environment, as with the clinical trials, there is an association with serious skin events, serious allergic responses, rashes requiring hospital treatment, even without meeting criteria for SJS or TEN and, as we ve said, some possible SJS cases. Importantly, many reports lack critical information that might have permitted a more definitive classification.

Comparing to gemifloxacin, there was a higher reporting rate, but however, such comparisons must be very cautiously made because of the uncertainties in both the numerator and the denominator for doing those calculations.

As a particular point about cefditoren, it has been marketed actually extensively overseas, particularly in Japan over the last decade, and Japanese post-marketing data has been associated with SJS and TEN. So given that knowledge, the relative -- the absence of U.S. reports of definitive cases in that category can be viewed as only giving limited reassurance.

The point here is that with the million or so

patients exposed to gemifloxacin to date, because of the short duration of the course of treatment, a week or two, and because of the relative rarity of SJS as spontaneous in the population, estimates range from about one to six per million person years.

We would not even expect spontaneously a single case of SJS out of this patient population, taking the drug for a week or two. So even a single case might be significant there.

So overall conclusions, the important adverse events include serious allergic reactions, Clostridium colitis, rashes requiring hospitalization, possibly SJS, possibly an interaction with Coumadin, and perhaps thrombocytopenia.

We would not view the post-marketing data as giving us reassurance about the cutaneous toxicity for the limitations that I ve described. The advice is that the magnitude of the benefit gained from the use in ABS needs to be clearly defined so it can be weighed against these risks.

Finally, I want to acknowledge all of the many colleagues at FDA who assisted me with this analysis.

DR. EDWARDS: Thank you very much. We re just a little bit behind our allotted question period, and I m going to take the prerogative to do the following thing. I d like to keep our lunch break at 12:15 so we can resume at 1:15 for the open public hearing, and if we have additional questions of either the sponsor or the FDA, those will be certainly part of the afternoon s discussion period.

So with that thought in mind, we d like to keep the questions sort of focused between now and 12:15, so we can take our break at that time. I m going to actually start with Rich here, who has indicated he had a question, and then I ll come to you, Don.

DR. FROTHINGHAM: Yes, thank you. This is a question for Dr. Tierney. When you discussed the MIC data, you presented the extremely low MIC values for respiratory pathogens, and then placed

that in the context of the low serum concentrations achieved by gemifloxacin.

However, that context wasn t provided in your slide 46, when you ranked the six respiratory quinolones on the basis of their IC50 for the HERG channel, which is a surrogate for QT prolongations. If you actually calculate a ratio between the HERG IC50 and either the serum peak or the AUC, it appears that gemifloxacin actually has the highest margin of safety among the six quinolones that you listed, and that comparison, that ratio, has been used in previous published reports.

Would you consider that ratio to be a reasonable approach to interpreting the HERG IC50 data as a surrogate for QT prolongation?

DR. TIERNEY: I may actually ask some of my colleagues for that sort of more general question. I think that the clinical data support that, and that s why obviously they always need to be presented together. I mean, the clinical trial data shows a very low, 2.3 milliseconds, increase. But I m just going to see whether Dr. Sacks could

answer that question?

DR. SACKS: I think your point is well made. I mean, obviously, the HERG toxicity is related to the concentration, especially in vivo, so I think that s correct. I don t think that we re presenting a particular problem with gemifloxacin with regard to that.

The other thing to bear in mind is obviously the HERG essay is very much a surrogate. It s somewhat removed from the clinical effects, and I think the clinical data is probably some more important, so I m not sure if anyone else has any comments here.

DR. EDWARDS: Yes, Don.

DR. PORETZ: The sponsor presented a slide from Dr. Gwaltney s chapter in Mandell s book about effective antibiotic treatment of ABS, and they listed seven drugs. How many drugs are approved by the FDA at the present time -- realizing there are all sorts of off-label prescriptions being written -- but how many drugs are approved by the FDA for ABS at the present time?

DR. POWERS: There are 20 different drugs. They re not individual drugs, because that counts including some that are approved at multiple dosages. So there are 20 different applications approved for acute bacterial sinusitis.

Some of those are -- if you count like amoxicillin, which has in its label approved for infections of the ear, nose, and throat. So labels have gotten much more specific, and more informative for clinicians, we we ve gone on.

DR. PORETZ: But as time goes on, resistance develops to some drugs. Does the FDA ever remove an indication?

DR. POWERS: Usually, the way the indications read are that the drug is effective for disease due to susceptible pathogens. That remains true. I mean, even penicillin is still active against skin infections caused by staph aureus, when it s susceptible to penicillin.

If you look at the labels in that way, they remain correct. What needs to change sometimes is maybe the susceptibility break point, and we need

to do a better job about updating the labels and making that accurate.

DR. EDWARDS: Yes, Peter?

DR. GROSS: On slide 10 that Dr. Tierney presented on microbiological results for Study 009, I got the sense that the implication was that haemophalis influenza was less susceptible with gemi than with cefuroxime, but the denominators for most of the ones, at least the ones on the lower part of the chart, are all small enough that it s hard to say there s any statistically significant difference between them.

DR. TIERNEY: I think that s correct. Actually, I had mentioned that for the bottom three organisms -- Klebsiella, staph aureus, and M. catarrhalis -- that at the time that this application was presented, there was concern that there weren t enough isolets there and results to be able to make conclusions about efficacy, and that the two organisms that there were enough isolets to really look at were streptococcus pneumoniae and haemophalis influenza.

If -- and so -- and just a -- it was a presentation to sort of look at what is the overall sort of benefit advantage efficacy in that perspective.

DR. EDWARDS: Yes?

DR. WIEDERMANN: This is another question for Dr. Tierney. On your last slide, you mention a 2 to 3% rate of patients being labeled quinolone allergic. I m not sure I caught where that number came from.

DR. TIERNEY: Well, I should say that that s speculative, and the reason being if someone develops a rash to gemifloxacin, I think practically what s going to happen, and is a clinician in the community going to feel comfortable giving that individual either gemifloxacin again or a quinolone.

So I think -- if I don t have a question mark there, I should. But I think the concern is, I think that s one just practical possibility, that people may be labeled quinolone allergic if, indeed, they develop a rash.

DR. EDWARDS: Yes?

DR. MALDONADO: On the same slide, you put there severe rash. How is severity defined?

DR. TIERNEY: That s a good question. Severity is usually investigator determined. There s often not a very particular definition of severe, and it will vary obviously in a clinical trial, from clinical trial to clinical trial, and to the community, as well.

DR. EDWARDS: Other questions? Dr. Tierney, I had one on your analysis of Study 186. There was a difference in efficacy in the intention to treat and the per-protocol analyses, and I was wondering if you can clarify any points that might tell us why that difference existed. Sorry, I don t have -- it was Study 186.

DR. TIERNEY: Is it for the end of therapy, or the follow-up? There s two -- I have two slides.

DR. EDWARDS: I think it was the end of therapy.

DR. TIERNEY: Okay. Okay, I m just -- that s slide nine. Just to -- the success rate is

actually quite high in the per-protocol population, and then when we look at the ITT, the rates go down for gemifloxacin five-day more than they do for gemifloxacin seven-day, and --

DR. EDWARDS: Yes, it looked like it went down quite a bit, actually.

DR. TIERNEY: So I think what are the things that cause when someone -- the end of therapy is going to be about day seven, just a couple of days after five days, versus day 18 to 24. So the assumption is -- I mean, one potential is that someone got worse in that period of time. It s a thought that is someone relapsing?

John, do you have anything further to add, between -- the difference between having end of therapy and follow-up?

DR. EDWARDS: All right. Other questions from the panel? Yes, Dr. Maldonado?

DR. MALDONADO: Yes. In the presentation by Dr. Albrecht this morning, I see in her slide number 12 that as recent as February of last year, the FDA had agreed that the drug was effective.

However, now, the efficacy of the drug or the effectiveness of the drug is being questioned, so where is the change? I mean, what kind of change happened between February of last year and today?

DR. ALBRECHT: To summarize what I mentioned, is when we spoke with the company in 2005, we agreed that when the applications were submitted initially in 99 and 2001, they had been analyzed using those parameters that had been agreed to in the original study designs, and this agreement was what we reiterated during our subsequent discussions with them.

But I also want to then elaborate that in context of that same agreement, we again reiterated that even though the parameters of efficacy had been met, the concerns regarding safety were such that they overrode those decisions or those conclusions of efficacy.

As far as what has changed, is we have a new efficacy supplement in-house, and as FDA, we need to review any new applications completely and comprehensively, so that includes review of both

the efficacy and the safety.

I think you ve heard a thorough review of the safety and as several speakers, including Dr. Powers and Dr. Tierney, mentioned, when we look at efficacy, we need to take into consideration other developments and other sort of new information that we have come to learn that may be relevant at the time that the application is being considered.

And as you heard, we mentioned that a number of open public workshops had taken place between 2002 and now, which made us need to look more carefully at the non-inferiority study design.

DR. MALDONADO: So a follow-up question to that, so the standard now is placebo controlled trials, is it, for ABS?

DR. ALBRECHT: Based on the recommendations that we heard at the October 2003 advisory committee on acute bacterial sinusitis, the recommendation was made that superiority study designs should be asked for, because it was not possible, based on the available placebo controlled studies, to determine what would be an appropriate

non-inferiority margin for those studies.

DR. EDWARDS: Dr. Bradley?

DR. BRADLEY: I have a question that relates to safety, and coming back to the rash, again. We ve heard, again going back to 2003, Dr. Shear giving us reassurance that this rash is mild and goes away quickly and is of no significance, and it s actually of some comfort to me that, having voted to approve the drug in 2003, that there haven t been a whole rash of Stevens-Johnson Syndrome patients, which was one of our concerns back then.

The way the FDA -- your review of the rash safety in your presentation included urticaria and all sorts of photosensitivity that the sponsor did not actually include in their presentation. Dr. Bigby, in 2003, expressed caution, and when we said would you treat one of your patients in your dermatology clinic with this type of drug knowing this rate of rash, he was very cautious and said it would be difficult for him.

Something -- I m paraphrasing you, but you made us all feel that this particular type of rash

could lead to something much worse, perhaps in a smaller proportion of the population.

With the new information that we have since 2003, biopsy samples on this high-risk population, do you feel more reassured that the rash is benign, or are you still concerned that there will be a rate of Stevens-Johnson Syndrome that may be lower than you were concerned about before, but still significant enough for you to not want to use the drug?

DR. EDWARDS: John, excuse me just a second. I m just wondering if you would mind if we postponed that question to the discussion.

DR. BRADLEY: Of course. It s --

DR. EDWARDS: It will fit perfectly into the discussion format, I believe.

DR. BRADLEY: It gives him a chance to think of an answer, too.

DR. EDWARDS: Yes, I -- and I m sure he appreciates being taken off the spot for the moment. Is that all right?

DR. BRADLEY: Of course.

DR. EDWARDS: All right. Yes, Rich?

DR. FROTHINGHAM: I have a question for the sponsor, and this goes back to an earlier question that Dr. Gutierrez asked about Study 344, the study that had two phases, Phase A and B, and the continuation between Phase A and Phase B. You mentioned that this continuation rate did not vary based on whether the patients had degrees of severity of rash.

As I looked at the data after that question was asked, it appears that among those who were given gemifloxacin in Phase A, those who had rash withdrew from the study at a 25% rate; that is, did not continue on into Phase B, whereas those who had no rash had only a 9% withdrawal.

That difference is statistically significant at a very low P value, the difference between 25% withdrawal and 9%. I m wondering if you can comment on that in the context of would that be considered withdrawal based on rash; was the rash something that was significant enough to lead to withdrawal of the patients from the trial?

DR. PATOU: I mean, the question, as I understood it was asked previously, was was there any difference in the nature of the rash amongst those who has rash who were withdrawn from trial. I think you re saying that of those withdrawn from trial, there were a greater number who had rash that withdrew, and I readily accept that.

But I think -- if I may ask if I m correct -- I think the concern was, was there any kind of an ascertainment bias that the individuals with rash who withdrew from Part B of the study somehow skewed the Part B? We did look carefully at those reports of rash, and they were not different to the overall population.

So I m not arguing that there wasn t a higher rate of withdrawal due to rash in the study; it s just that there wasn t anything atypical about that population that withdrew.

DR. FROTHINGHAM: Thank you.

DR. EDWARDS: Are there other questions at this time? Yes, please.

DR. MOSADDEGH: This is actually a question for

Dr. Ferguson. In the Lindbeck study, there s an obvious difference in the difference between the treatments and in the response rate over time, with the biggest difference -- I should day I m not advertising this as a wonderful study or anything; I m just asking about it because it s in your briefing book.

There s a clear difference between the comparison of therapies at say 28 days and the comparison at 10 days, which with the far more useful comparison in that it shows maybe a difference of being at say 10 days.

DR. FERGUSON: Slide one, please.

DR. MOSADDEGH: Yes, do you have a view on that? It seems to me the 28-day endpoint is almost designed to not be able to show a difference, which was what was used in some of your trials.

DR. FERGUSON: There were several endpoints in the study, and one of them was them was that at day 10, about 87% of the patients on antibiotic were improved or cured, compared to almost 60% on placebo. But if you look at the mean duration of

illness, when did they feel cured, the patients on amoxicillin felt cured at day nine; I think the patients on penicillin, day 11; the patients on placebo was something like day 17. If you go out to day 30, you find a high number of the patients on placebo are still symptomatic.

Now, this was the first of the Lindbeck studies that was shown with placebo controlled trials, and all of these patients had air-fluid level or total opacification on their sinus CT, in contrast to the other Lindbeck placebo controlled trial, where none of those patients had air-fluid level or opacification, and only had mucosal thickening, which is why we see a lesser result in that other placebo controlled trial.

DR. MOSADDEGH: Yes. I was really going to the question of when you d want to look for treatment effects, and this makes the argument that looking early is the only even remotely plausible time to look; is that right?

DR. FERGUSON: Oh, I agree with you so much. When I treat a patient clinically, I ask them in 48

hours, are you feeling better? And if they re not feeling better, I m changing therapy based on my culture, based on what I gave them before. You re exactly right about that.

DR. MOSADDEGH: That s going to lead to later questions later about whether you could just compare immediate therapy with delayed and get an actual answer, but that s for later.

DR. EDWARDS: At this point, if there are no additional burning questions, I d like to break for the lunch and we ll resume at 1:15 for the open public hearing. For the panel, there apparently is a reserve room for lunch, and we request that the issues not be discussed during lunch. Thank you very much, and we ll resume at 1:15.

(Off the record at 12:18 p.m.)

(On the record at 1:16 p.m.)

DR. EDWARDS: I d like to call this afternoon session to order. At this point, we re going to begin the open public hearing, and this is a part of this process we all feel is very important, and it s customary to read the introductory statement

before the open public hearing, which I will do now.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believe it is important to understand the context of an individual s presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor s payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial

relationships at the beginning of your statement, it will not preclude you from speaking.

At this time, I would like to invite our first public speaker for the open forum, Mark Cohen, to the podium, please. Right. I m asked to remind the speakers that the allotted time is five minutes.

DR. COHEN: Yes, there we go. Okay. Good afternoon. My name is Mark Cohen and I have absolutely no financial relationship whatsoever to the sponsor.

I am the Food and Drug Safety Director of the Government Accountability Project. GAP is a 29-year-old nonprofit public interest group that promotes government and corporate responsibility by advancing occupational free speech, defending whistle-blowers, and empowering citizen activists. Our clients include FDA and drug company employees.

I m here today to express concerns held both within and without FDA that the Agency is not following its own regulations in two readily approving drugs, antibiotics in particular, without

actual proof of their efficacy. These drugs, like gemifloxacin, inevitably carry with them significant adverse safety profiles. Moreover, their inappropriate use contributes to the very real and growing public health crisis of antibiotic resistance.

There are two basic models for the study of drugs, superiority trials, as placebo controlled trials, or the misnamed non-inferiority trials, which are better called acceptably inferior trials.

In special circumstances, acceptably inferior trials make sense for less serious indications, as well as serious ones. For example, even if a new drug is less effective than its comparator drug, it might also be less toxic or require fewer doses.

But absent such special circumstances, there is no scientific justification for not requiring a placebo or superiority trial, and no justification for failing to show that the new drug is more effective than a sugar pill. After all, what good are fewer doses if the drug is ineffective?

If it isn t a proven treatment modality, a

drug that causes even a single adverse health impact is not morally or legally acceptable, especially when the drug s use contributes to the spread of antibiotic resistance. This kind of requirement for proven benefits to mitigate the harms of drugs has been part of FDA s own rules for over a half of century, yet the Agency continues to ignore it in the area of antibiotic studies.

This is the issue we confront with gemifloxacin and other antibiotics, being approved willy-nilly for less serious indications. A study reported today in the Journal of the American Medical Association finds that as between children given antibiotics and analgesics for ear infections, and those given only analgesics, there was no statistically significant difference between the groups in the frequency of subsequent fever, ultalga (phonetic), or unscheduled visits for medical care.

A study such as this shows that there is a need to know when antibiotics work, in whom they work, and that placebo controlled trials can be

done and are being done. Yet in the last decade, the FDA has approved, through non-inferiority trials over 60 applications for antibiotics for less serious respiratory infections.

It s a house of cards. Often, the comparator drugs themselves have not been proven more effective than placebo. The stunning truth is, as designed, non-inferiority trials fail to ensure that a new drug is better than no treatment at all for some of these less serious diseases.

Non-inferiority trials are a useful tool in the right situation, but the abuse of them is shameful and unethical. The FDA should not be exposing patients to potential risks in trials that do not prove the drug s benefits, and it ought not be approving drugs of unproven efficacy that carry harmful side effects and compound the problems of antibiotic resistance.

Just last week, a bipartisan group of five members of the House and Senate, citing the Key-Tech experience, requested that the Government Accountability Office -- that s the GAO, not my

group -- that the GAO evaluate the FDA s oversight and reliance on non-inferiority trials to establish effectiveness.

This letter followed on a previous request in June by Congress to address these issues, a request largely ignored by FDA. A GAO study could spur a legislative remedy by Congress to the abuse of non-inferiority trials. I ll leave you a copy of this letter from the members of Congress.

In the meantime, it falls upon this advisory committee to --

DR. EDWARDS: If you d like to complete that last sentence, or just come quickly to the end point, that s fine. This was an electronic --

DR. COHEN: We were really there.

DR. EDWARDS: Yes. As you might have gathered, it s an automatic timer. I m sorry.

DR. COHEN: Right, yes. In the meantime, it falls upon this advisory committee to advise FDA to follow its own regulations and recommend that gemifloxacin and like drugs not be approved unless and until they are truly shown effective and safe.

We do need new antibiotics, but ones for serious and life-threatening diseases, and we need antibiotics that work, not drugs that are unproven against less serious diseases.

The American public expects that the FDA will protect us, not serve as a rubber stamp for industry. Thank you for your consideration and time.

DR. EDWARDS: Thank you for those important comments. I d now like to go on to Kristin Suthers for her comments.

DR. SUTHERS: Okay. Good afternoon. My name is Kristin Suthers, and I am pleased to submit comments on behalf of the National Women s Health Network regarding this new drug application for gemifloxacin for the treatment of acute bacterial sinusitis.

The National Women s Health Network works to improve the health of all women by developing and promoting a critical analysis of health issues in order to effect a public policy and support consumer decision-making. The network is supported

by our members and funding from private foundations. We do not accept, nor do I accept, funding from pharmaceutical or medical device manufacturers in any form.

Our comments and suggestions are divided into two issues. First, we question whether the study methodology, also known as a non-inferiority trial, is the appropriate means to determine the efficacy of gemifloxacin for acute bacterial sinusitis.

Second, we question why women were more likely to exhibit a rash due to gemifloxacin for a condition that is not gender-specific, and until the origin of the sex difference in rash incidence is understood, we strongly urge the FDA not to approve this product for acute bacterial sinusitis.

Much has been written about the use of non-inferiority trials in the FDA drug approval process, and gemifloxacin is a prime example of why this type of study methodology is inappropriate for determining the efficacy of drugs for non-life-threatening conditions.

In the case of gemifloxacin, the comparative

therapeutic benefit appears to offer no greater advantage to similar products that area already available on the market, but more importantly, we have no idea if gemifloxacin offers any therapeutic, at all, since it was not compared to a placebo in company studies.

What the non-inferiority studies do show, however, is that there is a greater likelihood of rashes for women who take gemifloxacin compared to other drugs for the same condition; clearly, an unnecessary risk that outweighs an unproven benefit.

Based on company studies, FDA knows the incidence of rashes among women is greater for gemifloxacin compared to another FDA-approved product for acute bacterial sinusitis.

It is especially concerning to us that women were more likely to exhibit a rash due to gemifloxacin for a condition that is not gender-specific. This is disturbing and leads one to wonder if there are other, unobserved sequella for women, given that the origin of the sex difference

in rash incidence is unknown.

A skin rash that may seem inconsequential to a clinician or in the context of data analysis may cause significant suffering to an individual woman based on her own unique health circumstances. This unnecessary suffering should not be minimized or disregarded because some clinicians consider it irrelevant.

Gemifloxacin has an adverse risk-benefit profile for acute bacterial sinusitis, and is particularly risky for women. The National Women s Health Network urges the FDA to deny approval of this application. Thank you.

DR. EDWARDS: Thank you very much for those comments. Are there any other individuals who would like to contribute to the open public forum at this time? If so, would they please identify themselves?

Thank you very much. We ll now move on to the general discussion, and before I ask for the FDA to present the questions and committee deliberation, directions, I d like to mention that we re

scheduled to end this meeting at 5:00 this evening, and I know there are many people with flight reservations and other commitments, and we re going to make every conceivable effort to be finished at 5:00, and that will happen unless some major unforeseen event occurs here.

So within that context, I d like to keep the questions and discussion focused, realizing that we have a relatively small period of time in which to discuss this very important issue.

With that, I d like to ask Dr. Renata Albrecht to give the charge to the committee for the discussion.

DR. ALBRECHT: Thank you, Dr. Edwards. Actually, if I may, I d like to start by thanking the presenters, both from Oscient and FDA, for giving really very thorough, very comprehensive, and very informative presentations, and also, to actually single out two FDA staff that you haven t seen, but have done all the work behind the scenes to make today possible.

One is Dr. Steve Gitterman, our Deputy

Director, who I think is still doing things and not here with us, and the other is our Regulatory Project Manager, Dr. Brenda Marx. So I just wanted to thank them.

Let me turn to the task that we have before the committee and the issues that we d like for you to help us deliberate on. As you heard during the presentations this morning, there was information presented on the efficacy of gemifloxacin in context of the indication of acute bacterial sinusitis.

You heard about the study design, you heard about the study populations, the study endpoints, the outcome, and the fact that these were non-inferiority study designs, as well as open studies. In addition, you heard from Dr. Powers about the challenges of interpreting non-inferiority study designs, and he also reviewed the literature on available placebo controlled studies in this indication, and identified some of the challenges in setting non-inferiority margins in this setting.

You also heard discussions about safety this morning, both from the company and FDA; information from adverse event reporting in clinical studies on the cutaneous adverse events, as well as other adverse events; information from post-marketing on the spontaneously reported adverse events, including cutaneous adverse events; some data presented by the company on the FORCE study; and also, on the practitioners prescribing and use study.

Taking all that information that you ve heard today, we re interested in your views on both the efficacy of the product, as well as safety. So as far as efficacy, we re interested in your views on the level of evidence, or on the persuasiveness of the evidence to support efficacy, as well as whether you believe efficacy has been demonstrated, has been demonstrated in certain settings, or has not been demonstrated, and what you think could be done to demonstrate efficacy.

We re also interested in your perspective on safety, whether you believe that the safety profile

is or is not of concern, whether there are specific aspects of safety that are concerning, and whether, in fact, there is enough information to address the safety profile or whether you believe additional information is necessary.

Finally, we re interested in your assessment of the risk of gemifloxacin compared to your interpretation of the benefit of gemifloxacin in the indication of acute bacterial sinusitis.

So that brings us to the question, which we have posted for you, which is: do the safety and effectiveness data presented demonstrate an acceptable risk-benefit profile of Factive for the five-day treatment of patients with acute bacterial sinusitis? I ll hold off on reading the corollary questions until later.

DR. EDWARDS: I d like to organize a discussion by beginning with the topic of the efficacy. After we ve discussed that, then we ll move to the safety issues. So just to remind the panel members, we have the opportunity to ask for clarification of any points made, either by the sponsor or the FDA.

Let me begin the discussion. Is there anyone who would like to start off with a comment or a question of clarification? Yes, Jackie?

DR. GARDNER: In considering risk and benefit, we have today a lot -- seemingly a lot more information about risk than benefit, and I d like to ask the clinicians on the panel if they could help place in perspective where this product would be in their armamentarium, and whether they consider it to be necessary and advance something that they would use -- actually, following up probably the singling out of Dr. Bigby, but more generally than that, how do the clinicians feel about this product in terms of what it would provide for them as a treatment?

DR. EDWARDS: Before we get a specific answer, could I ask for the people who are actively in clinical practice now to identify themselves, so I will know who to direct the discussion to? Okay. That s a large group. All right.

Would anyone like to start responding to the question of, in general, how do we feel about how

this agent would fit into our clinical use, what are our concerns? It s a more general question, right? Yes?

DR. TUNKEL: Yes, I would say that if I was presented with a patient who had what I believed to be acute bacterial sinusitis, if it was someone who really had not been on antimicrobial therapy, I was seeing them for the first time, I would likely not use gemifloxacin as my initial approach to therapy, but I might use other available agents, such as amoxicillin, clavulanic acid, perhaps cefuroxime axetil.

I think I would only consider use of gemifloxacin, if it were approved, in the patient who had been on multiple courses of antimicrobial therapy who I felt was not getting better and who I felt had clinical evidence of -- and radiographic evidence of sinusitis that I thought was bacterial.

DR. EDWARDS: Dr. Poretz?

DR. PORETZ: I personally believe that in this country, antibiotics are way, way overused. A diagnosis of sinusitis, I think, is over-diagnosed.

I think many times, when a patient comes to a physician s office and they have facial discomfort or congestion, an easy diagnoses to make is sinusitis, but in reality, I don t believe they have bacterial sinusitis as many times as it s supposedly diagnosed.

I asked before how many drugs are approved by the FDA for the treatment of bacterial sinusitis. John, I think you told me 20 some-odd drugs, depending upon the organism and sensitivity data. There are plenty of drugs available, as far as I can tell, to treat bacterial sinusitis at the present time, belonging to various groups, whether they be penicillin derivatives or cephalosporins or macrolides or quinolones, at the present time.

I m not sure that the addition of this drug would add anything to our armamentarium except for a greater incidence of rash.

DR. EDWARDS: Dr. Bradley?

DR. BRADLEY: I m pediatric infectious disease, so I certainly don t treat a lot of women who are 40 years old in my practice. However, there are

some nice parallels with otitis media, and often, the two entities pathophysiologically are compared.

In situations where there s extra risk, whether it s documented or perceived, the indications for particular drugs are different. So quinolone therapy in pediatric otitis was not pursued for plain old garden-variety acute otitis media; it was pursued for failures of treatment with standard first-line therapy or children with recurrences, frequent recurrences, who are known to have an increased risk of having resistant organisms.

I think that the microbiologic profile of this particular drug and the AUC/MIC ratio and its activity against quinolone strains of pneumococcus, makes it something that you would want to have if you needed it, and recognizing that women under 40 are at increased risk of adverse events certainly is important, but to not approve a drug for all of the other age groups and men seems to be throwing the baby out with the bathwater.

So I m wondering if there s some way that as

we deliberate, that instead of just approving it for garden-variety sinusitis, knowing that many of them truly are viral, whether there s some way that we can look at a specific subgroup.

Now, these studies were done with acute bacterial sinusitis and not with failure of treatment of sinusitis, or frequent relapses, so the mix of organisms and the resistance patterns for what we have here will be different than if we did a subsequent study. But I just -- I think that this drug has unique microbiologic properties, and that it can be a value in failures, as was mentioned.

So if you have a patient who you believe has bacterial sinusitis, and they don t respond, and you re looking for a second drug to treat them with because you believe that the organisms are resistant, then this seems to have the microbiologic profile that would give you the reassurance that this might be the best drug to go to as a second-line therapy.

DR. EDWARDS: John, let me ask you to take that

thought a little bit further. What sort of things could you envision helping you make the decision to go to this drug? For instance, would it be positive culture from a tap, or how would you decide when you needed this agent? I realize that s a tough question, but let s -- maybe we could think about it a little bit.

DR. BRADLEY: Well, I think in the older children, adolescents, if there s chronic disease, and there are certainly children with anatomic anomalies -- they get in car accidents, their sinuses have been rearranged -- who get frequent sinus infections, this would be a drug that I would use if I had evidence that the organisms were more resistant than those I could just treat with amoxicillin.

I would still, because of the adverse event profile with the rash, I would be reluctant to use it in girls unless I knew that I was actually treating a bacterial pathogen for which there was no other safer therapy.

DR. EDWARDS: Okay. Thank you. Yes, Joan?

DR. HILTON: I have a comment about the excellent microbiological profile. On Page 30, in Table 7, I was impressed by the ratio of AUC/MIC, but I did notice that those two pieces of data came from different sources. So ideally, those ratios would be based on within patient data.

So there was also a question asked as to what studies might be done in the future, and within patient analysis of this type would be a lot better than this sort of ecological correlation style study.

DR. TOWNSEND: I think that the data certainly do suggest that this drug has the potential for being very efficacious for the treatment of acute bacterial sinusitis. The problem for me is that I don t think it s been proved. I think that unfortunately, the study, as they have been done, don t demonstrate, to me, that the drug is any better than a placebo.

So if I m given a choice of using one of the 20 other drugs that is already indicated for treating acute bacterial sinusitis and this drug,

I d be inclined to choose one of the other ones that at least there s some data suggesting that it s better than placebo.

Then this one, now, I think certainly studies can be done to demonstrate that this drug is better than placebo, but I m not sure that what we have right now do that.

DR. EDWARDS: So if I could summarize your comment, you re concerned about the validity of the efficacy data, as we ve seen it today? Yes. Right. Dr. Kauffman, please.

DR. KAUFFMAN: Thank you, Jack. Just a quick comment that I too am worried about the fact that we just don t have the data, we don t have any microbiologic data, for the five-day, and that s really what the indication is going to be for. Five days clearly decreases the risk, but I m not sure then the benefit has been proved, unfortunately.

DR. EDWARDS: Rich?

DR. FROTHINGHAM: I came away from this discussion actually convinced that gemifloxacin is

highly likely to be effective against acute bacterial sinusitis. I agree with all of the concerns about the trial design and so forth, but I also think about the microbiology and I think about the experience of the whole group of antibiotics together.

This drug looks like it should be highly active, and so I would tend to -- I would think that the evidence for efficacy, both from clinical trial data and from theoretical considerations of how we think antibiotics work, is pretty compelling, so I have no problem with that part of it.

DR. EDWARDS: Marian, what are your thoughts?

DR. GUTIERREZ: Well, I, like John, am also a pediatrician, so there would only be specific circumstances in which I might consider using this drug.

I agree that I think that the in vitro data and some of the study data shows that this drug could be effective, and I think that the place that it might be utilized would be in a situation, such

a Dr. Bradley spoke about, in a complicated case of sinusitis, not in uncomplicated sinusitis.

My concern in sort of listening to this discussion is trying to very carefully weigh the risks versus the benefits.

One of things I see as a potential risk with use of this drug is not so much the rash itself per se, but the implications of what happens after a patient appears with a rash. They get switched to a different antibiotic, which, again, may cause an increased rate of resistance, or they may get placed on steroids or have other interventions done that, in themselves, may actually be more significant than the rash itself. So those are my concerns.

DR. EDWARDS: Peter?

DR. GROSS: Most of us, when we pick a drug, select a drug based on toxicity, spectrum, efficacy, and cost. I distinguish efficacy from antibiotic spectrum because, for example, with ceftriaxone, while in vitro staph aureus may be susceptible to ceftriaxone, there are many clinical

failures, so most of us aren t going to use it for that.

But I think to make a decision on toxicity versus the other 20 drugs that are available, I don t think we really have had the information presented to us that we need to make that particular decision. Right now, it has an excessive incidence of a rash, but how about the other side effects? Do the other drugs have a higher incidence of diarrhea? Are we more likely to see C. dif with other drugs than we are with gemi? I think that s one of the quandaries that we have to face in making this decision.

DR. EDWARDS: Anyone else like to respond? I m sorry. Dr. Wiedermann?

DR. WIEDERMANN: Thank you. Again, I m speaking as a pediatrician, but maybe not so much to the pediatric aspects of this. I think we have a couple things going here. I, too, am -- if I had to be from the in vitro data -- reasonably comforted that this drug is likely to be effective in acute bacterial sinusitis, but I think historically, we ve all seen situations where in

vitro things look good, animal data look good, and then it just doesn t pan out in humans.

I think given that we re talking about a relatively mild, often self-limited disease, I would want to see a little more evidence of efficacy in humans before relying on that.

Then from the side effects standpoint, I think one thing to consider is that drug rashes are sort of the gremlins of primary care medical practice. Drug rashes, as opposed to loose stools or other antibiotic side effects, I think, are much more likely to precipitate a cascade of tests and treatments that may be unnecessary.

I mean, we ve seen in those three cases that were possibly Stevens-Johnson Syndrome, but maybe weren t, clearly, there was a cascade of events going on, and those patients may have received unnecessary tests and treatment.

So even if there is no increased risk of Stevens-Johnson Syndrome, the fact that there are rashes, minor rashes alone, mean that there s a risk of a lot more tests and treatments being done,

and that concerns me.

DR. EDWARDS: Dr. Poretz? Oh, excuse me. One point of clarification, if I could. It s a little hard for me to keep track of who s on deck, and if you can kind of identify yourself to Sohail while you re trying to get our attention, that would be helpful, and then he ll sort of feed the -- feed me. Okay? So when you re trying to catch an eye, there are two of them here we need to keep track of.

All right, Rich. I m sorry. Go ahead.

DR. FROTHINGHAM: That s fine. I did want to respond a little bit on the in vitro -- the value that I place on in vitro testing for quinolones. I certainly agree with the other respondents that you can t predict, from what happens in a test tube, what s going to happen in human beings in a broad and general sense with antibiotics.

However, I would say that we have a pretty good record of predicting, with the quinolone class, efficacy based on MIC/AUC ratios. In fact, this is the one area where this PK/PD thing has

actually held up in the clinics. It doesn t hold up for Ceftra (phonetic). It doesn t hold up very well for betalactams, I agree.

But for quinolones, if it gets into the urine and it has these concentrations, it pretty much works, and if it achieves these good ratios in the respiratory tract, it pretty well works. I think this drug is very likely to work, since cipro works, leva works, I think it s highly likely that this drug will work against sinusitis.

There is, of course, in the clinical trials, in addition to the clinical outcome data, there is bacteriology that supports that idea, in terms of very good eradication rates of these organisms.

So efficacy is not a problem for me. We ll talk about other problems later.

DR. EDWARDS: I guess I ll just express my own opinion at the moment, based on many of the comments you have made, Rich, and somewhat of accord with John s comments. I believe this drug would work in acute sinusitis. It would be definitely not a first choice agent for me, and

something that I would go to reserve for special circumstances, and therefore, more in a salvage sort of perspective.

Again, the in vitro data is perhaps a little more compelling to me than the difficulties we re all going to have in interpreting a non-inferiority study for this particular indication, but the combination and what we do have available in the in vitro data makes me think it will work, as well.

But then again, we re all going to have to weigh those considerations against the risk-benefit, which the FDA is really asking us to address specifically. Yes, Dr. Poretz?

DR. PORETZ: Again, I want to reiterate what I said before. I think that quinolones are so overused in our country at the present time. I m very, very fearful that the continued use -- and if this drug is marketed, it will just increase another member of that class, and we re going to see, and we are seeing, more and more drug resistance.

Now, this drug is already approved for the

treatment of pneumonia and acute exacerbations of chronic bronchitis, so the drug is on the market and like a lot of other drugs, can be used off-label for various other entities. So it s not like no one would have access to this drug. I m just very, very concerned about resistance.

DR. EDWARDS: Dr. Tunkel?

DR. TUNKEL: Yes, I m just going to make a similar comment to Dr. Poretz, because in the prescribing patterns that the sponsor provided, in fact, sinusitis was a pretty common reason that this drug was prescribed, and in fact, in patients who were being treated for sinusitis, more than 50% got seven or more days of therapy.

And maybe like more of a question or for a clarification, if this drug is approved for five days for acute bacterial sinusitis, do we actually have more regulation of its use, or do we feel more comfortable that it s at least being used in the right way, for treatment of bacterial sinusitis? I just want to throw that question out.

DR. EDWARDS: I think we re going to come back

to that question specifically as we go on through the discussion, but I understand exactly where you re headed with it. Dr. Bradley?

DR. BRADLEY: Yes. I ve got a question for Dr. Albrecht, and it s a fairly broad, general question on clinical trial design. Dr. Powers certainly eloquently showed all the reasons why our past views of how acute bacterial sinusitis clinical trial design won t work, and future drugs that come to you for approval clearly need to look at either placebo controlled or somehow tightening that delta.

But for -- if one looks at the guidances, which are published -- and I know that you ve mentioned that there s internal discussion, and we ve certainly discussed it in the advisory committee.

But Dr. Edwards and I are on an IDSA Task Force to try and work with the FDA to facilitate drug development. One of the issues that we ve identified and certainly was part of one of the workshops was that when a company has a product

that they would like to get approved for a certain indication, they come to you, and you tell them what they need to do, and they commit the resources and they do the study.

Several years down the line, when they have the study pretty much done and are sharing information with you, they, I guess, have some reason to suspect that what you agreed to at the very beginning would be what you would agree to at the very end, unless there s some life-threatening change, something serious about the product that comes up that would not allow you to approve it.

I m just wondering, as you talk about changing the definitions of how you would look at drug efficacy for sinusitis and the internal discussions, how fair it is now to ask for a placebo controlled trial before you feel comfortable approving the drug for acute bacterial sinusitis.

I get this from reading the FDA briefing documents that you shared with us that said that you actually told the company that you would not --

that they got a non-approvable (sic) letter and that we re actually having this discussion after you had told them that you felt that it was not approvable.

Maybe I should rephrase that question.

DR. EDWARDS: John, I need to know exactly what the question was. That s not clear to me.

DR. BRADLEY: Is it fair to change the rules halfway through the clinical trial?

DR. EDWARDS: I thought that s what it was. Thank you.

DR. ALBRECHT: When the company -- and as you know from the briefing material, the sponsorship or the application -- the ownership of the product has been transferred periodically. But when these studies were conducted and analyzed, if I may just sort of reiterate what I had mentioned earlier, they were judged by the parameters that they were designed to be judged by.

The reason for the decision that was rendered -- and I realize this is exactly the question we re asking you to discuss now, and I ll come back to

that -- but the decision that we rendered was based on looking at the results of those trials, based on the parameters that we understood and believed to be acceptable at the time this was done.

Based on using those parameters, while we agreed that those parameters had been met, and therefore, we interpreted the product as effective, we also looked at the safety profile and concluded it did not outweigh the -- or did not -- rather, the risk outweighed what we interpreted as the benefit. So we did interpret the results in context of the parameters that had been set out initially.

We are today looking at the same product, but looking at more data. There s more data in terms of clinical studies, one more. There s additional data on safety. But time has passed, and if I may, there were illusions earlier to other quinolones that we no longer have available, let s say.

Let me just in general say as we have learned more about those quinolones, although in the past, we may have approved them for certain indications,

today, with more knowledge, we would not make the same decision.

So I think, as you alluded to, if there is compelling new information that is material to our discussion, we should take it into consideration. Frivolous information, certainly, we can point out for being frivolous, but material information is very important to take into consideration.

So that s why today we re asking the committee to weigh in on both how persuasive is the information that s being presented for efficacy, given that the first time that question was asked was seven years ago? And along the same lines, given the additional information on safety, how persuasive is that new information, either giving a sense of comfort or confirming the earlier concerns the Agency has.

So I don t know if that addressed your question, but close enough.

DR. EDWARDS: Renata, could I try this summary of your answer and see if it matches, if I could? You don t feel that you have changed the rules, as

John sort of implies, and still feel that the analysis of the efficacy stands as -- similarly to when this has been last reviewed, but your central concern is over the efficacy at this point.

I m sorry, the analysis of the efficacy stands as previously viewed. Your central concern is now over the safety issue. Is that -- do I understand it correctly?

DR. ALBRECHT: I think what we agree with is the way that the data have been analyzed, that the analysis was done as it was done. The question is whether the interpretation, which in 99, was done believing that a margin of 10% was appropriate, because we had used similar margins for indications that are not as questionable in terms of the spontaneous rate, for example, whether it s meningitis or pneumonia.

So the question isn t whether the results have changed, but rather, whether our interpretation in 2006 needs to take into consideration the issues that Dr. Powers has brought up, which is how do you interpret the results of a non-inferiority study?

DR. EDWARDS: Okay. Well, that s very helpful. Thank you. Dr. Temple?

DR. TEMPLE: There s nothing more uncomfortable than discovering that something you ve been doing isn t quite right, or good enough, but it happens from time to time.

We are faced with the requirements of a law and regulations such that if we conclude that something we thought was sufficient to establish effectiveness no longer convinces us that it is, we really are not allowed to continue on that path, uncomfortable as it is to tell someone that what they did four years ago wasn t good enough.

This isn t the only time this sort of thing has arisen. We made the same discovery in oncology some years ago. We were allowing approvals of drugs if they showed that the difference between two treatments was less than a certain effect on the hazard ratio, and we woke up, we realized that we were doing that, we were saying, Okay, as long as it s within 20%, it s okay, when we didn t know that the control drug had a 20% effect.

We had to stop doing that, because we realized we weren t fulfilling the requirements of law. I think that s what John s been saying here. He says you can t, based on the available data, say what the non-inferiority margin is, so that under the rules that describe how to use an active controlled trial, you don t meet the test of having an interpretable study.

DR. EDWARDS: Then could I ask John this question? Is the bulk of the re-analysis of the appropriateness of the non-inferiority trial based on work that s been published since the Year 2000? That would be the placebo controlled trials.

DR. POWERS: I think eight -- so we analyzed 17 in total. Eight of them have been published since 2000. So a little less than half of those are fairly recent publications. So I wouldn t say the bulk of it, because we want to analyze all of that information. But a good bit of it is recent, if that s your question.

DR. EDWARDS: Right, that s -- I m trying to get a feeling for -- we re in a situation where

we re looking at evolving understanding of the value of the placebo controlled trial and sinusitis.

DR. POWERS: Right. Right, and even since --

DR. EDWARDS: And it has changed during the time this application has been being reviewed.

DR. POWERS: Sure, and I think --

DR. EDWARDS: Is that a fair statement?

DR. POWERS: Yes, I think so, and even -- I mentioned that since we discussed this last in October of 2003, there have been three more placebo controlled trials published since then, and all three of those fail to show evidence of a benefit that would allow you to choose a non-inferiority margin.

So we are continuing to accrue this information as we go.

DR. EDWARDS: I would like to do this, if I may. Undoubtedly, one of the people in this room who ve had the most experience with the management of sinusitis is Dr. Ferguson, and I wonder if you would mind commenting on the comments that we

clinicians have made. Most of us are either internists or pediatricians, and not specialists in ear, nose, and throat. So, please.

DR. FERGUSON: Well, there are several points I d like to make. I think there s a challenging accurately diagnosing the patient who truly has bacterial sinus disease, and I have reviewed in detail at least seven of the studies published since 2000, and only one in adults even had radiographs, and that was the Boucher (phonetic) study I referred to before.

So I really have to discredit all of these placebo controlled trials that have been done since 2000, since they didn t have radiographs and they didn t have maxillary sinus taps, which are what we require now before we allow a patient into a trial to determine whether the antibiotic is effective.

But when I see a patient who has what I think is sinusitis, I am really pretty careful to look for a double sickening. Did they get worse after getting -- did they worsen at three days, start to get better, and then worsen again? Because those

patients in our tap studies had a higher incidence of bacteria. Do they have persistence of symptoms at seven and 10 days. I m not talking about they still have symptoms, but they re slowly getting better. Are they still sick?

In my practice, I get a lot of cultures. If you come to see me, I m either going to get an endoscopic aspirate, or if you re really sick, I may do a therapeutic tap. So I m a little bit different from the general practitioner, yet a do a lot of speaking to general practitioners and family practitioners, and I can tell you that they do follow guidelines, and they are careful in using antibiotics.

I have patients who do not want an antibiotic if you tell them that they re going to get better. It s only when they are truly symptomatic, not just with facial pain, but with associated nasal purulence, and sometimes, you need radiographic confirmation.

Now, several of you have spoken where you would use floroquinolones, and I think those are

really apt. You do not want to use a floroquinolone in the patient you think has run-of-the-mill acute bacterial sinusitis. That is disrespectful of the class. It s going to breed resistance.

But when you do have a patient who you really think needs a floroquinolone, based on culture, based on failure to improve with other antibiotics, then you want to use a drug that is going to have the least likelihood of promoting resistance. That s why I like gemifloxacin.

Speaking to the women in the audience, when you come to me and I think you need a floroquinolone, I m not going to just say, Here, take gemifloxacin. We talk about the risks and the benefits of any antibiotic, and if I think you need a floroquinolone, I m going to say, Well, we have gemifloxacin here, which I can give you, and it s a five-day course of therapy. Or, I can use moxifloxacin, and it s a 10-day course of therapy.

One patient will say, When I take long courses of antibiotics, I get a yeast infection, so

we may not want to use that. I m willing to take a 3% risk or less of a rash that you assure me is benign.

So it s a dialogue with each patient, and you don t tell the patient what you want, you make that decision with the patient and you make it responsibly.

There are other ways to look at how you can determine whether an antibiotic is effective or not besides having a placebo controlled trial, which we don t have any good ones to compare to. That s looking at patients who had double taps.

I d like to pull up a slide that we had in your briefing book, and that Dr. Powers had referred to, that has the Carnfeldt, Hamery (phonetic), and Gwaltney studies. These were studies done over 15 years ago, and these are double-tap studies. Could I have that slide on, please? Slide on.

As we go through this, the 1975 study, you see in this double-tap study that patients who had an MIC of the antibiotic in the tap that was greater

than the causative bacteria, 90% of them had no bacteria present on the second tap. But if the MIC of the bacteria -- of the antibiotic was lower, then you see that there were a lot of bacteria present here on double-tap.

As you go down into the harm rate (phonetic) and you look at the patients who had an inappropriate antibiotic and had a double-tap, you see that the number of bacteriologic cures was 0%. They still had bacteriology there.

If you look at Carnfeldt s 1990 study, where he compared cefixime to ceclor, the ceclor was actually a worse antibiotic, and we see that the patients on the ceclor, 74% of them still had -- were bacteriological cures, which compares to the 91% who were more the appropriate antibiotic for what was tapped, who were bacteriological cures.

Finally, Dr. Gwaltney s study, looking at a number of different trials that he did over the course of study, found that patients who were on sub-optimal doses, such as ceclor twice a day, were much more likely to have bacteria present and much

less likely to have a bacterial cure.

So you can look at this sort of dose response curve of sub-optimal antibiotics, and you can draw some parallels as to whether you use an antibiotic that has appropriate PK/PD measurements for the bacteria and can go from there to its efficacy, and that s a little bit short of doing the placebo controlled trials, which have not been done yet that we can look to.

Sorry, that was a long answer.

DR. EDWARDS: Dr. Patou, did you want to make a comment?

DR. PATOU: I just want to make one comment, because we talked about the bar and about non-inferiority not being acceptable now. Now, I think it s (inaudible) to point out that are no new guidelines that have been issued to guide companies how to do a study in this indication.

There have been four approvals since the AdCom in 2003 for this indication, based on non-inferiority design. Fully, two of those approvals occurred in 2005, following our own

discussions with the FDA about the approvability of gemifloxacin according to these old rules.

So I did think it was important to understand that we did what was asked of us, we ve conducted studies to the same standard and rigor, we believe, to other sponsors, and they ve all been approved, and some of them very recently, based on this methodology.

DR. EDWARDS: Okay. Thank you. Within the context of Dr. Ferguson s comments, I think it s appropriate that I call on Dr. Powers now to reflect a little more on the placebo controlled trial issue, and then I d like to ask Dr. Temple to make a comment, and then we ll get back in order, if we can, but we have a bit of a discussion going on here at the moment.

DR. POWERS: Thanks, Jack. I wanted to go through this study by Carnfeldt, because it was kind of instructive of how can we extrapolate from microbiological data to what happens to people clinically?

I think first of all, it s important to

understand that our regulatory standard of what makes a drug effective is how it affects how people feel, function, or survive, and that what happens to a micro-organism is a surrogate, or a potential surrogate, for that. The question is how well does that surrogate function in predicting what might happen to people?

So in this study by Carnfeldt, they compared cefixime at 200 milligrams twice a day to cefaclor 500 milligrams twice a day. Both of those drugs were given for 10 days. Then they compared the clinical outcomes and they also compared the microbiological outcomes. A sinus puncture was done at baseline prior to when people were enrolled, and a second puncture was done in people at day 12 to 15, after they had completed it.

And it was randomized two to one, and the only reason I bring that up is because you ll notice the denominators are a little different from each other. They had the same entry and out -- or not the same, but similar entry and outcome criteria as what is in our under revision 1998 FDA draft

guidance.

What they showed was also -- I wanted to point this out. There were more baseline positive cultures in the cefixime group than the cefaclor group, and we rely on randomization to try to make sure that the groups have equal numbers, but that doesn t always pan out sometimes, and misclassification can occur.

The interesting thing here is, though, that the MIC 90s (phonetic) for cefixime were .06 and the MIC 90s (phonetic) for cefaclor, eight, against haemophalis influenza. So if you were going to see that translate into a clinical difference, you would expect to see it here, where there s a big difference in microbiological activity in a test tube.

So but what they showed was there was no difference in overall clinical outcomes, no difference in bacteriological outcomes overall, and no difference in the subset of people with haemophalis influenza, and not because they had too small a subset, because interestingly, in this

study, haemophalis influenza was the most common isolet, making up 42% of people.

So the microbiological outcomes -- this is the primary analysis, not the subgroup analysis that Dr. Ferguson presented -- but overall, microbiological outcomes were 88.9% in cefixime versus 84.9% in cefaclor, which is a difference of 4% in favor of cefixime, but the confidence intervals cross zero, showing no difference.

The interesting thing is the clinical outcomes were higher than that, cefixime, 95% and cefaclor, 97%. So it leans the other direction, actually, with a point estimate in favor of cefaclor in this particular setting.

So it also shows that there s a much higher success rate clinically than there is microbiologically, which means that a good number of people -- actually, 14% of them -- who had bacteria still present in their sinus at the follow-up tap, were completely better clinically, which shows that that correlation is certainly not 100%.

But there s another interesting thing about this, and that is despite the microbiological advantages of cefixime in the test tube, it actually caused more adverse reactions in people. So 31% of people had adverse reactions on cefixime in this study, versus 19% in cefaclor.

So it didn t -- the microbiological advantages in the test tube didn t translate into a clinical benefit in people, didn t translate into a microbiological benefit, and actually, the drug had more adverse events. So that s what we re always concerned about when we re talking about surrogates is does it really predict the overall net benefits and risks for people?

So in this study, what we saw is the correlation of microbiological and clinical outcomes is certainly not perfect. More people will get better, because this is a self-resolving disease, and a number of people who have a positive culture at the end of treatment, even after drug, are going to get better anyway.

DR. EDWARDS: Dr. Temple?

DR. TEMPLE: I don t think I have too much to add to that, but I did want to make an observation about what Dr. Ferguson said. I m no ID person, so I don t really know the details of this, but what she described about how she chooses what therapy to give people sounds to me right on the money. I m sure that s exactly what you re supposed to do.

That s exactly why non-inferiority studies are so difficult, because what you re trying to do is show no difference and you -- between treatments, or no difference beyond a certain size, and you don t have control over these conditions in such a way that you know exactly what the effect size of the control is, unless you have something to refer to that tells you what it is in well done placebo controlled trials that tell you how these various factors influence the result.

But if you don t have that, you don t really have any way of pinning down what the effect size of the active control is in this particular population that got into the trial.

Again, I guess I m still assuming that you do

want to find actual clinical evidence of effectiveness and that bacteriology isn t sufficient. If that were a satisfactory surrogate, I don t think we d be having this discussion.

DR. EDWARDS: Okay. Well, we re discussing many different issues here simultaneously. We re discussing the surrogates, we re discussing non-inferiority trial design, we re discussing FDA changing its analysis of available data as time has gone on. Obviously, this is a complex situation that all we can do is openly discuss.

I don t think I m going to try to summarize this last discussion right now, this -- maybe I will. Dr. Patou made the point that there have been continued approvals on -- for sinusitis on the basis of non-inferiority trials.

Dr. Ferguson is not as convinced by the placebo controlled trials as perhaps the FDA is regarding the value of the placebo controlled trial. I m not exactly sure what the platform for that was, but I think that it has to do with the kind of diagnostic tests that are being done

currently, more sophisticated.

Is that a fair -- are those comments fair? Just trying to make sure we all understand what we ve all said. Okay. Then I m going to move on to Dr. Wong, who s been waiting patiently to make a comment.

DR. WONG-BERINGER: I have a comment based on the findings presented with the FDA briefing package, and that refers to Study 206 of the five-day open-label bacteriologic study, where I ve noticed that when it was broken down, in terms of the background of these patients, those with allergic rhinitis have about a 20% lower response rate.

When we look at just the U.S. population, which I think consisted of about 50 patients there, there was a -- about 40% of the U.S. population had allergic rhinitis, and of those, the success rate was only 73% versus those without allergic rhinitis.

I guess that raised a question in my mind, in terms of if that were truly reflective of the

population that we deal with here and practice, does that then raise a possibility of treatment beyond the five-day, if it were approved for that, for our population here, and hence, possible increased risk from that?

DR. EDWARDS: Would someone like to address that question? Dr. Tierney?

DR. TIERNEY: I d actually like Dr. Wong to -- I m not really sure I understand your question, and let me just see if I do. Is your question that if actually the population that would be treated has a higher incidence or a similar incidence of allergic rhinitis, if that would predict that they would -- because they wouldn t get better, (inaudible) frequently at five days, get more therapy.

I actually think that s a question we probably can t answer. I think it s one of our concerns is what happens if people don t get only five days and get more, which is going to happen to some degree, that that increases the risk. So I think you ve sort of hit the nose on the head on one of the things we were concerned about. But would that

happen? I think that s hard to know.

DR. WONG-BERINGER: I guess my question also was directed to Dr. Ferguson, if she could comment if that is the type of patient that we see here?

DR. FERGUSON: In four of the trials, the incidence of allergic rhinitis was about what we expect in the population, between 15 and 25%. In the comparator trials, there was similar response in the allergic versus the non-allergic patients.

Actually, in most of the trials, the allergic patients had a slightly, but not statistically significant, difference from the non-allergic patients. In the second open-label trial, which was also actually a tap study, Study 333, we have almost 49% of that population being allergic, and in that study, there was no difference in the per-protocol success rate. They were equivalent.

But I think that the point you bring up is good. One is that patients who have allergic rhinitis may be mis-diagnosed as having sinus disease, when they truly don t have bacterial sinus disease. Fortunately, in the open-label tap

studies, we do know those patients who have bacteria, and in 333, where they have that 49% allergic rhinitis, we have equal success rate in those patients.

Secondly, there may be some slight predisposition to have acute bacterial sinusitis if you have allergies, and that s -- I only know of one study in the literature that supports that, and it s sort of strange that we don t see more allergic patients in the studies that were done in Europe, and I don t understand that.

DR. PATOU: I just wanted to add that if we had the sinusitis indication on the label, and the comment about five days of therapy, it would allow us to advise physicians about the appropriate use of this antibiotic in that setting. At the moment, we can provide no guidance whatsoever, and so they will continue to use the drug as -- based upon their prior experience, and not according to the data we ve shown here.

DR. EDWARDS: Dr. Bradley?

DR. BRADLEY: I actually had a question earlier

about microbiologic outcomes, and certainly acknowledging, as Dr. Powers had mentioned, that micro is a surrogate for clinical, and clinical is really where we re at.

In the otitis area, double taps were begun and became one of the standards of studies, both to identify the organism that you re dealing with up front, as well as to look at how quickly eradication occurs.

It was revealing that as you looked at taps at different points in the treatment course, you had different rates of eradication, and to pick the appropriate endpoint as to when to do the second microbiologic evaluation, actually, was a bit more complicated than people thought.

In the one study that you commented on, it looked as though the second tap was done at the end of two weeks of treatment which, according to the graph on Page 42, is about the point where placebo and treatment start to come together.

So and again, I don t know what -- as the FDA puts together revisions on guidances for sinusitis,

how they re going to put together the micro evaluation, because double sinus tap seems to be a whole lot harder and certainly in pediatrics, might be unethical to get the micro data that you need.

In one of our meetings, someone presented data on an indwelling catheter that you just take a suction sample of every day on treatment. Again, all of this information certainly goes to the Agency, and I know you think very carefully about it and come out with the guidances.

Other than the fact that we ve been talking about this over the past three years, again, I m not -- in reviewing these data, I m not sure how the new design for efficacy, taking safety out of the equation for a moment, but efficacy, how that should impact this particular study evaluation by the committee.

DR. TIERNEY: I d like to address that, and one particular way is one of the things that s very different -- well, I shouldn t say very different now, but it was relatively clear for the two previous decisions for non-approvals that the

risk-benefit ratio wasn t there, and that by the basis of the standards for those trials at the time, statement was made the trials show efficacy, but the risk isn t justified.

Now -- so that was a decision that was made. Now, another application has been submitted, and so that from November 2005 until it will turn out to be December 2006, we have to evaluate that information based on the best way we can evaluate that information at this point in time. I don t think we can say we can go back to 2000 or 2002, so we need to look at it.

I think one of the reasons that there s also such a careful look, because now -- before, it was -- there was no question. It wasn t -- it was something that we weren t going to consider. We have to very closely determine the risk-benefit ratio. In order to do that, we have to really closely determine what s the effect size? What s the benefit?

In order to do that, we have to use everything we can, and now, that s why, in the evolution of

understanding of how you look at non-inferiority trials and how you look at ABS, which was public? I mean, the 2003 advisory committee made very public recommendations about what to in sinusitis.

So I think that s why we re where we are now. I m not sure -- the bacteriology question, I may leave to John, but I don t know if I ve addressed part of your question.

DR. BRADLEY: Okay. In terms of what the committee discusses, it s sort of like this discussion. There are a lot of things that are brought up, many points to consider, and then the Agency puts them all together and comes out with a guidance. I haven t seen any guidance or anything public, anything that represents your summation of all of the discussion, which is actually what we re all looking for.

DR. TIERNEY: John, anything further on that?

DR. POWERS: We want to get them out as soon as we can, too, so believe me. What we -- in compiling that previous information, what it appears to be, from what we put together from the

literature and the October 2003 advisory committee was, it appears that you need a sinus puncture to define the disease at baseline. That s a key. I think pretty much everybody on the committee was unanimous on that the last time.

The second question is when we look at this data of how well the microbiology correlates with what happens to people at the end, it actually underestimates how people are doing. So it would make your point estimates look lower, it doesn t predict how people are doing, and it would actually make your study harder to do.

So what we want to know is we want to use microbiological information to define the disease, but what we re concerned about is how does it affect how people feel and function on the other end? The mortality in all of these placebo controlled trials of 2,700 people was zero. No one died, even the person who got the brain abscess who, by the way, was randomized to placebo, got switched to amoxicillin, and then developed the brain abscess while he was on amoxicillin. So it s

not exactly a clean case, either. So the answer to your question, John, is we d want to use the microbiological information at baseline, but we re not -- really don t know how that helps us on the other end of the outcome.

DR. BRADLEY: Thank you.

DR. EDWARDS: Rich?

DR. FROTHINGHAM: I ve been listening with great interest in this discussion about the different guidelines of doing these trials, and would just comment on some real world perspectives.

One perspective is that we re using a whole lot more antibiotics for sinusitis than we should. I agree with everyone there. We re using a whole lot more quinolones than we should. And yet, I m not convinced that approving or not approving this is going to have a big real world impact on either of those. This is likely to still remain a relatively niche drug.

However, there is some sense of fairness here that I think is being discussed. We know there s no quinolone placebo controlled trial at all. We

heard that data. Never happened in sinusitis. However, we have approvals for at least four quinolones that I know of, probably five or six, for sinusitis. Cipro and Levo both have the approval for sinusitis, and it s not based on any better data.

So I guess on the line of thinking that sometimes we do discover new things, and sometimes, we go back and we put warnings onto a lot of labels, and maybe that s okay. Leave the other labels there totally untouched, not even an asterisk next to them, and then say, well, we need a higher standard now for future quinolones. It seems a little paradoxical to me.

DR. EDWARDS: Yes, John?

DR. POWERS: I guess at some point, you have to address the question of does this obviate us ever moving forward in science? If we keep saying we re going to do everything the way we ve always done it before, it obviates any advance whatsoever.

Now, somebody s going to get caught in the middle of that, because I ve never been at the FDA

where there s a day I m sitting around staring at the wall going, I hope somebody sends something in today. So at some point, you have to make a change, and somebody s going to get caught in the middle of that change.

What we re doing now is we re looking at this information. Sohail, could you bring up one of my slides? Could you bring up slide 42? This came up before, back in 1970, and somebody asked the question of, Gee, well, you ve approved all these other drugs this way, and in fact, you approved our drug that way. So -- you can just hit 42 and enter. There we go.

So Upjohn (phonetic) had a drug, and they came in with this quote. The totality of materials, which included 54 separate articles, the materials submitted over the years since the product was first approved, and the clinical experience and totality clearly satisfied the substantial evidence claim that the law requires.

It says the clinical experience, widespread throughout the world, used by thousands upon

thousands of doctors and 750 million doses, is a very significant factor.

In other words, people have been using these drugs, so that should be a standard. But here s what the courts actually said in reply. Next slide.

The Commissioner concludes that Congress itself has described the type of evidence that is suitable to support claims of effectiveness. The claims must be supported by adequate and well-controlled investigations. This means that the experimental factors must be so controlled that the effectiveness of an anti-infective drug on the disease process in patients (not what happens to the organism) can be compared with the effect of no treatment or of a recognized treatment of patients with the same disease or condition.

Skip two slides. One more. No, back up. So what they concluded, then, was the in vitro studies are suggestive of some effectiveness, meaning you have a nice hypothesis in laboratory experiments using artificially colored microorganisms as test

systems, but because the studies are not at all correlated with clinical trial experience, they cannot be used as a basis for concluding the drugs will have the effectiveness claim for them when used to treat naturally occurring clinical disease in man.

So here we are, 36 years later, still kind of asking this same question. Again, it s not just an issue of fairness; it s an issue of are we really meeting what the law s requirement is to protect people and make sure that these drugs are effective before they use them?

DR. EDWARDS: Okay. We need to go to Dr. Hilton next. Joan?

DR. HILTON: Thanks. I d like to talk about the non-inferiority interpretation as the biostatistician on the committee. This is my area of biostatistic methodologic research as non-inferiority trials.

I think I just want to point out that it s not the non-inferiority trial design that we re questioning here, it s the evidence. It s the

definition of the margin, in this case.

If we look at Table 24, on Page 55 of the sponsor s document, and look at the 95 confidence center (phonetic) rules for the controlled trials, if there is no benefit for the comparator relative to placebo, then we can think of these confidence intervals as comparing gemifloxacin to placebo.

If you look at the lower end of the confidence bound, that means that gemifloxacin could be as much as 7% worse than placebo. That s really scary. If you look at the upper end, it could be 3 to 7% better.

So just the risk of essentially no effectiveness is a great possibility here, because we don t have placebo controlled trials to demonstrate the comparator is really effective.

DR. EDWARDS: Ed, did you want to speak directly to that point?

DR. COX: Well, a more general comment related somewhat to the last comment. That is that obviously, there s a lot of complicated issues here that we re all trying to grapple with. We ve heard

information presented about the placebo controlled trials. We ve heard information about the safety and efficacy data within the gemifloxacin application.

There s also history here, previous actions on the NDA. I think, at this point, it would be valuable for us to hear your comments with regards to -- given all the information we have here, given what we know from the analysis of the placebo controlled trials, what we think with regards to the efficacy from the clinical trials here, with regards to the five-day indication for sinusitis.

So it would be valuable for us to hear your comments with regards to what we can conclude from the efficacy data based on all the information that we have here today, and I think that s part of the component -- one of the components here, as we get to the question with regards to risk and benefit, the other aspect being safety.

So I hope that helps a little bit with regards to some of what we are hoping to get with regards to advice from the committee.

DR. EDWARDS: Ed, let me make this suggestion, which is only a suggestion, but I m wondering if it would be of value at this time if we had a hand vote regarding the efficacy unrelated to the safety issues, interpretation of the efficacy unrelated to the safety, and then proceeded with the discussion from there.

Because at the end, we re going to do a risk-benefit vote, but would it be a benefit for you all at this point for us to, in light of the discussion that we ve just had going on, which has been very intense and extensive, do that maneuver? Would that -- what are your thoughts about that?

DR. COX: Yes, I ll leave that to you, Dr. Edwards, but I think if there s been enough discussion of it, it seems that there s been still some question as to I think what folks are being asked to do here, and if you would like to do that, certainly, as the Chairman, that s your choice to do so.

I guess I just want to make clear that we do think it will be valuable for folks to think about

the efficacy data, given all that we have here in front of us today. Okay?

DR. EDWARDS: So I m in the position of trying to get a poll to see if we should vote or not, and maybe I could just see if I could get a feeling for it. I would sort of like to ask the question of the voting members of the panel, whether -- irrespective of the safety data, whether they feel that the data we ve reviewed clearly demonstrate efficacy of the agent, given for five days in ABS.

DR. FROTHINGHAM: Can you tell us who are voting members?

DR. EDWARDS: The voting members start with Marian and go around the table, all the way down to the very end. Dr. Maldonado is not, I m sorry, with Jackie. Dr. Maldonado is not, Sohail is not. The rest of us are all voting members. Should we do that? I m not getting a lot of head nods. Or shall we just continue with discussion? I m not sure that we re going to -- well, I think we ll do it then.

DR. WIEDERMANN: You re talking about all

comers, acute bacterial sinusitis, clearly effective?

DR. EDWARDS: Five days.

DR. WIEDERMANN: Yes. I just -- because there are a lot of qualifiers you could put in there, and that s -- it s really when the qualifiers come in that I have a problem.

DR. EDWARDS: Right. And this is without the safety taken into consideration, so this is not a risk-benefit analysis.

DR. WIEDERMANN: Right, right.

DR. EDWARDS: Does everyone understand --

DR. MALDONADO: Can I ask a question?

DR. EDWARDS: Yes.

DR. MALDONADO: The question is just related to Bud (phonetic) Wiedermann. Because if you have a standard -- like for example, if the standard that the committee wants is a placebo controlled trial to prove definitively that gemifloxacin is superior, you would just not (phonetic) have it there, because the data is not here.

But if the standard is the standard that they

use, because that s a standard -- even all (phonetic) standard -- then the question is different, too. I mean, it s still their frequency, but what s the rule that you re going to use to measure that frequency? Is it the new rule, so the placebo controlled, or the old rule?

DR. WIEDERMANN: That was sort of my point. If you say clearly effective, then that s going to drive me to a superiority trial, and we don t have that evidence.

DR. EDWARDS: Then I was --

DR. WIEDERMANN: There are other qualifiers. I don t -- in my mind, factoring in the in vitro data, I don t care so much about non-typable haemophalis influenza and Moraxella. I care a lot about pneumococcus, because that s where we re likely to get more problems. It s a more virulent organism. We see it with otitis media and we see it with sinusitis.

So almost the way you stated your question, I think, made it -- well, certainly, you made it tough for me to say yes. I don t know about the

other members.

DR. EDWARDS: Dr. Temple, we re now discussing -- still discussing whether we re going to vote.

DR. TEMPLE: Yes, I don t know if this will help, but from the point of view of the agency in trying to carry out what it has to do, and being able to use your advice. What we have to conclude to say yes to a sinusitis claim is that there are well-controlled studies that show that the drug has the effect that it s claimed, that showed that it works.

So for us, that s always the same question, and we don t actually even start to weigh benefit against risk until we can conclude there s a benefit. So the first thought for us is always have they established whether there s effectiveness?

Now, there could be a debate about whether something other than a placebo controlled trial can establish effectiveness, some other kind of trial, and the committee members may have their own views on that. It s my impression -- again, this is my

business -- that we usually believe you actually need clinical trial data, not just sensitivity data. So I m assuming that, but you can tell me I m wrong if I m wrong.

So it strikes me that the question that you re really asking people is whether they think there is the expected under the law level of evidence that gemifloxacin has the effect in sinusitis that is being claimed.

DR. EDWARDS: Right.

DR. FROTHINGHAM: Jack?

DR. EDWARDS: Yes?

DR. FROTHINGHAM: Whatever you have us vote on, and I think it would be very helpful for us to vote on something, I would like to suggest that you have Sohail type the question up, so we have the exact words, because it s clearly effective versus effective, that s a big difference -- effective in five-day course.

I think what you re asking is is Factive effective for acute bacterial sinusitis in a five-day course? Maybe that s the question, or is

it a little different question? Anyway, whatever you want to ask us, please type it up there.

DR. EDWARDS: Yes. Dr. Tierney? No, you should be okay. I think there s --

DR. TIERNEY: Ah, there we go. Just whatever you do in that, it might be useful to use the wording from the proposed label, in terms of what indication the company s asking for.

DR. EDWARDS: Yes?

DR. TIERNEY: So we ll have to --

DR. KWEDER: I m sorry, I m not sitting at the table, happily. I m Dr. Sandra Kweder. I m the Deputy Director of the Office of New Drugs, and before you decide whether to vote or what exactly you re going to vote on, I think it is important -- Dr. Temple alluded to this earlier, and several of you have raised the question about what is the standard?

We are always in a position, as science evolves, to look at common questions in new ways, and I think that s some of what you ve heard today in some of the discussion, how oftentimes, for many

fields -- infectious disease, oncology, you name it -- our thinking about clinical trials and the basis of evidence evolves. That s what science is about.

Once we do change and we do evolve, that doesn t mean that we can t make new decisions, and our standards for an approval or a non-approval or labeling may not be different for a product that otherwise appears similar to what s already on the market.

For example, if you look at what the standard for approval for amoxicillin was at the time that it was approved, you d probably be appalled. We learned a lot since then, but we would never today accept the basis of evidence upon which that drug was approved. Ditto for a cyclofere (phonetic). We would never accept today the data upon which those were approved under our scientific standards for what we consider acceptable for a product to go on the market today.

So I would urge you not to get bogged down in what about all these other drugs that have labeling for sinusitis and what are we going to do about

those? That is an important question, regardless of what the decision is we make today, any time we start to change our thinking about how a product should be studied.

We do have ways of dealing with that, and we re not asking you guys to have to bear the burden of figuring that out today. We may ask you at another time, but it s not on the docket for discussion today. We face this all the time. So don t feel burdened by whatever decision you make today is going to affect all the things that came before in a necessarily good or bad way.

So I just wanted to lay that to rest, because I think that some of you are feeling a little bit like, Oh, my gosh, if I go this way, this ll happen; if I go that way, something else ll happen.

As far as the issue of guidelines and the lack of what might be considered an up-to-date guidance for industry on clinical trials for sinusitis, we are often in a position where we have to make decisions based on evidence in advance of a written

guideline for a particular indication. That happens to us all the time.

I do agree that we probably should have had something out and published on acute bacterial sinusitis and guidance or that that s more up-to-date than what s out there, but the fact remains that we re often in this position and we should not let the lack of a written guidance document deter our thinking or at least not allow it to hinder our ability to have a discussion and move forward.

DR. EDWARDS: Thank you very much for those comments, and thank you for empathizing with the difficult position we re all in. Yes, Dr. Temple?

DR. TEMPLE: One short thing. The -- Sandy already addressed the question of guidelines in the -- or guidance in the sinusitis, but the general question of how to use or whether to use non-inferiority studies is not new.

We actually had an early, somewhat primitive version of it, as John showed you, in 1985. I ve personally been writing about it since 1980.

There s an international guideline that was widely promulgated in 2000 that everyone in the drug industry understands perfectly well, and there have been a lot of conferences on this matter in antibiotics subsequently.

So it s true the details aren t there, and everybody s already expressed their regret, but the general but the general idea of what it takes to make a credible non-inferiority study -- and again, this isn t being against non-inferiority studies. It s when they re okay. That s the question -- is not exactly hot news.

DR. EDWARDS: Yes?

DR. O NEILL: Yes, I d just like to follow-up on that. The guidance that Bob is referring to is the ICH E10 guidance, which was the active control clinical trial guidance, which was published in 2000.

What I found interesting in the presentation by the sponsor, there was not one reference to the principles that you need to look at to establish whether the non-inferiority design is an eligible

design.

You have to go through that mental exercise, and that mental exercise is a combination of looking at the historical data that is available, and in fact, that s exactly what John Powers did, walking through that and coming to the decision that the risk in doing this design outweighs some other form of trial, maybe a superiority trial.

There are big risks associated with a non-inferiority trial. It is not the trial you want to start with if you have another choice, because there are risks in making a wrong decision, and that s what this is about. It s not the design, it s the evidence that allows you to conclude that you re making the right decision as a basis from the data that you have.

I think that s what is at issue here. There s an article in the Annuls of Internal Medicine on this very issue that came out three weeks ago. It talks about the risks associated with getting it wrong. It goes through all of the issues that we ve been talking about right now. It restates

what s in the ICH E10 document.

There s a Consor (phonetic) document that has come out within the last three months saying We ve got a problem in the medical literature in the way non-inferiority trials are reported. We gotta fix it. And there s some guidances about how to fix it.

So what I m saying is this isn t new today. This has been going on and well-recognized, and these principles are out there. It s a matter of living by the principles, which essentially are thinking through the problem, thinking through the logic of whether you should or should not use a design, and then making the decision on the basis of that.

DR. EDWARDS: Dr. Patou, I d like to ask you to reflect on the recent comments.

DR. PATOU: Yes, I d like to make a number of comments. I d like to start by saying that when a sponsor embarks upon a clinical trial program for a new antibiotic, the company meets with the FDA, and there s an active dialog over the appropriateness