isolate with an MIC of 4, will we both be likely to get coverage? I think those are two different questions that are being asked. Is that correct?

DR. CODERRE: In here I am pointing out the most conservative value for target attainment time above MIC 35 percent of the time. And, this is for specific organisms at that particular target attainment, and 90 percent is the value that is most indicative of in vivo efficacy. All I am saying is that this is a little bit below that 90 percent when you look at 35 percent time above MIC.

DR. REX: But it is also done against a group where you have deliberately left in very high MIC isolates, which actually clinically you would take out once you knew that they existed. I mean, you wouldn't continue to treat somebody with an MIC of infinity knowing that the target attainment isn't there. Thanks. That was my question; that was my clarification.

DR. TOWNSEND: Dr. Bennett?

DR. BENNETT: I think we have to be careful not to over-interpret cultures of endotracheal aspirates of patients with ventilator-associated pneumonia who are failing. We have a problem, that is, first microbiological

assessment was often not done in 09 or it was only 37 percent who even had microbiology.

So, who do you culture? It is the failing patients. So, you are not necessarily sampling the patients who are doing well so there is a bias towards those cultures. But, most importantly, so many of the isolates of the cultures you are talking about are on a biofilm within the endotracheal tube.

DR. CODERRE: Correct.

DR. BENNETT: And Pseudomonas and Staph. aureus are certainly ones that are famous for forming biofilms. These biofilms are worse constantly with bronchial secretions that have lower concentrations typically than you would obtain in blood which would be more likely to cause resistance, and they may not at all be important in the pathogenesis of what is going on with the patients= lungs. So, clinically we often ignore those cultures. So, I would be very careful in trying to interpret the data you just showed us.

DR. TOWNSEND: Dr. Rex?

DR. REX: I actually do have one other question. You pointed out the imipenem and the meropenem data. Do you have any conclusions about whether qualitatively what we

have seen here for doripenem is different, better or worse than any other drug analyzed in this way? I think that is an important question for future drugs to understand how an analysis would be done and what you would think about it.

DR. CODERRE: Well, I think there is a lot of comparability between the 2 or the 3 drugs. You know, I would hesitate to make a sweeping statement as to whether one was better than the other. That is only my opinion.

DR. REX: So, resistance to one, resistance to the other, you saw some of each.

DR. CODERRE: We saw some of each, yes.

DR. REX: Thanks.

DR. TOWNSEND: Dr. Calhoun?

DR. CALHOUN: I have two questions about the resistance development studies. Question number one is, is it the position of the FDA then that this drug should only be used in the context of an aminoglycoside?

DR. TOWNSEND: Dr. Cox?

DR. COX: Yes, I don't think we have developed a position on that yet. You know, I think we are here today to discuss the study, trying to get, you know, advice on the results that were seen. So, I think it would be premature

to answer that question.

DR. CALHOUN: Well, I agree so the second question is have you done a sample size analysis of how many isolates you really need to do in order to demonstrate whether you need to have a second agent? Because my guess is that an N of 6 is not big enough.

DR. CODERRE: No.

DR. CALHOUN: So, you haven't done that?

DR. CODERRE: No.

DR. CALHOUN: So, the point of this slide was? Maybe I am being dense here but I am missing the point of that particular slide.

DR. CODERRE: I think it shows that through multiple passage studies you don't see a tremendous amount of difference between doripenem, meropenem and imipenem.

DR. CALHOUN: No, I am sorry, I was talking about the gentamicin additive study.

DR. CODERRE: I think the gentamicin study simply shows that, as we know, when we have combinations of drug we have a much lower possibility of development of resistance rather than when a drug is administered as monotherapy.

DR. CALHOUN: Right. So, just so that I am clear,

you just said that you don't have enough information to know that this is definitive and you are not making a recommendation that this drug be used in combination with an aminoglycoside. Am I understanding that right?

DR. CODERRE: Well, I think the question asked of me before was whether I thought one carbapenem was better than the other. I think that is a different question. If you are asking me whether I think this would work better in monotherapy or combination therapy, I think it would work better in combination therapy.

DR. COX: Yes, and I think too as we move towards the questions, you know, one of the questions focuses around the assessment of doripenem, and I think that is, you know, one of the key questions that we will be asking here today and that is, you know, the safety and efficacy of doripenem. So, I think we need to get through those questions and discuss that issue.

DR. TOWNSEND: Dr. Edwards?

DR. EDWARDS: The sponsor also did a serial passage study. Can you compare the results you just showed to their study?

DR. CODERRE: Right, it is the same study I

believe.

DR. EDWARDS: Thanks.

DR. TOWNSEND: Dr. Leggett, you had a question?

DR. LEGGETT: The statement was made about combination versus single therapy. My only comment was going to be that these are in vitro serial passage studies. There are many, many passages between those steps and reality. There is a lot.

DR. TOWNSEND: Dr. Rex?

DR. REX: I want to apologize for unclear wording a moment ago. I asked whether one drug was better than another. The context was development of resistance in this specific way when analyzed. I was not talking about clinical data. I was asking you to comment on the behavior microbiologically and whether they were similar or not in that way.

DR. CODERRE: I think they are similar in that regard.

DR. TOWNSEND: Any other questions of Dr. Coderre?

[No response]

Thank you. Dr. Laessig?

DR. LAESSIG: Thank you, Dr. Townsend. At this point we are turning to the questions and we certainly appreciate all the valuable discussion and the good points that have been raised thus far, and we realize we have put a fairly sizeable task before you with these questions and all the information that we are looking to gather.

Since the questions will actually be read into the record I am not going to do that at this point. There are just a few things that I want you all to keep in mind.

Basically questions 1 through 4 are specific to this application, while question 5 and also to some extent question 1 are relevant to future trials for this indication.

Questions 1, 2 and 3 are basically questions where you will be asked to vote. When voting on questions 2 and 3 and giving your verbal response, if you could please state why you voted the way you have and if there is any other information that you would like to see. And I will turn it back to you.

Questions to the Committee

DR. TOWNSEND: All right, thank you. So, here are the questions that FDA has charged the committee for us to

answer today. Again, the first two questions I believe are yes or no answers.

I will ask the question and then we will go around asking you to say yes or no. Feel free to briefly, or at length, discuss the rationale for your answer. So, the first question, and if you don't mind, Dr. Calhoun, we will start with you.

Is there sufficient scientific justification to support the applicant's proposed non-inferiority clinical trial design with a non-inferiority margin of 20 percent in nosocomial pneumonia, including ventilator-associated pneumonia?

Actually, we are doing simultaneous voting, yes/no, with your little gizmos there. Everybody has to vote yes or no and then we will go around and you can say what your answer was.

Is there sufficient scientific justification to support the applicant's proposed non-inferiority clinical trial design with a non-inferiority margin of 20 percent in nosocomial pneumonia, including ventilator-associated pneumonia? Please answer yes or no.

[The committee votes electronically]

Everybody can just press hard again. We have four yes votes and nine no votes. For the record, could the members who voted yes please raise their hands? Members who voted yes, please raise your hands again. Again, we will start with Dr. Calhoun, if you could read into the record your vote and briefly if you want to justify your yes or no vote?

DR. CALHOUN: Bill Calhoun. I vote yes. It is a qualified yes in that I am not sure that the scientific justification is particularly strong but I don't see an ethical alternative pathway to the implementation of new agents.

DR. TOWNSEND: Dr. Ohl?

DR. OHL: I voted no with caveats that this is not a question that is easily answered and that I did not answer the question. I did not see scientific evidence to support a 20 percent justification. And, I am scared to death you are going to ask me what the number should be. And, I will probably change that answer a billion times before we get to it. And, it doesn't reflect anymore on the clinical trial other than just scientific evidence to support the margin.

DR. TOWNSEND: Dr. Bennett?

DR. BENNETT: I don't think we have a scientific rationale for a delta, and I don't think the FDA has made a convincing argument that they have one either. So, the question is should we use a precedent and I suspect there is a precedent and it might well be 20 percent. I don't know what the precedent is in previous applications that have been approved for this indication.

DR. TOWNSEND: Dr. Dowell?

DR. DOWELL: I voted no. I didn't think there was strong justification presented for 20 percent. I didn't think actually there was much discussion about that and I don't know what the company could have done. I think it was wrong by the FDA to try and present data to justify 10 percent. So.

DR. TOWNSEND: Dr. Smith?

DR. A. SMITH: I guess what I am going to say is redundant. I agree with what everyone has already said. I just don't think we are going to be able to ever answer the question clearly and to everybody's satisfaction. I just think it is very difficult to do given what we have to work with.

DR. TOWNSEND: Dr. Leggett?

DR. LEGGETT: The trouble with non-inferiority marginsB-first as regards this trial, I think that they did it as well as they were expected to do, but there is, unfortunately, no gold standard and we danced around that with talking about mortality as sort of being the hard standard. But the trouble is that there is a lot of distance between killing of the bug and killing of the patient, and the mortality data doesn't tell us anything about the only thing the antibiotic is supposed to do, which is kill the bug.

But the hard part that comes in, as has been pointed out, is that not only is there the sort of microbiological creep that this committee and the FDA has looked at in the past with regards with otitis media and this kind of thing is, is this really placebo, but here the question is we are at a very high efficacy standpoint and, as has been pointed out, the adjunctive care is going up so there is creep in the inappropriate delayed placebo effect.

So, it really does behoove us I think, going forward, to look at a more conservative delta because we are getting smaller, and I would point out that that is also going to entail, unfortunately, in terms of protocol design

going forward, that it is going to be even harder, not only that you are going to have to get bigger but with all our ventilator bundles, and the like, our incidence of nosocomial pneumonia, especially ventilator-associated pneumonia, is going way down. At my hospital we have not had one in over six months. So, this is a problem going forward but at the current time I don't think that a 20 percent inferiority margin is justified.

DR. TOWNSEND: Dr. Stoller?

DR. STOLLER: I voted no, answering the letter of the question, although the question is kind of loaded. For reasons we have stated, as we have heard, I think there is very little scientific rationale for any estimate, not the least of which is 20 percent. So, I would agree with prior comments that in the absence and the void of any rationale that precedent might prevail.

I think that one of the particular shortcomings here is the reach, as Dr. Fleming has reminded us, between models that are based on mortality estimates from historical studies and clinical effectiveness studies, which is what we are asked to comment on here. So, I think for several shortcomings in the extrapolation I think it is an

unanswerable question and I would say no.

DR. TOWNSEND: Dr. Brantly?

DR. BRANTLY: I voted yes and share similar opinions as Dr. Calhoun, but also I have to echo some of Dr. Edwards point, which is that in the absence of data I think we have to go with historical approaches to the non-inferiority.

DR. TOWNSEND: Dr. Hilton?

DR. HILTON: I felt that the question should have included a specification of the endpoint of interest because the margin is specific to an endpoint. So, that is my first point.

Secondly, since all of the confidence intervals, the overall confidence intervals for clinical efficacy were 9.1 percent and more superior from that point, I was thinking of 20 percent as being just fine but, actually, I realize I am thinking about that in exactly the reverse manner. So, I would like to swap my vote for a no, if that is possible.

Finally, I was thinking of this question not in terms of interpreting the results of the trials but more as a general comment about non-inferiority margins for this

disease.

DR. TOWNSEND: Dr. Edwards?

DR. EDWARDS: I voted no within the context of the letter of the question. I personally do not know what the appropriate confidence interval should be and whether 20 percent is the correct figure, and I think that determining that level scientifically is an unattainable goal. The data just are not available for us to do that. Therefore, I think the margin is going to be obtained by consensus and I would strongly favor a rather lengthy process of driving that consensus.

So, until we have had an opportunity to do that, I felt that 20 percent is a figure I just can't entirely accept at this point in time and, indeed, consensus derivation.

DR. TOWNSEND: Dr. Fleming?

DR. FLEMING: I voted no. Just to extend what Dr. Hilton is saying, she is correct that a margin is very specific to the circumstance so when we speak about a margin it must be specific to what the active comparator is and, for that matter, what the context of the use of that active comparator is. It is specific to an endpoint. So, I

interpreted the question, because the sponsor had proposed the 20 percent margin relative to the clinical response measure that that was the specific endpoint.

There are a number of issues here. The clinical response measure is already problematic. It is a composite of symptoms and surrogate endpoints and there is a vague use of clinical judgment being implemented in open-label trials. And, all of this complexity adds to the context of defining what the margin would be.

The arguments that have been given to defend the margin have been based entirely on using historical evidence to establish a margin for mortality and then arguing that that can be extrapolated. It is an invalid argument. There is strong evidence to the contrary, that you can't presume a margin for one endpoint to apply to another endpoint.

A third issue is that even the derivation of the margin for the mortality endpoint is very complicated. The FDA has made important strides toward achieving this, as has already been discussed. However, there are many issues that make that FDA derivation of the margin for mortality fragile, including the use of non-randomized trials, separating out appropriate versus inappropriate treatments

and judging the difference in the outcome as specific to treatment but it could be readily attributable to significant confounding in the characteristics.

Then, lack of proper attention to the constancy assumption. The whole goal here isn't to understand what the effect of an antibiotic is in a historical context. It is to understand what the effect of the active comparator is. And, if circumstances change, then extrapolating those assumptions, those estimates, is treacherous and things have changed. There is emergence of resistance to piperacillin. There is substantial use of supportive care, both antibiotics before randomization and during randomization, that readily attenuate what the additive effect of intervention would be.

There are also in these trials high levels of irregularities in terms of quality of study conduct which further bias you toward insensitivity to treatment differences.

So, all of these issues need to be weighed in when you look at what would be a valid non-inferiority margin. It would not be possible to scientifically justify the margin as 20 percent. Questions have been raised is a

smaller margin possible. There is no data.

Well, absence of evidence doesn't allow you to arbitrarily define a margin. In fact, the ICH guidelines are crystal-clear on this. The FDA guidelines are crystal-clear on this for antimicrobials, that one needs evidence-based margins. So, in the absence of evidence for a margin one does need to use other endpoints, or one needs to do superiority trials in order to be able to interpret whether or not a therapy, when it looks similar to a comparator, is similarly ineffective or similarly effective.

DR. TOWNSEND: Thank you. I also voted no for many of the same reasons that have already been commented on here. I will just say very briefly in summary that I am not sure that 20 percent is the wrong margin; I am not sure that it is the correct margin. I don't think we have the data to demonstrate that this is the correct margin to use. Dr. Rehm?

DR. REHM: We have heard some very compelling arguments for no and, having voted yes, I find it in light of recent discussion difficult to justify, quite frankly, but I would have to say I took this question at perhaps a little more general level, and in a condition that is

inherently difficult, perhaps impossible, to quantitate in terms of various aspects, I did vote yes.

I would, however, also like to comment at some point on the specific breakout of ventilator-associated pneumonia within that proposed indication. I don't think this is really the right time to discuss that but I would like to come back to it later.

DR. TOWNSEND: All right, thank you very much. Dr. Rex?

DR. REX: I don't get a vote, nor do I want one, but am I allowed to make a comment at this point?

DR. TOWNSEND: Yes, you are.

DR. REX: My comment today is based on an industry perspective, and my comments, thus, are not about doripenem but, rather, are going to take a broader viewpoint.

Those of us who work in this area do so because of the growing critical need for novel antimicrobial agents. It has been said, and it is very true, that modern medical care is not possible without effective antimicrobials. In particular, modern ICU care is absolutely not possible without such agents.

Unfortunately, our current drugs are failing.

This is highlighted by publications such as those from the IDSA, "Bad Bugs; No Drugs" surveillance data, as presented today, and newspaper and magazine articles. Thus, it is absolutely critical that we have a clear regulatory path in the approval of new agents, especially new agents for use in the critical care setting.

New approaches to nosocomial pneumonia and its variants are particularly important because this entity is a major cause of mortality and morbidity. I was delighted to hear about Dr. Leggett=s experience with the aggressive pneumonia bundles and also my experience in epidemiology. You can drive the rates down but you still have people that get in trouble.

Unfortunately, it is not going to be easy. Dr. Fleming has crystalized, as he always does for us, the issues surrounding approvals for nosocomial pneumonia. We start with our lack of placebo-controlled data. We don't have any. We are not going to have any. Actually, recall that at the CAP workshop FDA asked us if we could do placebo-control studies in CAP. The answer was a resounding no, and I was delighted to see that question did not reappear today because I think we know the answer.

Again, as stated by Dr. Fleming, whereas we do believe that antibiotics have an effect, and we do, we have a limited ability to estimate the effect of adding an antibiotic on top of all the other supportive therapies in place.

Now, this is where it gets tough. Mortality measures are attractive because they are simple, easy to count. Everybody can define it. But Dr. Fleming has pointed out some of the issues with measuring it at different time points. I will also note two other issues. First, I would point out something that is subtle. We don't allow people to die of the kinds of things that they used to die of. So, when you look at retrospective data sets you get people in there, particularly older studies, where you wouldn't let them die from that anymore. You just wouldn't.

The other issue with retrospective studies is that in prospective studies when you look at any given modern trial there is always an exclusion that says that if you are about to die, please do not enter this trial. Now, it makes good sense and in this particular case there was an exclusion in these studies for high APACHE scores, sort of an about to die exclusion.

Now, that is nice but it does have an effect when you try to compare with an older data set and I just want to point this out. Dr. Fleming would have, I am sure, later on if I had not. When you look at retrospective data sets you don't take people out who are about to die. I mean, you don't collect your own data sets. Everybody gets in. Right? You don't have any these exclusions so there is a difference.

So, these are enormous problems and what are we going to do? Unfortunately, you could easily conclude that there is no study possible, or at least no practical study that is possible. I must anticipate one of my subsequent comments now by saying that, for example, the idea for powering for a mortality-based outcome to a non-inferiority margin of 6 percent is not a solution. At 15 percent mortality, this leads to requirements to enroll 1,500 to 2,500 patients per trial. Perhaps I could do that if I only needed to do one trial in my entire clinical trial program, but can you imagine me doing two of those trials and having that be only piece of the trial of the overall program? No.

So, let's get back to the theme, what are we going to do? This actually reminds me of Swanson's rule number 2,

where Swanson was the CEO of Raytheon, and he says it is easier to get into something than to get out of it. We have actually gotten ourselves into this jam by thinking that the only sources of data we have are those that come from the realm of statistics and databases. Fortunately, and again as illustrated at the recent CAP workshop, we have more than that to draw from.

What we need instead is to remember we can use our understanding of microbiology and clinical medicine. We have a number of senior scientists at this table who collectively have a lot of insight into these domains and we can use these insights to inform and modify the statistical thinking. We have had some comments on that already.

Although difficult, combining such ex-trial information data from the trial is required. What are the sources of data? We have microbiology. In no other area of medicine do we have such a clean opportunity to separate the disease from the patient. MICs aren't perfect but, combined with our knowledge of resistance mechanisms, they teach us a lot.

Second, we build from the in vitro MIC data towards our use of in vivo models. Here we can begin to

take advantage of our extensive knowledge of bronchodynamics. We know how antibiotics work mechanistically. We also know how they work biologically in terms of the exposure required, both the shape and the duration. This guidance has been so extensively tested that to doubt its relevance now is tantamount at present to belonging to the flat earth society.

Third, we have sources of clinical data that we have not yet fully exploited. Again, we can look at the CAP workshop as a model. The more we looked, the more data we found. Actually, based on what I know at present, there are at least a few more papers that provide estimates of response in the appropriate/inappropriate comparison approach.

Dr. Paul Ambrose commented to me that he actually can go further than this and provide pharmacodynamic-based estimates. You may recall from the CAP workshop, if you were there, that he had data, per patient data correlating individual patients= blood exposures with their MICs and their outcome. They were very striking. You could look at people who, for whatever reason, got low exposure and had a higher MIC isolate and you could estimate their responses, a

lovely correlation that made perfect microbiological sense when you do all that.

So, to begin to conclude, and I know I need to shut up, what are the key points from the industry perspective? First, it is absolutely critical to industry, to physicians and to patients that we have a clear path for bringing forward new drugs. Again, I appreciate the comments on that.

For nosocomial pneumonia this means we need clear, detailed guidance on how to design studies for this entity. Generally, this will require discussion and review of all the data available on nosocomial pneumonia and how it can be used to inform trial design.

Second, today is not that day. Today is doripenem's day and the committee needs to focus its energies here. We are just not prepared for the more detailed discussion. We got all the briefing documents, the public did, 48 hours ago. We need something like the CAP workshop from earlier this year.

Third, and very importantly, until such time as we can have that general discussion we need to avoid locking down any strong conclusions. I have already given an

example of one such conclusion that you might draw, that mortality with a 6 percent margin is a solution. It is not.

Likewise, superiority trials are not possible for several reasons. First and foremost, we ensure that the comparator is fully and adequately done. Remember, we develop new drugs to address issues of resistance but when we are studying them what do we do? We take out the patients infected with the resistant isolates. We never let the drugs demonstrate their ability to do something. In this case you have to take out patients with resistant isolates. Their very advantage is taken away from them when we are doing clinical trials. So, we really should only draw firm conclusions today to the extent required to support the discussion of DORI.

Finally, and as I have the microphone and I am also a clinician as well as a drug developer, I will use this as a chance to interject a personal comment on how to use historical clinical data. For my money, the best data sets are those in which a prospective cohort comparison is done based on the analysis of appropriate/inappropriate therapy.

I recognize fully the critique, and Dr. Fleming

laid it out, that the groups so defined are not randomized. You didn't get inappropriate therapy by design. And, it may be that people who got inappropriate therapy had a resistant isolate because they had been in the ICU longer, because they were sicker, those sorts of things. But if you look at the individual studies, like the Luna 2006 study, you actually can go in and ask is that really an issue.

Look at the Luna 2006 study where they did this and they showed a mortality difference between appropriate and inappropriate of 35 percent. Then they say, wait, the APACHE scores are the same. Actually, they are 1 point lower in the group that got the inappropriate therapy. Now, that is 20 versus 19 and 1 point is not a difference. I know that. But it is the right direction; it is the right bias.

Actually, if you take the 4 good appropriate/inappropriate studies available to us, Celis, Kollef, Luna and Leone, I get a 35 percent difference in all-cause mortality and my simple calculation is that that is a 95 percent CI of 26-46 percent. You know, that affects us as interesting because it is consistent with prior precedent. It is consistent with lots of prior biology, and

it actually sort of feels right, makes clinical sense. I know that is not science but it is what you got.

So, again from a personal viewpoint, I think you could use this to drive pragmatically an argument for perhaps a 15 percent consensus-based margin for clinical response when comparing new drugs versus maximally dosed drug regimens in current use for this entity.

I also think we do have enough data to define reasonable disease and response definitions. We have seen some pretty good ones today. And, if you found all this was true, you know, a 15 percent margin would let you support a trial design of about 800 patients for reasonable outcome measures.

So, let me close with a final idea and here I am going to speak as an ex-academic who has battled infections in the ICU for more than 15 years, as an ex-epidemiologist who closed ICUs due to outbreaks of MDRS Nitobacter and finally, like everybody in this room, potentially a future patient who needs these drugs. Antibiotic discovery and development is a specialized area that carries both disadvantages and advantages. As someone who faces the challenge of convincing appropriate leaders to invest in

this area, I often argue that the disadvantages, like our tendency to place antibiotics on reserve, are counterbalanced by the advantages, our ability to use extensive preclinical in vitro and in vivo data, our ability to take guidance from pharmacokinetic and pharmacodynamic data.

Today's action by this committee will be noted and could easily influence the course of investment in this area. If you want new drugs, if you want new tools it is incumbent upon all of us to identify practical compromises that will move us down the road. If you can't identify those compromises today, then you at the very least need to leave room to develop them tomorrow.

I am not asking for wishful thinking but I am, contrariwise, not willing to settle for a view that the only conclusions we can draw are the ones that come out of an Excel spreadsheet. Thanks.

DR. TOWNSEND: Thank you, Dr. Rex, for your insightful comments. Dr. Fleming, did you have a comment to make?

DR. FLEMING: Yes, it certainly would be important to expand and respond in part. The comment that the 35

percent mortality difference, a suggestion that that is real, that that actually represents what piperacillin adds to the existing supportive care in the doripenem trial is completely without scientific justification and the argument that we could then justify a 15 percent margin, there is no scientific basis that ties those two together.

The argument that we are facing major morbidity and mortality is certainly true. It is the very reason that we need rigorous science to understand that when we are introducing alternative therapies we are not losing the major benefit that existing therapies are providing.

To say that we have a great amount of microbiology and other supportive evidence, that much of it is also preclinical, certainly that is important. That establishes proof of concept. When you then evaluate a therapy that has such microbiology it doesn't justify the conclusion that you, in fact, achieve the intended benefit that patients care about.

The bottom line--it is about patients. We want to look for therapies that will provide favorable benefit to risk for patients. In fact, it is not about patients having more choices; it is about patients having more informed

choices. And, if we introduce antibiotics that could, in fact, be less effective because they haven't been rigorously established I don't see the argument that that is doing patient benefit.

I mention isoganin. Isoganin is a broad-spectrum antibiotic for which there was great proof of concept. We could do a placebo-controlled trial because it was looking at prevention of VAP and that study was shockingly stopped early when there was excess mortality, completely inconsistent with all the microbiology and all the other indicators would have suggested should have happened. It is why we need evidence-based medicine in carefully conducted clinical trial.

The argument was also given in the CAP study, look, we don't let people die anymore so, therefore, we can't use mortality as an endpoint. Yet, when you look over the last 50 years the mortality in the CAP setting hasn't gone down. And, we also have studies indicating that immediate versus delayed therapy makes a difference.

So, it does matter. It does matter on outcome in mortality today as to whether or not we are introducing antibiotics that are maintaining the benefits that previous

antibiotics have achieved. The bottom line is this is about ensuring that we achieve what is a congressional mandate, which is substantial evidence of efficacy. Just because it may be difficult to achieve it doesn't mean that we have to achieve it. In fact, the numbers you gave for a mortality trial don't make that an unachievable study. In fact, the numbers I come up with are similar to yours, 1,500 patients. We have 1,000 patients that have been provided to us here. That is not a quantum leap larger.

In many clinical indications when we are studying interventions that have such an important benefit, antibiotics are critically important to providing benefit to patients. In settings where you have other interventions that provide such important benefit the idea of doing a 1,500 patient clinical development plan or clinical study is certainly not out of the realm of what is reasonable to assure, as is congressionally mandated, that we have substantial evidence of efficacy and favorable benefit to risk before marketing a product, particularly when this could be used instead of other effective therapies.

DR. TOWNSEND: Thank you, Dr. Fleming. In the interest of time we will keep going. I have been asked to

sort of summarize the vote. Again, the vote was 10 no, 3 yes.

The comments made, the comment among them I think most commonly being that there isn't enough information available, at least to this committee, to feel comfortable saying that a margin of 20 percent is, indeed, the appropriate margin for a non-inferiority margin for a clinical trial in nosocomial pneumonia, with clinical endpoints being the primary endpoint. Not that that is the wrong non-inferiority margin but, rather, that it is unknown that it is the correct one. And, that there simply is more discussion or review of the literature to determine what the correct margin may need to be.

There is certainly a need for determining what the information margin should be in these kinds of studies. It simply isn't available to us right now with the information that is available.

Next question, again, is a yes/no question so after I read the question, if you can press firmly, yes/no. Has the treatment effect of antibacterials been adequately quantified in the treatment of nosocomial pneumonia?

DR. FLEMING: Can we clarify the question before we

vote?

DR. TOWNSEND: Sure.

DR. FLEMING: So, this question is specifically relating to in general for all antibiotics, or is this specifically for the active comparator antibiotics that would be used in the context of the doripenem trials?

I mean, technically speaking, when you are formulating a non-inferiority margin it is based on the specific endpoint and the specific active comparator in the specific context in which the studies were don't. So, are you asking has the treatment effect of piperacillin and imipenem in the context of substantial concomitant meds in the doripenem trial, has that effect been adequately quantitated on clinical efficacy and mortality endpoints?

DR. COX: Yes, you know, as I think about it, I think we are referring to essentially, you know, the information that we presented here today in trying to justify the non-inferiority margin. So, has it been adequately quantitated?

We have heard some comments on that but, you know, if there are additional comments to that issue that would help us. Is that clarification sufficient, Dr. Fleming?

DR. FLEMING: Yes. So, what this question is really getting at, which logically makes sense as to what it should be getting at is, is there sufficient evidence that has been put forward that allows us to understand what the effect of piperacillin and imipenem would be in the context of the nature of supportive care, the level of adherence that these interventions had, etc., in the doripenem trial.

DR. COX: That is correct.

DR. OHL: Or is it any antibacterial that potentially could be used for nosocomial pneumonia and not just the two?

DR. COX: If you would like to make a comment to that effect, I think that is fine also, if you would like to include that in your comments. I think, you know, specifically the data that we presented here was more specific to imipenem and pip/tazo.

DR. FLEMING: This is the FDA's call, but on these three sub-points do you actually want a vote or is a discussion of these three points adequate for your purposes?

DR. LAESSIG: Yes, I think obviously different people have sort of addressed different points here so I don't think we need to vote again. I mean, if there is

anything else that anyone wants to add in this regard, that would be great.

DR. TOWNSEND: Dr. Hilton?

DR. HILTON: I would like to add that in addition to the statistical considerations about definition of the non-inferiority margin that we have been talking about today, there are clinical considerations, like what is the tolerance for additional deaths? For example, 6 percent additional deaths of 1,000, would we really be willing to tolerate that?

The same with clinical cure. Twenty percent is a number that maybe, you know, on a piece of paper looks fine but when it is your sibling, someone you care about, is 20 percent really something we are willing to tolerate?

So, it seems to me that both of those angles have veto power and we want the more conservative of the two. You know, what are we willing to live with clinically, and what is the boundary that will show efficacy statistically?

DR. TOWNSEND: Dr. Leggett?

DR. LEGGETT: I would like to go along with that and in terms of my comments, they were sort of incorporated in what I had to say about the other points, but in terms of

picking a number, you know, how are we going to say, following up on Joan=s point, that 35 percent time above MIC cutoff has to be 90 percent? Then we are going to say, well, that is 10 percent from 100 percent. Then we are going to say we can allow 20 percent of the people to die? I mean, you know, what percent becomes a real percent?

Then, the other major problem with this, and it has been a long-time problem and this study is another example where we are trying to say that a new drug has to be all by itself and, yet, we are comparing it to something that FDA approved, drugs supposed to be used in combination. Then, in real life very seldom are we giving monotherapy for ventilator-associated pneumonia in the ICU.

So, if we are trying to make the studies here also generalizable to real life I think we have to sortB-the FDA has to find a way to get around the single drug versus single drug comparison that I think you also talked about, Tom.

In the whole context of things are we really in most cases talking about a couple of days of amikacin, or whatever, plus doripenem and then moving downward? I think it is very hard to say that we must have a single drug

versus a single drug when, in reality, that is not what we are doing anymore.

DR. TOWNSEND: Dr. Dowell?

DR. DOWELL: I took this first question to be do we buy into the idea of this non-inferiority trial approach because we buy into the idea that you can quantify that there is a difference between an antibiotic and a placebo for nosocomial pneumonia.

I might have guessed, coming here, that it would have been tough to buy into that. But I found myself to be strongly persuaded by the data presented by the FDA that there really is a difference between placebo and treatment for this indication and that it is not subtle. It is a dramatic difference and it is based on four or so historical trials.

I am not really optimistic that if you hold another series of hearings and spend more time that you will do much other than rehash those same four historical trials and look at them from a bunch of different angles. So, I would just say for that question my answer would be yes, I am persuaded and I am actually not persuaded that lots more discussion is going to be tremendously helpful.

DR. TOWNSEND: Thank you. Dr. Edwards?

DR. EDWARDS: Just to follow up on Dr. Rex= comments, I agree with the comment just made that further discussion about the historical trials is likely to be non-rewarding. We may find a few additional papers but I am not sure they are going to shed much more light. I don't think we are going to have the evidence base from the historical trials in order to continue with the trial design.

But I would like to just make the point on record that I feel that a consensus conference or workshop with all of the stakeholders involved, including a representation of the clinicians who are managing these patients on a day to day basis, would be a very necessary tool for us to move forward in improving the clinical design.

DR. TOWNSEND: Dr. Bennett?

DR. BENNETT: I think of the doripenem study as a study of comparing two different regimens; not two different drugs, two different regimens. And, that is the way we do clinical practice, but it shouldn't be the way we do clinical trials because the FDA does not approve clinical regimens, they approve drugs.

So, what is the challenge to the industry is to

find a way that you can do the trial that actually compares the drugs. For example, if you have to have a follow-on oral therapy you do your test of cure before you do the oral therapy because then you haven't contaminated the results with the oral therapy, etc. Or, you find populations where you can severely limit any other therapy that is being given so you don't end up presenting data to the FDA that is an amalgamation of different drugs being used as part of a regimen.

DR. TOWNSEND: Thank you. Dr. Calhoun?

DR. CALHOUN: So, Dr. Fleming is I think probably unassailably correct in what he said. As I have thought about this, it seems to me, Tom, that the endpoint of that direction of thought is that one must do a placebo-controlled trial. That is the way to get definitive information, and I think there is fairly broad consensus, and you are part of that, that those are ethically indefensible in many, many settings in many diseases outside of infectious disease but certainly the infectious diseases that we are talking about here.

And, the clinical evidence and the experiential evidence of people who work in the field--efficacy, the four

trials that we have that suggest, given all the potential problems that you have articulated nicely that there is benefit, suggest that there is, in fact, some important clinical signal there.

That leads me to consider whether the model that we use for testing single drugs against each other is actually not the proper way, and perhaps this workshop that I think is a wonderful idea, perhaps this workshop could identify some mechanisms to incorporate some of the softer, less numerical data and use that as a platform upon which real progress can be made. Because I agree with Dr. Rex that we really need to identify a way forward, otherwise the crisis of infectious disease, which obviously affects me as a practicing pulmonary physician, doesn't see a solution, or I don't see a solution for that.

DR. TOWNSEND: Dr. Ohl?

DR. OHL: Specifically related to the question on the screen, I also wanted to make a comment. I was quite impressed with the FDA=s heroic attempts to come up with a margin for us and all that went into that analysis. It was a tremendous amount of work and I think there is some information in there.

Specifically, has the treatment effect of antibacterials been adequately quantified? I am not so sure. I would probably answer that no. Has it been qualified? I would say yes. I mean, there is an effect. We know that.

The quantification that was presented was based on the best data that is available, and I am not sure those studies actually get at what really nosocomial pneumonia really is as we see it in our intensive care units, particularly anymore. The world has changed very quickly since those studies were done.

Antimicrobial resistance now has rendered some nosocomial pneumonia completely untreatable. And, comorbidity has changed. A lot of comorbidity was factored out in those studies that were looked at, or some of it anyway. So, I don't think it has been quantified but I would say qualified. What exactly the number would be I don't know.

DR. TOWNSEND: Thank you. Any other comments? Go ahead, Dr. Fleming.

DR. FLEMING: We will be coming later in the discussion to designs of trials that would be appropriate,

that would be scientifically interpretable, that would be ethical in a setting where a placebo is added to what is an existing appropriate standard of care and such would be ethical. So, the isoganin trial that I referred to that was looking for prevention of VAP used an ethical placebo and it turned out that the placebo was the better arm.

In a setting where you are looking at adding onto existing antimicrobial, antibiotic therapy you could envision giving state-or-the-art therapy plus your intervention and that would be placebo controlled. But if you mean placebo controlled depriving patients of what are established strategies for clinical care with antibiotics, no, we shouldn't do that. In fact, in the CAP advisory committee two months ago I and all other committee members voted against such a placebo control design.

There are, however, approaches that can be used, and we are going to get to that, that could be non-inferiority based on a mortality endpoint or could be superiority based on other endpoints that would be an alternative option that one could consider.

DR. TOWNSEND: Thank you.

DR. FLEMING: By the way, is it jumping ahead? I

think my colleagues already began discussion of another very important consideration, which is the clinical relevance of the margin and that kind of bridges this point to the next item, (b).

DR. TOWNSEND: Right.

DR. FLEMING: And, the margin not only needs to be evidence-based in the sense that you can preserve a substantial fraction of the active comparator=s effect, but it needs to pass the clinical sense of what is an acceptable loss of efficacy. A non-inferiority trial doesn't prove you are the same. It doesn't prove you are similar. It rules out the margin. Hence, it rules out that you are unacceptably worse.

If you use a margin of 20 percent and you rule that out, technically what you can say is I know I am not more than 20 percent worse than the standard of care. I am ruling out I am unacceptably worse. Technically, that is what you should be marketing. That is the conclusion that you have.

What that means is that the margin does need to be rigorously clinically chosen. It does need to reflect what clinically you and the patient would be willing to lose.

So, if you set up a 20 percent margin you say you have a 60 percent cure rate with piperacillin, for example, and you argue that it is okay if you use doripenem as long as I can rule out 20 percent worse; as long as I can rule out I am 15 percent worse. Then, effectively you are saying it is acceptable to be 10 percent worse; it is acceptable to be 15 percent worse.

I will say, well, turn it around. Suppose existing therapy gave a 40 percent cure rate and you could improve that to 55 and you had a good safety profile would you be marching off with a claim of superiority? Would that be an important advance? You bet. Then why in the world can you justify a 20 percent loss if a 10 percent gain or a 14 percent gain would be an important advance?

Now, if we just take the sponsor=s argument for how we can translate this margin to mortality, they are arguing for allowing a reduction from 60 percent to a 40 percent success rate on clinical response. That is a relative ratio of 1.5 or an odds ratio of 2.25.

The mortality data that was used to justify that margin was in the context of 26 percent mortality. An odds ratio of 2.25 is 26 versus 44. That would logically be

saying it is okay if the control has 26 percent mortality as long as I can rule out that mortality doesn't get any higher than 44 percent. Patients and caregivers are just fine with a 10 percent or a 15 percent increase in mortality.

I have no sense as to how as a patient I would clinically justify that. So, if I am using a margin for mortality and I have a 10 percent baseline mortality on the active comparator and I use a margin of 6 percent, which might be okay, basically you have to say it is okay from a patient=s perspective to increase mortality from 10 percent to 15; you just can't increase it beyond that.

Or, if you argue that clinical response is an acceptable measure and you want a 20 percent margin and you have a 60 percent clinical response in your active comparator you have to say it is okay to drop it to 50 or 45 or 42. You just can't drop it to 40 because only that big a difference is clinically relevant.

The issue is it has to make sense turning it around. If the different in terms of a gain of that amount would be clinically important it is inconsistent to say that the different can be larger than that in the loss unless you are providing other very major benefits that are in the same

sense of clinical importance as the loss of efficacy.

DR. TOWNSEND: Thank you very much. Dr. Rex?

DR. REX: Thank you. I will try to be brief because I want to point us back to what we need to be talking about today which is doripenem. But I cannot let-Bthe statistical danger today is that everybody in the room, except for perhaps a few, are going into "my eyes glaze over" and I tease a little bit about that, but it is hard to follow the statistical logic if you haven't spent a lot of time studying it.

And, there are two themes here that I would like to very briefly highlight. One is that when you talk about a margin of, let's say, 15 percent if you are going to have an actual observation that stretches to that margin of 15 percent you have two ratios, two percentages, and you are going to say that they could differ by as much as 15 percent.

It is important to remember that the maximum actual difference in those two percentages let's say for a several hundred patient trial is going to be some number like 5, 6, 7 or 8 percent. So, they are not actually going to differ by 15 percent. The point estimates may differ. I

mean, I have a calculation in front of me here, if you have 800-patient studies you are going to differ in the range of 7 percent. So, the point estimates won't differ by 15 percent; they will differ by a smaller percentage.

So, there is a theoretical risk from the frequentist statistics models that says that, yes, this other thing could be out there. So, you have to think about that and decide what does that mean. And, I think that is one of the important issues you bring up at a workshop, what does that actually mean.

The other thing is this 50 percent retention of effect. It is a long discussion and you really have to have a good load of caffeine on board to dig through it. But there is a fundamental issue with the 50 percent retention issue that leads to some very illogical conclusions when you work your way through the analyses. I am sure that Dr. Fleming is very familiar with the work of, for example, Snappen et al., and others who make those arguments.

Now, there are pros and cons. It is a subtle debate but 50 percent retention is not necessarilyB-there is nothing magic about 50 percent. It actually leads to some logical inconsistencies. It is part of the reason I would

encourage us to have a good discussion about this one day when that is the topic because we can otherwise spin around endlessly on this today.

To come back to my earlier conclusions, draw conclusions today insofar as they are needed to analyze doripenem. Try to stay out of the weeds of a permanent conclusion about nosocomial pneumonia today because I think we are not prepped for it. We don't have all the right data or the right people at the table.

DR. TOWNSEND: Thank you. Do you have a brief comment to make?

DR. FLEMING: A brief comment. It is a complicated issue, but we are being asked to approve, or potentially approve an intervention today using the methodology. If we don't make an attempt to understand in basic principles what the strengths and limitations of that methodology would be how can we use that methodology to make a judgment?

Then, to just address one of your comments about the point estimate versus the confidence interval, yes, if you used the 20 percent margin that would mean your point estimate could indicate you are 8-10 percent worse and rule out you are 20 percent worse.

So, your point estimate is only telling you that you are 8 percent worse to 10 percent worse. But the reliability of that matters, and the data are consistent with being as much as 20 percent worse.

We don't declare superiority when your point estimate looks somewhat better. You have to have enough confidence and precision in that point estimate that you rule out that you are the same. Similarly here, you have to have enough precision and confidence that you can rule out that truth would be something that would be an unacceptable loss of efficacy.

So, the arguments that are being put forward here are entirely consistent with what you would do in a superiority trial. It is important to have a basic understanding of the assumptions and the weaknesses of non-inferiority if one chooses to use this approach as a way of replacing standard of care with an alternative therapy.

DR. TOWNSEND: Dr. Hilton? If we can make our comments brief? We only have maybe two hours left before people have to start taking off and we have some more work to do.

DR. HILTON: I just wanted to highlight the comment

that was made but maybe not in a large enough manner, and that is just that usually non-inferiority trials trade off loss of efficacy for some other very important advantage. In this setting that we are discussing today I think that has to do with the microbiology and the worry about susceptibility to various pathogens. But I am not super clear on that issue and I look forward to more advice on that.

DR. TOWNSEND: Dr. Bennett?

DR. BENNETT: We have been having this discussion about deltas when you have one endpoint. But when we turn to the doripenem study we have two endpoints. So, my question for Dr. Fleming, for a brief answer, is do we know how to adjust deltas where we have multiple endpoints?

DR. FLEMING: Well, there are a couple of aspects to what you are asking. There would certainly, first of all, be a different justification for the margin for each endpoint. So, you would have to go through, and this is a lot what the discussion has been aboutB-there is a lot more evidence here for what the margin would be for mortality. There is minimal, if any evidence, as to what the margin would be for clinical response.

Suppose there was a basis for defining those two margins, if you took the approach that you win when either of those margins is met, then you do have to adjust for the fact that you have given yourself two opportunities to win and you have to make some adjustment to that. Of course, the point to that adjustment would be if you took the approach that it was good enough to win on one versus the other and it didn't matter what the other result showed, so what if you win on clinical response but mortality is trending in the wrong direction? That ought to cause someone some considerable concern. So, the nature of the adjustment needs to take into account whether you can declare a win if just one of them is positive.

DR. TOWNSEND: I want to clarify from the FDA, are you satisfied with not voting yes/no on the sub-questions? Do you feel like we have answered them reasonably well enough?

DR. COX: The discussion is helpful. I don't think we need to vote on this.

DR. TOWNSEND: I think we will move on then to 1(b). Given the proposed margin of 20 percent, is it reasonable to accept this amount of loss in efficacy and

still conclude that the study drug is non-inferior to the active comparator, considering the seriousness of the disease? Comments?

DR. FLEMING: Several of us have already commented on that.

DR. TOWNSEND: No other comments on that? All right. I think we probably know the answer to this but I will read it: Does the committee recommend a different non-inferiority margin for this indication? If so, what is the recommended margin? I think probably the answer is we don't know.

DR. FLEMING: This gets into some of the discussion that we began. My sense is when one looks at the totality of the evidence that the FDA has put forward, as well as the totality of the evidence that has come forward from an extensive series of discussions through a workshop and a two-day advisory committee in the somewhat related CAP setting, there is considerable evidence about the effect of antibiotics on mortality.

My sense is that what has been put forward as a potential margin for mortality is actually quite consistent with what the extensive research in the CAP setting

indicated as well. So, essentially, the 5-6 percent margin that the FDA has spoken about for mortality is a reasonable point, subject to some important conditions.

One is that it matters whether this is 30 days post end of therapy versus 14 days after randomization after beginning therapy. As in the CAP setting, there is a lot of concern about the diluting that occurs if you are going considerably after the time of randomization. So, my sense is if you are talking about a 10-14-day mortality, then that 5-6 percent margin in the setting where the baseline rate is, as in the doripenem studies, 10-15 percent.

There is a lot of evidence for that, subject to it being implemented in trials that are conducted with high quality because the best way to camouflage or miss important differences is to put a lot of irregularities into your trial, having a lot of issues with adherence, with retention; having a lot of exclusions, not validating that the specific clinical condition exists in all patients at baseline, if you wanted to establish the appearance of non-inferiority is to put patients on that don't have pneumonia.

So, a non-inferiority trial does require an even higher level of rigor than a superiority trial because noise

moves you to no difference. In superiority, a fortiori, if you win, you win. But in non-inferiority noise creates the impression of no difference and it can lead you to miss.

So, my sense is there is a lot of substance to what the FDA has put forward. There are some concerns that I continue to have about the exact analysis, but I think it is pointing us in the right direction of saying you could do non-inferiority on roughly a 5 percent margin if the baseline rate of mortality is much less than 10 percent.

I won't go through the details of this. We went through this in great deal in the CAP discussion. You could still do non-inferiority but you would need to do it in a relative risk sense, basically ruling out about a 67 percent increase, which is what 10 versus 15 is. It is 67 percent increase. So, if your baseline rate is 3 the margin would be 5, 3 versus 5, meaning that you could have flexibility in putting lower risk people into a trial as long as you rule out a relative increase from a relative risk perspective.

There are other approaches, and later in the discussion we will come to that, that we have as well beyond non-inferiority that aren't placebo-controlled trials that could be don't in settings where we have difficulty doing a

non-inferiority on measures other than mortality.

DR. TOWNSEND: Any other comments, any specific comments on using clinical response and non-inferiority margins in those studies? Dr. Cox?

DR. COX: I know you commented and Dr. Fleming has commented on this particular sub-question. It would be helpful, you know, given the importance of the issue if we could hear from other folks. Essentially, if we could go around the table and if folks do have comments and they would volunteer those, that would be very helpful to us.

DR. TOWNSEND: Comments? Dr. Dowell?

DR. DOWELL: Ten percentB-I have heard 15 percent, I have heard 5 percent. I said before, you know, I think we have the four trials. There might be another trial or two. I do agree with what some of the committee members have said about we don't have all the areas of expertise or perspectives around this table right now, but I think there is value in bringing in additional perspectives.

On the other hand, I think there is also a cost in indecision in terms of John Rex' point about the need for a clear regulatory path forward. So, hearing what I have heard today, I would just throw out 10 percent for a non-

inferiority margin for the endpoint of clinical cure.

DR. TOWNSEND: So, clinical cure and not mortality.

DR. DOWELL: Not for mortality. Medical cure, 10 percent.

DR. TOWNSEND: Dr. Edwards?

DR. EDWARDS: Well, just adding some thoughts, the efforts by the FDA to develop that delta are heroic on the basis of the available data, and they depend entirely on the quality of the derivation of the surrogate placebo effect. And, the quality of that derivation is exceedingly fragile on the basis of the data we have available at this time.

When Dr. Sorbello was discussing his analysis of the data he used a minimum of 10 qualifiers for the quality of the data. I made a list of them, in case you need them. Therefore, to say that a 6 percent delta is where we should be I think is just not possible by the evidence base at the present time.

Again I am going to make the point that that delta is going to have to be derived by a consensus agreement for getting a delta that has a reality impact and reality guidance feature to it.

DR. TOWNSEND: Dr. Stoller?

DR. STOLLER: I would put my comments in the context of both Dr. Rex= comments and Dr. Hilton=s comments with regard to the impact of accepting an information margin. I suppose as a clinician the way we are used to thinking about accepting a decrement, particularly in an outcome as sober as mortality, would be the offsetting benefit.

So, perhaps treading lightly about making directives for future thought, one of the other ways to frame the discussion would be in the standard gamble kind of language. If you are willing to give this up in exchange for what benefit is that sacrifice demonstrated?

I think as we get to DORI that conversation is framed perhaps on some of the microbiologic data, but I think if there were a clear path forward that was trying to be articulated for regulatory approval it would frame that question much more explicitly and carefully than has been framed by the somewhat dissociated data about PK/PD data and in vitro data, and it would be rigorously defined in terms of what you are willing to give up if your bother or sister were being given this drug in exchange for the offsetting benefit either to that individual or societally.

But I think that issue needs to be articulated before the question of inferiority can be accepted with the consequences as sober as mortality.

DR. TOWNSEND: Dr. Leggett?

DR. LEGGETT: My further comments were only going to be that at a certain point we can make the non-inferiority margin what we want, but if it is below what we can actually test reliably it doesn't really matter because I think that as we get down to 10 percent or below we are below our lower limit of detection clinically with what we can do now to even differentiate the noise from the studies.

So, I think that if we add the noise of the studies plus the 20 percent, that seems to me too much, but I don't know that we can tell the different between 5 or 10 percent with all the noise that is in our studies as they are designed right now. That is the way my thoughts were going.

DR. TOWNSEND: Dr. Hilton, did you have a comment?

DR. HILTON: I would just like to echo Dr. Stoller=s comments.

DR. TOWNSEND: Thank you. Dr. Rex?

DR. REX: So, I find it useful to think about what

this would mean, and I am chained by looking at an Excel spreadsheet. If you said you expected to see a 70 percent response rate, and I picked 70 because that is half way between the two response rates for the CE population that we are seeing for DORI. There is an 80 and there is sort of a 65 so I am just using 70 as a possibility. If you said you wanted a 10 percent margin with that, that is 882 patients but they all have to be evaluable so you have to, you know, round that up to 1,200 or so in order to have enough to lock out the ones that you can't evaluate. If you went to 12.5 percent, now you are down to about 600 patients.

That is the size that you are dealing with here, the difference between 800 and, let's say, if you go towards 15 percent you get down to about 400 patients for the entire trial. Again, you have to add a fair number on in order to have your evaluable subset.

So, at 10 percent you are kind of right at the edge of what is feasible for a single trial, remembering that that trial is not the only trial in the program. You could have another trial to go with it. Like, in this case, there are other indications already approved.

So, it is important to remember the context and I

think that is the thing that is so critical here. You know, pneumonia is different. At each site it is a little bit different and it is possible for a drug not work in one site and work in another. So, we are going to be looking for outcomes. But Dr. Leggett said this and I have heard it said before, there is a limit to the amount of noise we can drive out of this system and you are probably right at it with 10 percent.

I just would make the observation that there is nothing magic about 10. You know, what about 12.5? What about 15? You know, we all do this because we have 10 fingers and 10 toes but, you know, you could have other numerical bases to pick other different numbers and reason yourself into those being equally valuable as well.

So, there is going to be consensus. I know there is not a lot of time to have more workshops but you really want to get this right, and you want to have it said in a way that is convincing and compelling for the next drug that comes along.

Look at the way this application has come forth. How long ago were these studies designed? A number of years ago and they received good advice at that time about how to

design them, and things change as you go forward. It is like turning the Titanic to change a clinical trial program. You have to point it in the right direction at the start because turning it is very, very, very hard, if not impossible.

So, that is why I think this really does matter, that we say this in a way that everybody gets happy with or gets minimally unhappy with. I mean, that is my plea. I know this is tough. I guess I just have to stop there by saying, you know, you are talking about right at the edge of doability when you think about it as only one piece of an entire puzzle at 10 percent.

DR. TOWNSEND: Dr. Fleming?

DR. FLEMING: Dr. Rex, in terms of turning the Titanic, what we are discussing today is coming in line with what has been in the ICH guidelines for years and years and what many other clinical scientists have already understood. So, if these studies were designed three, four, five, six, seven, eight years ago, the principles that we are talking about today have certainly been well articulated and clearly disseminated through the ICH guidelines prior to the time that these studies were designed.

The argument that you have just given for the 800-person study for a 10 percent margin actually is nicely positioning the argument for being able to do mortality. Yes, based on what we have today we are pushing the limits of what we know when we do small trials. But if we did an 800-person trial we would be able to reliably discern the difference between 10 percent worse and no different. In fact, if you did two such studies you would be in a position to be able to also, in the aggregate of the two trials, discern whether or not there is excess mortality.

So, you have just given the argument why it isn't so outside the realm of a reasonable approach to be able to do a pooled mortality trial in addition to looking at other endpoint in two studies.

DR. TOWNSEND: Dr. Rehm?

DR. REHM: I guess I wanted to add on to what Dr. Rex was saying as well, and I guess, again, make a plea from the clinical side. The studies were put together when they were put together. We are perhaps interpreting them in a different context than they were put together. Despite all the potential issues with some of the data, there are still bits of information there that I think are relevant. And, I

would hope that we could use those data somehow in order to further the cause of keeping antibiotic trials going.

DR. TOWNSEND: Thank you. Dr. Ohl?

DR. OHL: Very briefly, I just wanted to add my thoughts as I have been hearing this discussion. Non-inferiority is clearly plausible. I think there is a number. I agree with the workshop. I think it would be helpful, and a consensus on this so that industry could move forward with some confidence would be very helpful. We need more drugs from this indication. And, I think the number will be somewhere between 10 and 15 percent.

DR. TOWNSEND: Thank you. Dr. Brantly, and then I think we will move on after this one.

DR. BRANTLY: So, I just wanted to make a comment about Dr. Fleming=s sample size, and to go towards something as far as how to get noise out of the system as far as clinical trials, and particularly complex ICU-based types of trials. The fact is that you get the best data usually out of clinical trial networks, groups of individuals that have a lot of experience. Those networks are actually quite small in general and basically they are fairly limited in the number of studies they can do on a regular basis.

So, expanding out, particularly going to places to add numbers where investigators are not experienced, basically adds substantial noise to the system. As I said on other committees for the FDA, I have noticed that that ends up being an Achilles's foot for many of these studies requiring large numbers of subjects, that the data is missing oftentimes and, as you say, for a non-inferiority study missing data is terrible.

DR. FLEMING: Just for clarification, these two studies have 1,000 people. The number we are talking about is 1,500 people and, in essence, some of this could be done in the context of certain patients within the studies only being assessed for mortality because you need a bigger sample size for the mortality but you don't need a bigger sample size for many of the other assessments.

So, in a recent related discussion that occurred in the metabolic advisory committee on July 1 and 2, a couple of weeks ago, where the decision was made that all anti-diabetic drugs need to be studied for clinical endpoints, including macrovascular complications, it was recognized that to do those large-scale trials can be done in a more efficient way, particularly when you are looking

at a clinical endpoint.

This would be ideal; it is mortality. So, you are not having to actually even do three halves of the development here in your processing. You would only have to have three halves the total numbers of patients, some of who may be assessed for less than the totality of the outcome.

DR. TOWNSEND: Thank you. We will move on then to question 2. Again, this is a yes/no question so I will read the question and you can answer:

Has the clinical efficacy of doripenem at dosages of 500 mg q8h 1-hour IV infusion and 500 mg q8h 4-hour IV infusion been adequately demonstrated to support approval in patients with nosocomial pneumonia, including ventilator-associated pneumonia?

[The committee votes electronically]

Everybody, one more time, please, with vigor. All right, we have 7 voting yes and 6 voting no. I guess we go around again. Dr. Bennett, if you wouldn't mind, we will start with you, if you can let us know how you voted and why.

DR. BENNETT: I voted no because I felt the quality of the data was not adequate to make that assessment. I

realize these are very difficult studies to do and they are very expensive because the amount of data you are collecting requires a lot of on-the-ground work.

But having said that, I think there are so many irregularities here it is hard for me to accept the conclusion that there is non-inferiority.

DR. TOWNSEND: Thank you. Dr. Dowell?

DR. DOWELL: I am checking to see what I voted because I was back and forth, but I voted yes. I voted yes and I think it was very close. I think a lot of this discussion has been around the non-inferiority margin.

There is a separate issue for me which is the blinding of the study, which I think is an area that the FDA can focus some time and energy on because a lot of my hesitation about the answer to this question has to do with the blinding and the subjectivity of the endpoint of clinical cure. I do feel like there is a potential there for figuring out ways to do blinding despite the constraints in a study like this and to have a much more robust and reliable clinical cure endpoint.

DR. TOWNSEND: Dr. Smith?

DR. M. SMITH: I voted yes but I am conflicted. I

was very disturbed by DORI-09 and the patients who I think probably didn't have pneumonia. In my mind I have sort of thrown them out but, at the same time, the points that Dr. Rex has brought upB-what I do is clinical work primarily and to be able to have another drug means an awful lot. Though I really think by the letter of the law the studies did not meet the criteria, I think DORI is probably as good. I mean, I don't think it is that much different than imipenem and I am just thinking practically that, as far as resistance is concerned, out in the real world when you don't have options and you are pulling out your last grey hair that you really do need to have something else to select from. So, I am conflicted.

DR. TOWNSEND: Thank you. Dr. Leggett?

DR. LEGGETT: This asks for my opinion about its clinical efficacy so I think that my first response to that is, one, is it plausible? Does it make sense to me? Is doripenem totally different from other carbapenems? Is it totally different from beta-lactams? And, the answer is it seems very plausible that it should be just as effective as anything else. The half-life is the same. It does not have huge protein binding, da, da, da. I can't come up with a

difference that should make doripenem different than all the other Ame too@ drugs that came before it.

Then, it is already approved for infections. They may not be similar. I would cut out the urinary tract infection because we have, you know, micrograms of gazzilian in the urine. But intra-abdominal infections, it was already approved for. So, I don't see exactly, other than it must be I think harder to treat adequately intra-abdominal infections than it would be to treat pneumonia in terms of the surface to volume and a bunch of other problems.

Then I ask, okay, we have some drugs that are already approved for nosocomial pneumonia, such as piperacillin/tazobactam. So, if we are looking at this study as not showing it for doripenem do we then say that Zosyn in the same study was not good enough because that is a comparator drug? If there are problems with the study, then we have to sort of say, well, in this study it was good enough to show that Zosyn works but doripenem didn't.

So, I have trouble when our comparator drug has already been approved, and that is both imipenem for serious pneumonia and Zosyn for nosocomial pneumonia. I have a lot

of difficulty understanding how I can say that doripenem clinically is not as efficacious, aside from all the statistics that we just got finished talking about.

DR. TOWNSEND: Thanks. Dr. Stoller?

DR. STOLLER: I voted yes with great reservation, and I often find myself wishing on committees like this that we be asked to vote on the dichotomous answer yes/no, and then with a Likert scale of our level of confidence in the vote. Were I asked to do that, I would say that my level of confidence in my yes decision would be very low.

I say that on the strength of what I regard to be methodologic shortcomings, leaving aside the non-inferiority issues in this study and they largely aggregate around many of the issues we discussed. They include my lack of confidence of the actual eligibility of patients who participated in this and the obvious shortcoming that occurs because there is lack of blinding in DORI-10 and even the blinded evaluation committee was aware of the investigator assignment outcome in DORI-09, which I think are methodologic shortcomings that are easily curtailed.

Candidly, I reject the argument that because these patients are complex that they don't lend themselves to a

blinded evaluation committee. Many more complex clinical issues than nosocomial pneumonia have been grappled with in that way, as I think everyone here understands.

I think Dr. Fleming's point about noise in non-inferiority trials driving to a conclusion of non-inferiority are very powerful in the context of these methodologic shortcomings about blinding, about recruitment of non-established index condition.

So, I voted yes with great reservation and perhaps more important than my yes/no vote are the issues, which I give qualification to my yes, around methodologic rigor for studies going forward, which I think gets to Dr. Rex' point about a clear methodologic path. I think it absolutely should require the same level of methodologic rigor in the assignment of therapy and the judgment of outcome as we would insist in any other context, which I think is lacking here.

DR. TOWNSEND: Thank you. Dr. Brantly?

DR. BRANTLY: I voted yes and I share the same concerns that Dr. Stoller does.

DR. TOWNSEND: Thank you. Dr. Hilton?

DR. HILTON: I voted no. When the target non-

inferiority margin was defined as 20 percent and the actual margin achieved was 9.1 percent, on face value the results look very impressive but it is the credibility of that achieved margin that I am really concerned about.

I am concerned about the 50 percent roughly in each trial of randomized patients not making it into the analysis data set. That just scares me. That is a huge fraction.

Also, I am very concerned in the DORI-09 trial about how comparable the treatment was across patients. There were lots of opportunities for optional adjuvant therapies. There was rollover from IV to by mouth, etc. So, the credibility of the results makes me question it. Thank you.

DR. TOWNSEND: Thank you. Dr. Edwards?

DR. EDWARDS: Well, this was a difficult question to answer and one has to take the totality of the evidence and the totality of the situation and the reality and be guided by the statistical analysis. We all like to have a perfect statistical study but we are not going to get a perfect statistical study. It is not an attainable goal at the present time when we are dealing with patients who are

critically ill and have multiple therapeutic factors being applied to them and are receiving multiple drugs which may have an effect on the endpoint.

I think the factors that made me sway to the side of yes included that the primary endpoint, and I realize all the controversy regarding the validity of that, was superior to the comparator drugs in the two studies. Also, although we have reflected on the quality of the minus 9 percent, I still have to buy that figure within the overall design of the study.

So, taking all things into consideration and understanding, from a clinical perspective, not just the concern about these pathogens that this drug interacts with but also about the availability of agents we have at the present time, I voted yes on this question.

DR. TOWNSEND: Thank you. Dr. Fleming?

DR. FLEMING: I agree with Dr. Stoller and his comments about what might be the most effective way for a committee such as this to interact with FDA. We are, by our name, an advisory committee. I am always perplexed, and have been for 20 years serving on these committees, perplexed as to why we are voting. It seems to me it is

much more important for us to convey our reasoning because it is the FDA=s decision.

And, the reasoning is complicated and it is often completely inadequately captured by a yes/no vote. I agree with Dr. Edwards. We are not going to get perfection. However, this study would not be the poster child for coming close.

It is an issue, in non-inferiority where are you in terms of the level of rigor that you have, and when we have issues about whether we have adequately defined the patient population, when we have issues about large fractions of people having low CPIS, when we have issues about large number of people being excluded, not just because they didn't have the bug based on information on randomization, but based on inadequate study drug post randomization, concomitant treatment violations, test of cure assessments outside the window happening in 14, 27 and 23 percent of patients respectively, to be able to understand that we are still seeing a clear, sensitive signal to a different that exists, I have a great difficulty in justifying that.

Furthermore, we have large fractions of people who

were taking adjunctive therapy that presumably could be making a difference and could be, in fact, camouflaging our ability or reducing our sensitivity. Then, these are open trials. And, if you have a proper endpoint, a mortality endpoint or something that is very objective you are more resilient to that scenario.

But what we are looking at is clinical response which is a composite of many elements, many of which are not, in fact, clinical endpoints. They are surrogate endpoints. Then we are using clinical judgment. And, we have a clinical judgment endpoint in the context of an open trial. All of these are factors that substantially impact the true reliability of the data.

The most reliable evidence is mortality. That is a very clear endpoint. It is most resilient to the lack of blinding, lack of having a blinded trial. And, what we see are some trends if not, in fact, signals that to me are concerning. A statistically significant increase in the 09 trial in all-cause mortality during the IV treatment period, 9 to 1 on pneumonia deaths.

I don't know if these are endpoints I should be using to answer the next question on safety. Maybe these

are safety concerns. On the other hand, maybe they are lack of efficacy concerns. In the end increased mortality is both. It is a suggestion of lesser efficacy. It is a suggestion of potential issues with safety.

So, my most interpretable evidence here leaves me at least with questions. If it doesn't prove that we have excess mortality, it is clearly a signal and signals such as this in other disease settings have led to the need for large-scale trials to be able to rule out that you would have such excesses. To me, this is the most reliable interpretable evidence we have and it is not pointing in the right direction.

So, I have serious concerns about the precedent that this type of data would be judged as sufficient basis to meet the congressional mandate that we have substantial evidence of efficacy. That is not an FDA choice. That is a congressional mandate.

DR. TOWNSEND: Thank you. I think if this study were done as perfectly as we would like it to have been done, with the numbers we would like, and without the worry about some of the problems with data collection, and with blinding, and with patients who were in the study, etc., I

think it would probably demonstrate that doripenem is effective, indeed, in patients with nosocomial pneumonia.

Unfortunately, I don't think this study demonstrates that. I think there are enough problems with the data for me to be suspicious about its effect, or at least about whether or not its effect was actually demonstrated in the study for a number of the reasons that have already been elucidated here.

I would agree, I am a little bit concerned that the data that were presented here are considered acceptable as demonstrating that the drug demonstrated that it was effective in treating nosocomial pneumonia. I think there are enough problems with the study that I would be reluctant to accept these data. Dr. Rehm?

DR. REHM: Thank you. I voted no, again a highly qualified no but I would have to say that the final deciding factor for me was the inclusion of the last phrase, including ventilator-associated pneumonia.

I guess this is where I can perhaps make my editorial comment. Since ventilator-associated pneumonia is a subset of nosocomial pneumonia, and since the numbers of patients studied with ventilator-associated pneumonia was

relatively small, and since we have concerns about methodology, outcomes, and so on, I find the addition of that qualifier unfounded. I might have voted yes had this simply said effective for nosocomial pneumonia.

DR. TOWNSEND: Thank you. Dr. Calhoun?

DR. CALHOUN: I voted no as well. I think the decision was pretty close. Actually, I was about to make the same comment as Dr. Rehm. Perhaps the straw that broke the camel=s back for me was the inclusion of ventilator-associated pneumonia because I am not compelled by those data at all.

Concerns about the really unnecessarily loose experimental design and conduct, I think are really problematic. The study did not need to be done so loosely. The unblinded assessment team in 10; the fact that many of these people may not have had pneumonia because they didn't meet appropriate criteria; the fact that there were so many variations and options for concomitant therapy, switching to oral therapy in DORI-09; and, again, ventilator-associated pneumonia inclusion in that particular question led me to vote no.

DR. TOWNSEND: Thank you. Dr. Ohl?

DR. OHL: I also found this a difficult vote, which eventually ended in a yes, with about as much confidence as I have in the stock market. I ended up bringing myself back to a clinician, standing in my ICU and saying, you know, talk about a messy and noisy disease. There probably are none greater than ventilator-associated pneumonia. Pick up a chart on any one patient and the cardiologist writes notes and it is clearly pneumonia, and the pulmonologist writes this is clearly heart failure, and the ID guy just says it is a drug reaction. And, no one agrees on anything in ventilator-associated pneumonia.

We can't even define it well enough so that we can get accurate rates of ventilator-associated pneumonia from the standpoint of, you know, a hospital epidemiologist, and anyone who thinks they have a very accurate rate in their hospital is probably a little disillusioned.

So, it is a messy disease. So, what we end up coming down to, echoing Dr. Leggett, is, is it plausible for doripenem to have efficacy? Yes, it is plausible. Is the study population reasonably close to what I see in my ICU? I would suspect that probably at least 25 percent, maybe as high as 50 percent of my patients in my ICU population

getting treated for ventilator-associated pneumonia don't have it.

So, when you put these studies together, I mean, did it reflect our practice? I think it did. I am not positive but I think it did. Having said that, that is why I ended up with my yes vote.

I do have some specific comments and concerns that I would like to bring up. I think the chest x-ray issues were probably answered by the late data that came in, although I would have been more satisfied to see more specifics on that.

I think that DORI-09 is done, you know, for early VAP. So, any VAP indication that is given should probably make sure that it is well pointed out or thought about. It doesn't include late VAP which is a very different disease microbiologically speaking.

Third, the DORI-10 baseline pathogens that are listed, and this is supposed to be in a setting of patients where two-thirds have late VAP, and the second most common organism cultured was Haemophilus influenzae which is really not a late VAP organism. That is an early VAP organism and, thus, tends to make me think that these patients may have

been somewhat different, maybe by geography. I am not sure whyB-I don't know why.

There is a lot of subjectivity at the level of the investigators= assessment of clinical cure. I was not satisfied that it just didn't end up coming down to the investigator at the end, saying, well, I think he is better. Again, I reflect my own ICU practice where five of us can stand around and we can't decide whether the patient is better or not. How do you put that on a form? It would be better to have some better objectivity.

Combination therapy-Bhey, it is what happens. There is no way in these studies to be able to factor it out. In my ICU it would almost now be substandard care to not add a second agent to cover for resistant pathogens. In some hospitals now that is becoming colistin, which is very disappointing.

I think it was interesting using the 4-hour infusion in the studies. I am a believer in pharmacodynamics so I think that this is probably the way we are going to be going for future applicants and FDA. I think that longer infusion times need to be looked at and studied, and this is one of the first studies to come out to

do that.

So, I think these patients were less sick than what we would like to see, with not as many having pneumonia as we would like to see. Again, it may be reflecting what really happens.

The pathogens and the microbiology were not well defined. It tends to be confusing to me for late onset pneumonia. So, an indication that includes late onset VAP with potentially resistant pathogens would be a stretch for me. Early onset VAP, I could potentially go for it.

DR. TOWNSEND: Thank you. So, to sum up, we have 7 yes votes and 6 no votes. On the yes side, many of the members thought that in light of the drug=s similarity to other drugs and its microbiologic data it was plausible to consider that it would be effective in this situationB-when you think that it would not be effective for treatment for nosocomial pneumonia, it achieved its clinical endpoints and that there is a practical need for a drug like this.

Those on the no side pointed out that there were irregularities in the methodology and the conduct of the study that made the data somewhat suspect; that there was excess mortality which certainly raised some eyebrows; and

also the complication of adjuvant therapy which made it hard to interpret the data.

We will move on to 3. Based on the overall safety profile, is doripenem safe for use in the proposed indication, nosocomial pneumonia, including ventilator-associated pneumonia, at dosages of 500 mg q8h for a 1-hour IV infusion and 500 mg q8h for a 4-hour infusion for the proposed 7-14 treatment duration?

Again, a yes/no vote and press enthusiastically.

[The committee votes electronically]

As we did before, we will go around the room. Dr. Stoller, if you don't mind, we will start with you. We have 7 yes votes and 4 no votes.

DR. STOLLER: Thank you. I voted no, reflecting my schizophrenia about my prior response. In voting no I took note of the higher earlier mortality during the 14-day interval. Again, I took note of the fact that stratified by location in DORI-09 the mortality rate in the United States and North America was, in fact, higher in those DORI recipients than in comparator.

I don't propose to fully understand that but, again, looking towards going forward with advice to sponsors

going forward, I think that the burden of proof about regional variation should be to assure comparable therapy in all venues so that the issues don't linger out of doubt. I think I am hard-pressed to explain why that difference exists but I would argue that I am hard-pressed to understand why it might not be real. And, I think the burden of proof in that context is on demonstrating that it is related to some artifact unrelated to the safety of the drug.

So, those two signals which are really, I think as Dr. Fleming pointed out before, the flip side of the efficacy argumentB-I think the two are tied at the hip in the context of an anti-infective in this regard that caused me to vote no.

I was not concerned about the usual safety considerations of drugs in terms of seizures or any of the other adverse events. I want to qualify that my vote, no, regards the flip side of the efficacy issue, not concerns about the safety of the drug in the usual context of does it cause a tremendous excess of adverse events or adverse events that rise to the level of concern which, of course, is usually the safety question when posed to an FDA

committee.

So, I am aware I am answering a little bit out of the usual context but, again, it provides an opportunity to qualify the schizophrenia that I feel around the efficacy piece.

DR. TOWNSEND: Dr. Brantly?

DR. BRANTLY: I voted yes. While the mortality data had some concerns for me, I think the fact that they happened primarily in North America suggests some kind of anomaly in the data than if it had been distributed fairly equally among the other studies sites.

DR. TOWNSEND: Thank you. Dr. Hilton?

DR. HILTON: I voted no primarily because of concerns about the mortality data. But I did hear that in DORI seems to be better with respect to cerebrovascular issues so I just want to go on record that I am in the ambivalent category for those reasons.

DR. TOWNSEND: Dr. Edwards?

DR. EDWARDS: I voted yes, and did have the same concerns that others have described regarding the mortality, but consider that more as part of the efficacy question.

DR. TOWNSEND: Thank you. Dr. Fleming?

DR. FLEMING: No agent is without safety risks. Everything comes down to benefit to risk. So, I interpreted this question to specifically be is there adequate evidence to establish safety in the context of benefit to risk. If I had been persuaded that there was substantial evidence of efficacy the bar that I would use for judging whether the safety profile was acceptable would be different. However, I have serious concerns about the reliability of efficacy. Therefore, suggestions that may exist or irregularities in trial design that may weaken my ability to detect safety signals leave me unable to conclude that there is adequate evidence for safety.

So, essentially because of the uncertainty about efficacy and because of the mortality data that I don't think proves mortality harm but is a signal, and it is a signal in the context with considerable uncertainty about efficacy, and in a trial where there are substantial irregularities that not just impact the ability to reliably discern efficacy signals, or efficacy, but also safety, I was unable to say that these studies reliably establish safety.

DR. TOWNSEND: Thank you. Well, I am going to flip-

flop. I had actually voted yes but I have been, on further review, persuaded to vote no. The arguments made by Dr. Stoller and Dr. Fleming have convinced me that, again, I am not convinced that it is unsafe; I am simply not convinced that it is safe enough to use. So, I am going to change my vote to no. Dr. Rehm?

DR. REHM: I took the question in the more traditional manner and voted yes, for reasons that have already been elucidated by others.

DR. TOWNSEND: Thank you. Dr. Calhoun?

DR. CALHOUN: So, I voted yes. I share a little bit of angst about the mortality signal. The 9 to 1 mortality signal gets my attention too. I guess that angst was mitigated a little bit by the failure to see that signal in DORI-10, even though they were different studies and different design issues, etc.

I was also assuaged a bit by the fact that it seemed to be regional, as Dr. Stoller pointed out. So, it may have to do with practice patterns or something else. I guess the caveat here is that going forward I think the onus is certainly on the sponsor to ensure that there is an appropriate postmarketing system that accurately and

completely records mortality and other serious adverse events.

DR. TOWNSEND: Thank you. Dr. Ohl?

DR. OHL: I voted yes for the same reasons. I assessed the question as the traditional aspects, and my thoughts on the mortality aspects have already been stated.

DR. TOWNSEND: Dr. Bennett?

DR. BENNETT: Safety is something that takes much larger numbers than efficacy. So, I think it will take a long time to get the reassurance that we have with the other carbapenems that this has the same safety. On the other hand, we have to go with what we see before us.

I think that mortality, gross mortality, is often seriously a function of the comorbidities. Relying on randomization to make those equal, they often turn out not to be equal. So, although it may be a signal, it is not enough of a signal to concern me and that is why I voted yes.

DR. TOWNSEND: Thank you. Dr. Dowell?

DR. DOWELL: Yes, with the same caveats that this is based on 1,000 patients and not 10,000 patients.

DR. TOWNSEND: Dr. Smith:

DR. M. SMITH: I voted no because I think Dr. Stoller and I are having the same illusion or delusion, I am not sure which. But I was very concerned about the DORI-09 and excess mortality because my thinking is that that is a group who probably doesn't have the disease and we shouldn't have seen those deaths. I sort of tried to raise the question before of what is that signal, what makes that group different, and I am concerned.

DR. TOWNSEND: Thank you. Dr. Leggett?

DR. LEGGETT: I voted yes based on overall safety and for a lot of the reasons that were spoken to before.

DR. TOWNSEND: Thank you. So, to sum up, the final tally is 8 yes, 5 no, everyone sharing the same concern about the excess mortality demonstrated in the DORI-09 study; those voting yes feeling like it may have been an anomaly; may have been a reflection of regional differences; and also that it may not be a reflection as much of safety as it is of lack of efficacy; and also that it may be just a matter of needing numbers to demonstrate safety. Those voting no, all sharing the concern about excess mortality.

Why don't we take a five-minute breakB-a ten-minute break? Ten-minute break and come back here at 3:50.

[Brief recess]

DR. TOWNSEND: I think we will go ahead and get started. We are in the home stretch here. We have two questions left which are not yes/no voting questions but just for discussion. So, we will jump right in.

Question 4, please discuss whether the in vitro and clinical susceptibility data suggest that doripenem is inappropriate for the treatment of nosocomial pneumonia or ventilator-associated pneumonia due to Pseudomonas aeruginosa or any other organism.

Anybody want to take a crack at it? Shall we go around? I guess we will go around. Dr. Calhoun, do you have any comments to make on that one?

DR. CALHOUN: Well, being a pulmonologist rather than a microbiologist, my thoughts are a little bit top level but I guess the MIC data that I saw, the comparative efficacy data with other carbapenems would lead me to say that this is appropriate for treatment. That is, it is not inappropriate for treatment.

DR. OHL: I think that the microbiology data is similar to that of other carbapenems from what is presented. I don't believe there is any more risk of resistance

occurring with it, with the serial passages and such.

A comment just to interject here because I don't know where else to put it is that the combination therapy issues are still totally not known. So.

DR. TOWNSEND: Dr. Bennett?

DR. BENNETT: Everything I have seen looks like all the other carbapenems.

DR. TOWNSEND: Dr. Edwards?

DR. EDWARDS: I am afraid I have the exact same comment.

DR. TOWNSEND: That is okay. Dr. Rehm?

DR. REHM: I think, you know, if we could rephrase the question maybe in the context of all of us paying more and more attention to MICs, we need to be cognizant of organisms that have a high MIC at baseline. Of course, nosocomial pneumonias and VAPs, if you get a second isolate it will almost always have a higher MIC. We have seen some rise in MIC over the three-year trend in the data we were shown, and these are baseline or generalized, I guess, but I just think we have to be cautious about watching it, and it is probably no different than many other beta-lactams that are currently marketed as far as that is concerned.

DR. TOWNSEND: Thank you. Dr. Leggett?

DR. LEGGETT: In order to not discontinue the past statements, I would actually have to say I go along with everything but I would also add that what is probably just as important is what is not discussed in this, and that is that the bugs with the metallo beta-lactamase are not even part of the study, and that is going to be a more major problem coming up than what we have been looking at.

DR. TOWNSEND: Thank you. Any other comments? We probably all well agree that it is at least as good as what we have in terms of the carbapenems and we all just need to be careful about the possibility to develop a resistance.

All right, we will move on to question 5, study design issues for future clinical trials for antibacterial drug development for the treatment of nosocomial pneumonia and ventilator-associated pneumonia.

(a), discuss the appropriate study populations for clinical efficacy trials in nosocomial pneumonia and ventilator-associated pneumonia, including the proportion of patients with VAP, and discuss whether clinical trials for this indication should be designed to enrich the study population for infections due to Pseudomonas aeruginosa.

Dr. Rehm?

DR. REHM: May I be a broken record and just ask for information about this VAP indication? My understanding is that there is no other antibiotic currently that has an indication for ventilator-associated pneumonia.

DR. TOWNSEND: Correct.

DR. REHM: Do we need to differentiate?

DR. COX: Yes, in essence, I mean, you know, it differentiates folks who are on a ventilator and, you know, who may have different pathogens, may have other comorbid conditions. To that extent, it would reflect the populations studied. So, it sort of is a subset within that overall group of nosocomial pneumonia. We really are looking for, you know, who are the types of patients that would be in these studies. So. But if you have particular thoughts specific about ventilator-associated pneumonia, please volunteer them to us.

DR. REHM: Well, first of all, it is probably the toughest clinical thing I think that we deal with in definition and in everything else that we have been talking about all day today. But the pathogens isolated from patients with known or suspected VAP at baseline are more

likely to be at least somewhat resistant than are those in a population of kind of general nosocomial pneumonia.

Getting back to question 4 and the need to pay attention to MICs at baseline and looking at those potentially multi-resistant organisms, especially in today's milieu, I think means that we have to be extraordinarily careful about giving that indication. It really I think potentially says a lot and I am not sure that we are prepared to say that. You know, on a clinical basis, I don't know whether clinicians really need to have that differentiation between nosocomial and VAP as far as FDA approval is concerned.

DR. TOWNSEND: Dr. Calhoun?

DR. CALHOUN: I agree with you that we may not need to have that differentiation, but if the differentiation is made, and there are actually some immunologic and physiologic reasons why it might be important to do so, that I will articulate in just a minute, then there should be I think guidance from the FDA on how to operationalize ventilator-associated pneumonia. We have had several comments that I will echo that it is almost a syndromic diagnosis as opposed to a specific diagnosis. And, having

some operational guidelines on how to build a trial that will include the appropriate individuals I think would be important.

So, the reasons that it might be somewhat different include the fact that there is ventilator-associated lung injury or volume associated lung injury so to the extent there is plasma leak and biological fluids coming into the airway make it a little different than the person sitting on a ward. These people are, by definition, sicker. So, to the extent they have organ dysfunction or perhaps multi-organ dysfunction, immune dysregulation, macrophages don't work, neutrophils don't work, etc., etc., they will be susceptible to different kinds of organisms and, in fact, their host defense mechanisms may not work as well. So, different sorts of regimens may be necessary. We all know these sorts of clinical characteristics.

So, it might be important to differentiate but, if it is, then I think that guidance from the agency would be very helpful in understanding how to build an appropriate trial.

DR. TOWNSEND: Dr. Brantly?

DR. BRANTLY: I would like to reiterate what I said

earlier about the clinical populations to be studied. I think particularly in nosocomial pneumonia and VAP studies need to be performed in trial networks and in areas where there is similar support as far as the quality or the concentration of medicine. When you have a vast difference in the baseline delivery of medicine, there are going to be increasing amounts of noise.

I take with note what Thomas mentions about mortality won't make that much difference, but if we are going to use clinical endpoints we really need to have some kind of a standard of care and you can't get that when you spread it across countries where standard of care is very, very different.

DR. TOWNSEND: Dr. Edwards?

DR. EDWARDS: If we were going to have a separate indication for VAP, and I guess we do at the present time, but if we were to explore that more deeply I think it would be really important to define it more carefully than it is now in terms of adjunctive care that is applied for patients on ventilators. For instance, there could be a considerable difference in success rates or endpoints depending on frequency of suctioning, oxygen delivery, use of PEEP. And,

I was able to think of about ten things just right off the top of my head that are likely to be at variance from institution to institution according to practices and could make a considerable difference.

So, just using the overall concept of VAP without trying to define some homogeneity in the adjunctive care I think really does make it difficult to interpret endpoint results.

DR. TOWNSEND: Thank you. Dr. Rex?

DR. REX: The question of HAP and VAP points out also the question of size. Dr. Brantly said something very important about size and heterogeneity studies. When you start trying to do very large trialsB-this is going to spin back around to the non-inferiority question and I apologize for the circular logic-Bbut we have talked about the potential to do it. Can you do a 3,000-person study? In theory, sure. I can in theory do a 3,000-person study and I can in theory do a 5,000-person study. But practically speaking, when I go out to try to find high quality sites, as I try to do 3,000-patient studies in less than a geologic time period I am forced to pick up sites where I am going to be less and less comfortable with the quality of the data.

Furthermore, nosocomial pneumonia is a complex disease. It is not like enrolling diabetic patients who are otherwise walking around, doing their normal deal. You know, they don't need a lot of other ancillary care. Here I am talking about very sophisticated--

DR. FLEMING: Were you listening on July 1st and 2nd? That was a huge issue on July 1st and 2nd advisory committee with the fact that ancillary care is multidimensional in diabetic settings. So, understanding effects is every bit as complicated there as here.

DR. REX: Let me pick a different example. I apologize, you are correct. There are questions of podiatry and many other things--

DR. FLEMING: What interventions are given there, and they affect your blood pressure; they affect your lipids, etc. So, there are all kinds of supportive care, and how does that affect the outcome beyond glucose lowering. So, it is just as complicated.

DR. REX: Well, I will need to rethink that. Your point is well taken. Perhaps what I am referring to is the intensity of the medical intervention that you have to drive for that individual in the intensive care unit. Much of my

experience is with doing studies like this in high intensity settings, and the effort required for each individual patient is extraordinarily high in terms of the data collection over a short period of time. It actually makes the studies hard to implement, which gets to Dr. Brantly=s point that not everybody can do the study. They may have the patients but they can't actually do the study at the quality level that you want and collect the data that you want.

So, that is another one of the issues about requiring very large sample sizes in these studies. What you in effect do is push us into more blurring of the data, whereas if we get comfortable with designs and sizes that permit numbers that are in the range of the size of the study you are seeing now, then we are reasonably likely to be able to get study sites where you can get higher quality of data.

It is just an observation to make about what happens when you push into very large sample sizes for ICU level care where there is an enormous disparity across ICUs. Dr. Brantly=s comment made me think about this. So, that is the end of my theme there.

DR. TOWNSEND: Thank you. Any other comments? Dr. Fleming?

DR. FLEMING: My sense in general here, just looking at the part of the question that refers to the proportion of patients with VAP, is that we would want good representation of both VAP and non-VAP patients in the NP setting. But my sense is that there could be considerable flexibility as to what percent actually have VAP.

As is probably apparent from the discussion to this point, I am very significantly influenced by the strong, strong evidence that antibiotics really make a difference in this setting most obviously through mortality. Mortality is such a critically important outcome for patients that if mortality in a non-inferiority assessment isn't the primary endpoint, it should be a key secondary endpoint. We should be designing these trials in ways to provide assurances that we can reasonably understand what the relative effects of existing therapies and experimental therapies are on an endpoint of such importance to patients where we know these interventions affect that endpoint.

So, my sense is that if we followed the analysis, and it is not just based on the FDA analysis, the extensive

analyses that were done in the related CAP setting, we would come up with similar answers that in 10-12 percent mortality setting a margin of around 5-6 percent is what the totality of the data would seem to justify, you are talking the need for 120 to 160 deaths that occur over the first 14 days.

By the way, you did achieve two-thirds of that in the collective studies here so we aren't talking about tripling the sample size of trials. We are talking about a 50 percent relative increase. And, the power of these studies is entirely driven by numbers of deaths, not specifically numbers of patients. So, if you are encouraging the enrollment of people who do carry a substantial risk of death you can actually somewhat reduce this added amount of sample size that you would need.

It was proposed I think by Dr. Temple in the CAP discussions that, in fact, if you establish an effect in a high risk setting, then that gives you your most sensitive measure to what the effect is on a key endpoint such as mortality, and one would be more willing to extrapolate that result to a lower risk setting.

So, in this spirit here, my sense is there could be a lot of flexibility but I would be encouraging people to