would help with post-marketing surveillance, perhaps.

DR. EDWARDS: All right. Dr. Temple?

DR. TEMPLE: There have been such programs for flutamide, accutane, things like that. They re pretty burdensome to the use of the drug and they re not used lightly. So, I mean, those things can be considered, but they re a lot of work. You have to -- the doctor has to do it in the office, can t just give a prescription. So it -- they re done for fairly serious concerns, birth defects and other really bad stuff.

I don t know. You have to advise us on whether you think this measures up to that, but that s what they re usually used for.

DR. EDWARDS: Yes, Rich?

DR. FROTHINGHAM: Yes, I mean, I ve brought out this can of worms for you folks to consider. I was really thinking in terms of the patient information

that is normally dispensed with the drug, and it s at the end of the package insert, and I ve received those sheets with medication, so I know that they do go to consumers.

As opposed to a specific additional -- I would agree that -- or at least I would state my impression that this is not a drug that has a life-threatening adverse effect that is unusual, simply an unusual incidence of a relatively mild effect, and that just adding that in a more prominent fashion to the package insert information that goes to the patient will be sufficient.

However, when it comes to sampling, I think that s a place where problems arise, because samples are distributed without knowledge of the drug, unfortunately, whereas prescriptions are normally written by people who have chosen that drug and know it better.

So, I mean, if sampling is to continue, I think there is some greater burden that ought to go forward, but I was not implying an additional burden for all prescriptions for this medication.

DR. EDWARDS: Yes, Dr. Albrecht?

DR. ALBRECHT: I had one last question, that if folks have finished talking about the labeling, that I actually wanted to explore, if perhaps people wanted to comment on it. This goes back directly to Dr. Ferguson s earlier review of the two publications that she cited.

So what my specific question is, as you heard today, in these clinical studies that were conducted, patients had radiographic evidence of sinusitis, along with clinical evidence, and in the subset of the studies, bacteriologic evidence.

Then I think, as Dr. Ferguson talked about the Bucher (phonetic) study, her observation was that in that study, it was based, I believe, purely on clinical signs and symptoms, and the latter was the study that failed to show a difference between augmentin and placebo.

So I guess I wanted to ask the committee whether they think there may be merit if the company pursues this indication, and perhaps looking at both types of studies; studies where

there are these diagnostic criteria that are met, which would be reflective of testing the safety and efficacy of the product in the patient population with the disease, and then perhaps studies that may be more reflective of empiric use of the product in patients believed to have sinusitis.

So I just didn t know if the committee members might want to comment on either the validity or usefulness of either or both types of study designs.

DR. EDWARDS: Yes, Dr. --

DR. WIEDERMANN: I think that the types of studies were -- they re really intended to mimic everyday practice. So patients with sinusitis don t get radiographs. I think those are useful. The problem comes in if some key element of use of the drug is based solely on that data.

But ideally, you could have a large study and a subset of the patients had sinus taps and radiographs and maybe even quantitative bacterial cultures, and were -- had a high degree of rigor, and then maybe a larger group that didn t have all

that. That really does mimic everyday practice, so I think there s good use of both types.

DR. EDWARDS: Carol? Dr. Kauffman?

DR. KAUFFMAN: My concern would be that a company might do that study -- and these studies cost lots of money -- and then they ll come to a panel and they ll say, Oh, but this isn t rigorous enough, so it seems like you better do a gold standard if you re going to do it.

DR. EDWARDS: Any other comments to those issues? Anything else, Dr. Albrecht? Should we -- are there any other issues we should discuss, any other points, any points of clarification?

DR. ALBRECHT: I m looking around to see if others have questions.

DR. EDWARDS: Any other questions?

DR. ALBRECHT: It looks like there are no further questions.

DR. EDWARDS: Okay. I d like to just make a couple of comments, and then bring the meeting to a close. This has been a very intense discussion that has revolved around the issues that are

debated extensively in the literature now regarding the non-inferiority trial design and surrogate markers in infectious diseases.

Clearly, those issues are being debated and of such concern because of a genuinely recognized need for our -- to continue to develop antimicrobial agents at a rate that keeps up with the resistance problem that we re experiencing at the present time.

The issue is in flux and the science is developing, and I think we ve had a healthy discussion about some of the issues today. The issue regarding the rash associated with gemifloxacin, I think all of us who voted no in this discussion are deeply sorry that this drug has that complication associated with it, and none of us would be here if the level of that problem were not at the level that it is at the present time, and I m sure that there s been concern for the fact that it may be a strong signal eventually, although it hasn t shown itself definitively at the present time for fatal cases of Stevens-Johnson Syndrome.

But we can only do what we feel is right based with those kinds of concerns in our background thinking, and do not have a discrete database, and so I think we ve all had to sort of vote with an element of concern for that issue, as we have seen similar sorts of adverse effects occur with drugs which have been used on a large scale, even with and without a strong signal. But obviously, it would be wonderful if this agent did not have that associated disadvantage.

The -- I really wanted to thank the sponsor for a very well-constructed, very concise, targeted presentation today, and I think all of us respect the efforts that they have been making in post-marketing attempts to continue with a safety profile that will be strong for the agent, and in these post-marketing studies. I think we all deeply appreciate your adhering to the post-marketing study suggestions that have been made.

I d like to thank the FDA for their presentations and all of the people who have put

hundreds of hours of effort into this meeting occurring, and to the panel members who have participated in this very difficult and very trying experience of having to review the situation that revolves around this agent.

So thank you all very much for your participation, and if there are no further issues or comments, then I will adjourn the meeting at this time. Thank you.

(Meeting adjourned at 4:15 p.m.)