[Slide]

In looking at potential endpoints, there were three endpoints that were apparent based upon the literature search, which were, one, all-cause mortality, second was attributable mortality, and third was clinical response.

But based on our search, the primary endpoint that we felt was most appropriate for determination of a non-inferiority margin for this indication was all-cause mortality. That was really where there was preponderance of the data and in our review, as we will discuss. We in particular were looking for all-cause mortality data in the intent-to-treat populations since that would maintain the integrity of the randomization that was used in the initial studies.

In terms of attributable mortality, we did find data which was somewhat limited but we had concerns both about the potential for some subjective attribution in these studies, and also a number of the studies were case control studies but there was a lot of heterogeneity in the matching that was done across studies, from study to study, which became a little bit problematic.

In terms of clinical response, although we did

find data from the comparative clinical trials regarding our active control agents, there was no placebo data in terms of a clinical response endpoint.

[Slide]

So, in order to determine the treatment effect of the active control over placebo, we had then to drive separate estimates of a placebo effect and an active control effect. Again, keeping in mind that we had no placebo-controlled studies, we had to use indirect evidence to provide us with an estimate of a placebo effect, whereas our active control effect was derived from comparative clinical trials.

[Slide]

What I want to do here is go through a series of slides just to present to you the key articles that we used in making our estimates of both placebo effect and the active control effect, again, keeping in mind that we used studies where we were able to get information on all-cause mortality from the ITT population.

In terms of getting an estimate of the placebo effect, one source were studies of inappropriate, delayed and inadequate initial treatment, and the 4 studies are

listed on the slide, with years of publication between 1988 and 2007.

I just wanted to note that, again, 3 of these studies were prospective cohorts. One was case control. But 3 of them involved only single centers. Only one was a multi-center study. Three of them also involved mechanically ventilated patients who developed ventilator-associated pneumonia.

The time period for mortality reporting was not well described really in many of these studies. There were very few that actually provided a specific mortality reporting rate. In this group of studies, referenced in this table, only the study by Luna provided a mortality reporting rate which was 28 days.

You will also note that when you can compare the various studies and the mortality rates between those treated with appropriate versus inappropriate initial therapy there is a lot of variability both across the studies and in terms of the rate differences between those 2 groups.

[Slide]

Now, in order to provide some supportive data for

an estimate of the placebo rate from inadequate, inappropriate and delayed initial treatment, we did find 2 studies of hospitalized patients infected with Pseudomonas pneumoniae who had pneumonia in which mortality data was provided in those who were left untreated.

Again, although these studies were published in the early '70s, they actually are retrospective studies reporting data from between 1967 and '69. So, again, we are looking back 40 years ago when very few agents were available and, obviously, over those 40 years there have been a number of changes in diagnosis management and technology for patients. But this gave us, again, a different view and a different bit of supportive data.

As you will note, the study populations were small and both of these studies were conducted at single centers, and they did involve confirmed Pseudomonas aeruginosa infections. Amongst the patients who were left untreated, interestingly, the mortality rates were similar, in the range of approximately 60 percent. However, in the one study by Stevens the patients who were treated actually did worse, with an 80 percent mortality.

Unfortunately, there were not a lot of specific

details in that study as to why the mortality rate was so much higher amongst the treated patients, except some comments referring to the very limited armamentarium of agents available to treat Pseudomonas at that time.

Again, for these studies we looked at all-cause mortality in ITT, but the specific time reporting period for the mortality data was not provided in those studies.

[Slide]

This slide and the following slide just summarize the studies that we used in terms of trying to estimate an active control treatment effect. In terms of piperacillin/tazobactam there were 4 studies, published between 1998 and 2006. Of note, all the studies involved dual therapy of piperacillin/tazobactam with an aminoglycoside. Two of them were open-label. They were double-blind. All were multi-center studies. There was only one study where the mortality reporting period was provided, which was the first study and that was mortality during and 30 days post treatment.

[Slide]

In terms of estimating the active control effect for imipenem, we utilized two randomized studies, one

published in >94, the other in 2003. Of note, one of the studies used monotherapy of imipenem. That is the first study by Fink and associates. The second study allowed use of an aminoglycoside for Pseudomonas infections.

But we felt one advantage of these two studies was that by limiting the exposure of patients to aminoglycosides we might have a better estimate of the true beneficial effect from imipenem as opposed to our pip/tazo experience where the preponderance of patients were treated with aminoglycosides as well as with piperacillin/tazobactam so we could potentially overestimate the benefit in those studies. In both of these studies as well for imipenem the mortality rates were reported up to 28-32 days post treatment.

[Slide]

I want to finish with just a couple of comments in terms of limitations of using historical, published observational and comparative studies from the literature to generate estimates of both the placebo and the active control effect. As I mentioned, there were no placebo-controlled studies so we had to look at other sources of information which would indirectly give us an indication of

what the placebo effect would be.

Secondly, there is no clinical response data for placebo studies which could give us a potential indication or an estimate of the placebo effect for this indication.

The other point is that there is a lot of variability and heterogeneity because we are looking at data across different studies which have different designs. Some are blind and some are not. The population sizes are small, especially for the studies that we used to try to estimate the placebo effect.

We have to keep obviously in mind the issue of advances in diagnosis and management of nosocomial pneumonia and ventilator-associated pneumonia over the 40-year period of time that we looked back and, certainly, technological advances to help to keep patients alive.

Confounding due to factors such as age, comorbid conditions and severity of the illness was looked at in some of the studies but, certainly, needed to be considered in trying to sort out some of the estimates from this data.

Lastly, generalizability, and this gets back to the issue that although the studies that we used to estimate the active control effect were predominantly multi-center

trials which might have better generalizability, the studies that we were able to identify and use to generate a placebo effect tend to be from single centers which might have more limited generalizability.

[Slide]

So, I think at this point I am going to turn the podium over to Dr. Komo who will continue on with the discussion about non-inferiority trials in general, and provide further discussion on the determination of the non-inferiority margin for this indication.

DR. KOMO: Good morning. I am Scott Komo and I am going to present the agency approach to determination of a non-inferiority margin. But first I would like to talk briefly about non-inferiority trial design.

[Slide]

First, for the objectives in a non-inferiority trial, non-inferiority trials are designed to determine whether the effect of a new treatment is not too inferior to an already approved treatment, with the decision based on an acceptable clinical margin, and to determine whether the new treatment would be superior to placebo if placebo were included in the study and, finally, to determine whether the

effect of the active control relative to placebo is well-characterized, reliable, clinically meaningful and consistent from trial to trial.

[Slide]

And to determine whether the historical evidence of sensitivity to drug effect, HESDE, exists. Also, we need to determine the critical design features of the historical placebo-controlled trials from which HESDE has been determined, and then to determine a scientifically justifiable non-inferiority margin, and finally to assure the quality of the non-inferiority trial and its conduct because subjectivity or imprecision can be rewarded in a non-inferiority trial by artificially making treatments look similar when, in fact, they are not similar.

[Slide]

This slide contains the characteristics of adequate and well-controlled studies as laid out in our regulations. I would just like to focus on several of these which I think are most pertinent for our discussion today.

Section (b)(2), the study design permits a valid comparison with the control to provide a qualitative assessment of the drug effect.

Section (b)(2)(iv) discusses active treatment and concurrent controls. If the intent of the trial is to show similarity of the test and control drugs the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of the test drug and active control can mean either that both drugs were effective or that neither was effective.

Section (b)(3), the method of selection of subjects provides adequate assurance that they have the disease or condition being studied. This is important for non-inferiority studies because they can artificially make treatments look similar when, in fact, they are not similar.

[Slide]

This is a situation where the test drug and the active control are similarly ineffective and non-inferiority trials would not be recommended.

[Slide]

In contrast, magnitude of benefit of the active control over placebo is large and both the test drug and the active control are similarly effective and non-inferiority trials could be interpretable if the magnitude of the effect could be quantified.

[Slide]

Now I would like to go over our agency approach to justify the non-inferiority margin. We took a fixed margin approach. We first need to estimate the active comparator treatment effect, or M1. Then we need to select a non-inferiority margin that preserves a fraction of M1 such that potential loss in efficacy is clinically acceptable.

[Slide]

As Dr. Sorbello has mentioned, we were unable to locate any placebo-controlled studies so we need to use a placebo surrogate. There were no studies that contained both active control and a placebo surrogate so we were unable to directly estimate the treatment effect. We had to estimate the mortality rate separately from the different studies and then take the difference between the two groups to estimate the treatment effect.

We constructed confidence intervals around the point estimates separately for both the placebo surrogate as well as active comparator. The conservative estimate of the mortality treatment effect for the control will be calculated as the difference between the lower bound of the 95 percent confidence interval for the placebo surrogate

group and the upper 95 percent confidence interval bound for the active comparator group. There are concerns in estimating the mortality treatment effect based on cross-study comparisons because of issues of comparability of the subjects.

[Slide]

As you recall, there are no placebo-controlled studies so the placebo rate cannot be directly estimated. The placebo estimate will be based on the mortality rate of patients who received inadequate, inappropriate or delayed initial therapy. We also will substantiate the placebo mortality rate based on untreated hospitalized nosocomial pneumonia patients with Pseudomonas aeruginosa.

[Slide]

These are the results for the 4 studies of nosocomial pneumonia patients treated with inadequate, inappropriate or delayed initial therapy that we discussed earlier. It can be seen that there is a fair amount of heterogeneity in the mortality rates between the studies, also that the studies are small. The summary row contains the results for Dersimonian Laird random effects meta-analysis.

[Slide]

These are the results for the 2 studies of untreated hospitalized nosocomial pneumonia patients with Pseudomonas aeruginosa. It should be noted that these 2 studies are very small. Again, the summary row contains the results for the random effects meta-analysis.

[Slide]

To estimate the placebo mortality rate we used the meta-analysis of patients who received inappropriate, inadequate or delayed initial therapy where the placebo mortality estimate was 59 percent, with a 95 percent confidence interval of 40-76 percent. Thus, the estimated placebo mortality rate is likely lower than 40 percent based on the lower confidence bound of the 95 percent CI.

This estimate was supported by the meta-analysis of the untreated hospitalized nosocomial pneumonia patients with Pseudomonas aeruginosa where the mortality estimate was 60 percent, with a 95 percent CI of 44-73 percent. So, the lower bound of 44 percent is close to the estimated placebo mortality rate of 40 percent.

[Slide]

These are the results of the 4 piperacillin/

tazobactam clinical studies. Again, there is a fair amount of heterogeneity between the mortality rates between the studies. The summary row has the results for the random effects meta-analysis.

[Slide]

To estimate the piperacillin/tazobactam mortality rate we used a meta-analysis of piperacillin/tazobactam clinical studies where the mortality estimate was 18 percent, with a 95 percent CI of 11-28 percent. Thus, the estimated piperacillin/tazobactam mortality rate is likely no higher than 28 percent based on the upper 95 percent confidence bound.

[Slide]

These are the results for the 2 imipenem clinical studies. The summary row contains the results for the meta-analysis.

[Slide]

To estimate the imipenem mortality rate we used a meta-analysis of the imipenem clinical studies where the mortality estimate was 17 percent, with a 95 percent CI of 13-22 percent. Thus, the estimated imipenem mortality rate is likely no higher than 22 percent based on the upper 95

percent confidence bound.

[Slide]

To estimate the piperacillin/tazobactam treatment effect we took the difference between the placebo estimate and the piperacillin/tazobactam estimate, which gives us 40 minus 28 percent. Thus, the estimated piperacillin/ tazobactam treatment effect is 12 percent.

[Slide]

Similarly, to estimate the treatment effect for imipenem we took the difference between the placebo estimate and the imipenem estimate, which is 40 minus 22 percent. Thus, the estimated piperacillin/tazobactam treatment effect is 18 percent.

[Slide]

As a supportive analysis we looked at the 4 studies that compared the mortality risk difference between the patients who received appropriate initial therapy and those that received inappropriate, inadequate or delayed initial therapy. This could also provide an estimate of the mortality treatment effect for antibacterial agents. These were the same 4 studies that were used to estimate the placebo rate.

It can be seen that there is a fair amount of heterogeneity in the mortality risk difference between the 4 studies. The summary row again contains the results for the random effects meta-analysis. It should be noted that the conservative estimate of the mortality difference of 16 percent based on the lower confidence bound is in the range of the estimated treatment effects for both the piperacillin/tazobactam and imipenem.

[Slide]

So, we have seen that the mortality treatment effect for the antibacterial agents ranged from 12-18 percent. We chose 12 percent as a conservative estimate of the treatment effect to allow for the uncertainties in the cross-study comparisons.

[Slide]

As you recall, the mortality treatment effect we just found was 12 percent. To determine the non-inferiority margin we take the product of the treatment effect M1 and the fraction of M1 that we want to preserve. For example, an NI margin of 6 percent preserves 50 percent of the treatment effect. We need to preserve a significant fraction of M1 because the non-inferiority margin is the

amount of increased mortality one is willing to accept and still consider a new drug non-inferior to an active comparator. A question for the committee is what fraction of the mortality treatment effect should be preserved.

[Slide]

This is the limitations of the observational studies of nosocomial pneumonia that Dr. Sorbello has presented earlier. I will just highlight them. As you recall, there are no placebo-controlled studies and there is marked variability and heterogeneity across the studies. Also, additional limitations with this approach were that observational studies of inappropriate, inadequate or delayed initial therapy were used to estimate the placebo rates and the studies were small. These studies had substantial heterogeneity in their mortality rates, and also the mortality rates for placebo and active comparator were estimated from different studies so there are concerns of comparability of subjects.

[Slide]

Now I would like to discuss clinical responses as an alternative endpoint where, in addition to observed clinical failures, all deaths are also considered clinical

failures. The pros of this endpoint are that it is clinically relevant; that the effect of rescue medication given to the patients who do poorly will not affect outcome because they are already a clinical failure; and also there is a likely higher event rate than mortality which may permit a smaller sample size.

The cons for this endpoint are that there are no placebo data so we are unable to estimate the treatment effect of antibacterial agents. Also, this is a more subjective endpoint than mortality which is a possible issue in non-inferiority studies, as we discussed earlier. Finally, this is a composite endpoint so we need to ensure that the mortality and clinical failure are in the same direction.

[Slide]

The mortality rates are necessarily lower than the clinical failure rates because mortality is a sub-component of clinical failure. In order to estimate the treatment effect of clinical response we need to find some way to extrapolate the mortality treatment effect to a clinical failure treatment effect because there are no placebo data so we are unable to directly estimate clinical response

treatment effect.

[Slide]

As a way to make this extrapolation, consider what happens if some patients receive effective rescue medication that prevents death. It may be plausible to extrapolate the mortality treatment effect to clinical response by assuming that the treatment effect for clinical response is at least as large as that for mortality. Making the above assumption, it may be possible to choose a larger non-inferiority margin, which preserves a smaller fraction of the treatment effect.

[Slide]

If the assumption of the similarity in the magnitude of the clinical response and mortality treatment effect is reasonable, we can now proceed to the determination of the non-inferiority margin for clinical response. The non-inferiority margin should not be larger than 12 percent because the assumed clinical response treatment effect should not be larger than the mortality treatment effect it was extrapolated from.

Also, the non-inferiority margin should preserve a fraction of the treatment effect, as we discussed earlier.

It may be possible to choose a larger non-inferiority margin, which preserves a smaller fraction of treatment effect, based on the administration of effective rescue medication.

Question, is it possible to extrapolate treatment effect from mortality to clinical response? If so, what non-inferiority margin should be used in clinical studies?

[Slide]

In summary, we feel that valid NI trials can be done in nosocomial pneumonia and ventilator-associated pneumonia with an all-cause mortality endpoint using a non-inferior margin that preserves a substantial fraction of the 12 percent treatment effect. Or, with clinical response as the endpoint where all deaths are considered clinical failures, if the extrapolation of benefit in mortality to clinical response can be scientifically justified.

Thank you. I would now like to turn it over to Dr. Smith who will discuss the efficacy results.

Questions from the Committee

DR. TOWNSEND: Actually, if the committee members have any questions why don't we have a little bit of time for questions and then we will take a break before Dr.

Smith=s presentation. Dr. Rex?

DR. REX: I have one technical question. The mortality rate used in the Leone study, 2007, appears to be different from the mortality data used for the other studies. Specifically, my reading of the Leone paper is that the 10 percent and 20 percent that were picked up were the attributable mortalities, whereas there is actually an all-cause mortality of 20 and 47, and that is the same kind of mortality used in the other three studies. So, it would actually make the apparent heterogeneity of the data points on that graph go down because it would move Leone a little bit to the right, if my reading of that paper is correct. So, I would just make that observation about Leone, 2007.

DR. TOWNSEND: Dr. Bennett?

DR. BENNETT: We seem to be having two discussions at once. One discussion is for future studies what should be the appropriate delta for whatever endpoint. We are talking about mortality or clinical response. Then, the other discussion is whether the 20 percent delta chosen by this company was appropriate and should now be reviewed.

But it would seem that if it is the second discussion then we should ask the agency when they appraise

J&J that this may not be an appropriate endpoint because after the study is over it seems an odd discussion to have.

DR. TOWNSEND: Dr. Cox?

DR. COX: So, when we are reviewing the results of a trial it is important at that point in time, you know, when we are looking at the study to make an assessment of what the appropriate margin is in order to be able to understand what the study is telling us about the treatment effect, and you are correct and ideally those decisions are made at the time the protocol is being developed.

But, you know, when the study is being reviewed it is important that we, during that assessment, can make an appraisal, you know, of whether the trial and the non-inferiority margin that is there is applicable to the study, and that is important in our ability to assess whether the trial is informative.

DR. TOWNSEND: Dr. Leggett?

DR. LEGGETT: A question. In coming up with the inappropriate, delayed and inadequate initial therapy trials looking at the mortality, a comment was made by Dr. Fleming that those older trials might have been an overestimate of mortality and I was wondering if there was some idea about

some of the things that might have been included in those older trials that are actually the same as in this trial--in other words, the use of adjunctive therapy and the like--so, while inappropriate, might still have been within the bounds of what was in adjunctive therapy.

In other words, were these older trials really that different from this current trial? That was my question, if there is any data from the FDA about that.

DR. SORBELLO: I guess I could say in terms of looking at the criteria for the definition of nosocomial pneumonia and ventilator-associated pneumonia in those studies, they did use, for instance, bronchoalveolar lavage specimens, many BAL specimens, you know, microbiology confirmation on that, kind of on that basis.

So, I think certainly in terms of trying to identify patients with NP and VAP, besides looking at clinical findings such as fever, white count and chest x-ray changes, I think at least microbiologically they are comparable.

When you look at the supportive studies, which were the studies which were really retrospective, back in the '60s, one study really specified what the clinical

criteria were. Both studies commented that the patients had normal chest x-rays. In terms of microbiology, there was really no bronchoscopic data. I am not even sure what level of bronchoscopy was available in the late '60s. But these are basically based on blood pleural fluid, autopsy specimens, tracheal suctioning.

So, again, being 40 years into the past where we may not have had bronch data, there could be some question there. But I think certainly the 4 studies involving inadequate, inappropriate or delayed therapy, at least in terms of trying to feel somewhat comfortable that the patients actually had the disease in question, I think they likely do.

Certainly, one limitation in terms of appropriate and inappropriate therapy is that the studies don't really describe on a case by case basis what regimen each patient had. So, you really don't get a great feel from patient to patient what regimen they were on and, you know, why was it inappropriate.

In terms of the 2 studies dating back to the '60s, then you are looking basically at drugs like colistin and polymyxin B. So, you really don't have much of a regimen

out there for those patients, and they were obviously a lot more toxic regimens. Maybe that is a part of some of the results we saw in those studies.

But, again, you know, we were very limited. We had limited data to go with so we kind of made our best estimates, recognizing the limitations that both of us had gone through with the data.

DR. TOWNSEND: Dr. Dowell?

DR. DOWELL: I am really impressed. This is great detective work, going back all that time. I was amused actually by the presentation where you talked about not really defining the duration of time at which you defined mortality. I assume if you waited long enough it was still 100 percent in all of the comparison arms.

My question, and maybe it is a point for later discussion as well, is focusing on the difference between the bounds of the 95 percent confidence interval and the point estimate for treatment effect. For example, I am looking at slide 27 of your presentation on page 9. You have conservatively described the treatment effect as about 10 percent or so, the difference between the lower bounds of the one confidence interval and the upper bounds of the

other.

But that could be described as the minimum treatment effect instead of the treatment effect because you could also say my best guess about the treatment effect would be I will take a point estimate of the upper figure and the point estimate of the lower figure and I get a treatment effect of more like 40 percent.

I mean, I think it is an issue that is going to come up in the discussion later on as well. Taking the extremes of the bounds is the most conservative approach, and you are sort of driven by the variability in the study. The other approach would be to take your best guess of the difference and then you are much less conservative but you are going with what, in fact, your best guess is and you have much more margin to work with. Do you want to say anything about the decision to be very conservative?

DR. KOMO: No, you are right, that was the most conservative estimate we chose there. I mean, we have concerns because these estimates were estimated across the studies so there are issues and we have concerns about the comparability of the patients across the two studies.

As we discussed here, a lot of data came over 40

years so there are a lot of changes in the patients, how they were treated, and what kind of regimens they received. So, there is some concern about the constancy and the effect of the drug over that time too. So, we were trying to be conservative to account for these things.

DR. FLEMING: Well, I am very appreciative of the FDA's very careful efforts to go through and to try to provide, as they have attempted, an evidence-based justification for the non-inferiority margin. The issue here is around is this, in fact, worst case. There are many issues that have to be taken into consideration, some of which I think need even more careful discussion than was provided in the FDA reviews.

If we look on slide 17 and 18, ideally what we like to do is do a comparison and here we are looking at piperacillin, and we would like to look at historical trials that would directly allow us to assess what the effect of the active comparator is. If in this data set we found that piperacillin was substantially better in its overall mortality than an active comparator we could be using these data directly as a much stronger basis for understanding the margin.

Well, actually though it goes in the wrong direction. There is about a 20 percent relative higher mortality on piperacillin against this active comparator which, by the way, is at least suggestive of concern about biocreep. We do non-inferiority against non-inferiority against non-inferiority and when we get to the efficacy data looking at doripenem we find, in the IV stage, it is worse survival against piperacillin which is worse survival against active comparator.

All of this, therefore, relies very heavily on a strong sense that that active comparator was really very favorable in its effect on mortality and the agency has attempted to go after this issue but there are a number of points that need to be brought out.

One is that the analysis they are doing here is based on non-randomized trials of what the active comparator or appropriate therapy would deliver. So, we worry a lot about whether those historical trial results relate to the doripenem trials and that is the constancy assumption. Are conditions different? So, could age, or could APACHE score, or comorbid conditions be effect modifiers?

But we actually also have to worry about them

being predictors here because our historical studies are being done in the absence of randomization. And, what is being done here is the separation, on slides F-50 and F-38, between appropriate/inappropriate antibiotics and we subdivide those two groups to see what the difference in mortality is.

Well, then we attribute that difference to therapy. Well, it is also due to selection factors that are inherently different. Those patients that are getting inappropriate therapy may well be harboring resistant pathogens and these patients are different from those who aren't. So, attributing the difference to the benefit of appropriate therapy is likely quite biased.

We had extensive discussion, this committee, two and a half months ago, about these issues in the CAP setting, and the IDSA had done a very detailed analysis, and Fleming and Powers put forward a manuscript with an even more detailed analysis. In those analyses there were careful considerations given of the confounders and adjustments were made, for example, on age and bacteremia, and these were found to be very important predictive factors and effect modifiers.

Furthermore, those analyses were done comparing no specific therapy to antibiotic use. So, you are not getting the same magnitude of apparent bias that you would have in these analyses when you are separating people out according to whether they received adequate or appropriate antibiotics versus not.

Another key issue that is underlying all this that needs to be carefully considered, and we have alluded to it already in the discussion with the sponsor, is the constancy assumption. Are things changing from the historical setting where we are getting the estimates to the current setting? What we care about when we showed that earlier slide of 20 versus 40, etc., we don't care as much directly about what was the effect just historically. We care about what is the effect of the active comparator in the doripenem trials, and are conditions different.

Well, first of all, we are hearing that there are lots of patients, 30-odd percent, that have resistance to piperacillin. Well, those patients aren't likely to get as much benefit from piperacillin as if you were delivering this in a population where there wasn't resistance.

Furthermore, there is a whole lot of amikacin and

anti MRSA therapy, etc., that is being given that clearly could be altering the magnitude, the relative magnitude of the effect of piperacillin or the effect of imipenem.

All these analyses are trying to get at what is the additive effect of the active comparator in the context of today's state-of-the-art supportive care. They are almost assuredly overestimated. The constancy assumption is almost assuredly not true.

So, when we look at these differences and estimates and say, look, the sponsor and the FDA is being conservative, underestimating--nonsense. These estimates are almost assuredly overestimates because of violations of the constancy assumption.

Then we get to one other key issue, and that is the data that we have here gives us clues. Antibiotics affect mortality. They do. We are not debating it. We didn't debate that in CAP. The question is to what magnitude they affect mortality so that we can do analyses based on margins for mortality. But we would like to be able to do analyses based on margins for other endpoints.

By the way, mortality isn't a single endpoint either. It is mortality during the 30 days post completion

of therapy. It could be mortality at 28 days. It could be mortality at 14 days. It could be mortality during the IV treatment. We discussed this at great length in CAP, arguing that the longer you follow the more you are going to dilute out what is the true signal. In a superiority trial you would say, well, if I still show an effect, a fortiori I have an effect. But in non-inferiority you are biasing toward showing no difference when, in fact, you may be less adequate.

And, the sponsor didn't point it out but the FDA pointed out the statistically significant higher death rate during the early IV therapy on doripenem compared to piperacillin. This was the very thing we worried about in the CAP setting. So, when you are doing non-inferiority on mortality the sponsor points out, well, we make the margin if we use 28-day mortality. By the way, not by my calculations. But even if you said you did, I worry about whether the 14-day or the 7-day mortality differences are, in fact, truly different.

Now, the last issue is that there is an enormous assumption being made that once we spend all this effort to get a non-inferiority margin for mortality we can assume the

same functional relationship; i.e., if antibiotics have the mortality rate then antibiotics would have the failure rate on clinical response.

Clinical response is a surrogate endpoint. Certainly it is a surrogate endpoint for mortality. To even validate a surrogate end is an enormously complicated process to show that an effect on clinical response reliably produces an effect on mortality. To actually go the step of saying not only it does, I can tell you it has the exact same functional relationship; i.e., if I reduce the failure rate in clinical response by a factor of 2, I reduce death rate by a factor of 2. That is an enormously strong assumption. It is almost assuredly not true, and it is the heart of both the sponsor=s and the FDA=s analyses if you wish to extrapolate this to clinical response.

Just thinking off the top of my head, there are many counter examples to this. So, in CAP we were talking about comparison of serum treatment, one of the first effective therapies in this setting, against an antipyretic. Well, surely the antipyretics are going to win on defervescence but serum therapy wins on mortality.

There are examples of MIA bacteremia where

chlorithromycin dose in AIDS patients provides a 6-fold reduction in bacterial load but a 5-fold increase in mortality, again, opposite relationship.

Isoganin was looked at in a placebo-controlled trial for prevention of VAP and even though there were many favorable preclinical and other laboratory assessments that made it look like this broad-spectrum antibiotic would be great, the trial was stopped when there was worse mortality. And, doripenem itself seems to have a slight positive trend on clinical response, but it has statistically significant worse survival, overall trending worse survival even later in time.

So, the thought that we can do a meta-analysis here on mortality and then just decree or declare that you are going to have the same functional relationship between clinical response and mortality requires an enormous amount of evidence to justify it. In fact, when that evidence is in hand it almost assuredly will show that relationship doesn't exist. And, these examples I gave show that relationship doesn't exist.

So, it seems as though the FDA absolutely is on target for the conservative adjustment based on the fact

that there are many, many assumptions that are being made that are almost assuredly not true, and there are many biases that are apparent that haven't been carefully discussed in the way that these analyses have been don't to justify the margin for mortality. The bottom line, at least there is some evidence about mortality. There is no historical evidence available to justify a margin on clinical response.

DR. TOWNSEND: Any other questions from the committee? If not, we will take a short break and reconvene at eleven o=clock.

[Brief recess]

DR. TOWNSEND: Let's get restarted. We will have Dr. Smith's presentation now and then go right into Dr. Sorbello's second presentation on safety. We will probably end up getting to lunch a little early today. Dr. Smith?

Clinical Efficacy of Doripenem

DR. SMITH: Thank you.

[Slide]

I am going to be talking about some of the issues that arose in the FDA evaluation of the clinical efficacy of doripenem in nosocomial pneumonia.

[Slide]

Just to briefly recap for you, DORI-09 was an open-label study that had patients enrolled who had nosocomial pneumonia or early onset ventilator-associated pneumonia. Doripenem was administered as a 1-hour infusion and compared with piperacillin/tazobactam. There was an option to switch to oral levofloxacin after day 3 and the total duration of therapy in this study was 7-14 days.

DORI-10 was an open-label study enrolling patients with ventilator-associated pneumonia. Doripenem was administered as a 4-hour infusion and compared with imipenem which was given in either of 2 regimens. There was no oral switch allowed in this study, and the total duration of therapy, again, was 7-14 days.

[Slide]

The inclusion criteria for DORI-09 were hospitalized patients with hospitalization greater than 48 hours or prior admission with discharge within the preceding 7 days. Intubated patients had to have a clinical pulmonary infection score of greater than or equal to 5. Patients were required to have a new or progressive infiltrate on chest radiograph, fever or white blood count abnormalities,

and they had to have either respiratory failure requiring mechanical ventilation or at least 2 of the clinical findings that are listed here.

[Slide]

Lower respiratory tract cultures were to be obtained before enrollment. For non-intubated patients specimens were obtained either as sputum by deep expectoration or tracheal aspiration, and the sputum was considered to be adequate if it had fewer than 10 squamous epithelial cells and more than 25 polymorphonuclear leukocytes.

Intubated patients could have specimens obtained by endotracheal aspiration or bronchoscopy, and the acceptability of these specimens was according to local guidelines. Blood cultures were also obtained from all patients.

[Slide]

Again, this study compared doripenem with piperacillin/tazobactam. Randomization was stratified by geographic region, APACHE II score and ventilator status. On enrollment, patients were prescribed adjunctive therapy with amikacin in most cases for potential Pseudomonas

aeruginosa infection.

Investigators were encouraged to continue IV study drug for the entire duration of treatment, but there was an option for an oral switch to levofloxacin that was permitted after at least 72 hours of IV study drug therapy if criteria for clinical improvement were met. Again, the total duration of therapy for both IV and oral was 7-14 days.

[Slide]

The primary endpoint in this study was clinical cure rate at the test of cure visit 7-14 days following the completion of all therapy. Final clinical outcomes were determined by a blinded evaluation committee of 10 physicians. These outcomes were determined based on data summarized from the case report forms from which references to study drug therapy received were removed. However, the committee members were aware of the investigators= unblinded determinations of clinical outcome.

[Slide]

The clinically evaluable and clinical modified intent-to-treat populations were co-primary for the analysis of efficacy. The clinical MITT population was all randomized patients who received any amount of study drug

and met a minimal definition for pneumonia, which was the presence of an infiltrate on chest x-ray and either fever of white blood cell count abnormality.

The clinically evaluable population was all randomized patients who met protocol-specified definition of nosocomial pneumonia who received adequate study therapy, had a valid test of cure assessment without any confounding factors, and if baseline pathogens were isolated at least one had to be susceptible to the study drug received.

The applicant determined non-inferiority of the lower bound of the 95 percent confidence interval of the difference in clinical success rates between the two drugs was greater than minus 20 percent.

[Slide]

These are the demographic and baseline characteristics of the randomize patients. The piperacillin patients were a little bit older but otherwise the populations were similar.

[Slide]

The study was primarily carried out in Eastern Europe and South America. Twenty percent of the patients were enrolled from North American sites; 28 percent of the

patients had ventilator-associated pneumonia. The baseline APACHE II scores are shown here. The median score was 13.

[Slide]

These are the applicant's determinations of patient evaluability. The applicant did identify at one study site, in Eastern Europe, for one investigator a situation in which the number of doses of drug that were entered on the case report forms didn't correspond to the number of vials that were prescribed or that were provided to the site, and the applicant did eliminate those data from efficacy determinations. The FDA inspected this site, as well as two other sites in DORI-09 and DORI-10 and found that in those other sites the study appeared to be carried out adequately and that the data should be considered reliable.

[Slide]

Some of the issues that arose in evaluating the data submitted by the subject include the following: There were some questions about how pneumonia was diagnosed. It is important in studies like this when you are looking at non-inferiority trials and the possibility of enrolling patients who may not have the condition of interest. I will

speak a little bit more about the clinical pulmonary infection scores and about some of the chest x-ray issues that we found.

There is also a lack of gram stain data to support the adequacy of most of the lower respiratory tract cultures that were obtained. And, there are questions about how to determine the effect of doripenem in nosocomial pneumonia in a situation in which the majority of patients received extensive adjunctive therapy, and in this study there was also provision for an oral switch.

[Slide]

This is the clinical pulmonary infection score that was used in this trial. This is a modification of a 12-point scale. What I would like to point out here is that, you know, again, there are values assigned for tracheal secretions, chest x-ray infiltrates, temperature, leukocytes and oxygenation. And, the applicant considered a score of 5 or more on this scale to be consistent with pneumonia. It was one of the inclusion criteria for ventilated patients.

However, there are studies in the literature, and I can cite one by Singh and Yu in particular, that suggest

that scores of greater than 6 are actually suggestive of pneumonia. In the Singh study, using the same 5 criteria that are listed here, they stated that patients who had scores of less than or equal to 6 were actually those who were unlikely to have pneumonia.

The applicant has pointed out that some of the other scales, the 12-point scale, would include microbiologic data. But for the microbiologic data, in order to assign points for that variable, you would need to have either a quantitative culture or a gram stain, and they did not submit either of those to us, and simply having a positive culture, in the absence of some kind of semiquantitative determination or gram stain support would result in a score of 0. So, I think the scores that were submitted are actually scores that the patients had.

[Slide]

Ventilated patients in DORI-09, you can see here that half of the patients and 41 percent in the piperacillin/tazobactam group in the MITT population had clinical pulmonary infection scores of 6 or less. In the clinically evaluable group it is nearly half for the doripenem patients and 27 percent in the piperacillin/

tazobactam group.

[Slide]

Regarding the chest x-ray evaluation, there were some questions because of the investigators= interpretation of some of the films. The applicant, when we asked about this, stated that radiologists were generally not part of the study personnel and were likely to have evaluated the radiographic findings objectively, in isolation from detailed information on the clinical status of the patient. In cases where the radiology report and the investigator=s description in the case report form differed, the investigator=s interpretation was generally regarded as more definitive.

This is potentially an issue in a non-inferiority trial in which an investigator reading the film that would permit entry of the patient into the study, and patients who have equivocal x-ray findings enrolled in a non-inferiority study will bias the trial toward a finding of non-inferiority.

The applicant subsequently identified patients who did not have new or progressive infiltrates consistent with pneumonia. This was based only on a radiologist report and

included patients with missing reports. And, in this study in the MITT population there were 18 patients, 9 of whom had no formal report, and in the clinically evaluable population there were 6 patients, 3 with no formal report.

[Slide]

The results of gram stain examinations of screening lower respiratory tract specimens were not recorded on the case report forms and were not included in the data sets. I think this is an important question because, although Dr. Wunderink raised questions about the utility of a gram stain in evaluation of these patients, the ATS/IDSA guidelines, in discussing clinical strategies for the evaluation of nosocomial pneumonia, do state that gram staining of polymorphonuclear leukocytes and macrophages, and careful examination of the morphology of any bacteria found to be present may improve diagnostic accuracy when correlated with culture results.

The applicant subsequently went back and obtained gram stain reports from local laboratories for expectorated sputum specimens from 129 patients, and 100 of these specimens were adequate by semiquantitative criteria.

I just want to point out though that most of the

patients in this study without ventilator-associated pneumonia had expectorated sputum specimens used for culture determination, also that cultures were obtained from 129 patients with ventilator-associated pneumonia. Most commonly these were endotracheal aspirate specimens and we have no supporting gram stain data to support the adequacy of these specimens.

[Slide]

On enrollment to DORI-09, patients in both arms were to be treated with amikacin. The protocol stated that if Pseudomonas aeruginosa was not confirmed by culture amikacin should be discontinued at the discretion of the investigator. If Pseudomonas aeruginosa was confirmed patients in the piperacillin/tazobactam arm were to continue receiving amikacin for approximately 5 days. This is consistent with the label for piperacillin/tazobactam.

For patients on the doripenem arm amikacin could be discontinued at the discretion of the investigator if the patient had improved clinically and the Pseudomonas aeruginosa isolate was susceptible to meropenem, which was a surrogate for doripenem.

[Slide]

This slide demonstrates the adjunctive therapy that was used in the clinically evaluable patients in this study. The left-hand column shows the adjunctive therapy and whether patients received it and, if so, for how long. The next column is the number of patients who received adjunctive therapy, and then whether or not Pseudomonas aeruginosa was isolated at baseline.

What I would like to point out here is the bottom two lines which show that in the doripenem group 95 patients, or 71 percent, received adjunctive aminoglycoside therapy for 3-5 days or more. In fact, 32 percent of them received it for more than 5 days. If you look at the number of patients who had Pseudomonas aeruginosa isolated, it was just a minority of these patients and, in fact, of the patients who had Pseudomonas aeruginosa isolated at baseline, none of the isolates were resistant to meropenem or doripenem in the clinically evaluable group.

[Slide]

Looking at the same situation with the vancomycin for methicillin-resistant Staphylococcus aureus, if MRSA was isolated or suspected use of vancomycin was permitted at the discretion of the investigator. Vancomycin was to be

discontinued within 48 hours if the respiratory specimen and blood culture were negative for MRSA.

[Slide]

This slide is structured similarly to the one a couple of slides ago. Directing your attention to the patients who received more than 3-5 days of adjunctive vancomycin therapy, you can see that really it was just 10 percent of the patients in the clinically evaluable group in the doripenem patients who received 3-5 days or more adjunctive therapy. I would also just point out that methicillin-resistant Staph. was not commonly isolated in this clinically evaluable group.

[Slide]

In the DORI-10 clinically evaluable group 60 of 134 patients, 45 percent, received combined IV and oral therapy. The median duration of IV therapy was 7 days; of oral therapy it was 5 days. Seventy-four patients, or 55 percent, received IV therapy only and the median duration was 10 days.

[Slide]

If we consider the clinically evaluable cures who received doripenem and you look at the numbers of patients

that received adjunctive therapy at the beginning of the study with an aminoglycoside, and then also considering those patients for whom levofloxacin was prescribed as an oral switch, you can see that there were substantial numbers of patients who actually received limited amounts of doripenem as single-agent therapy. In fact, in the clinically evaluable group 17 percent of the patients throughout the entire trial received either an aminoglycoside or levofloxacin and 35 percent of the patients received 2 or fewer days of doripenem alone.

[Slide]

These are the clinical outcomes at the test of cure visit that were shown earlier by the applicant. Looking at various clinically evaluable subgroups, I just want to point out that the cure rates were very high in patients who were enrolled at the European sites, much higher than those who were enrolled in either South America or North America although the numbers, particularly for North America, are somewhat limited.

[Slide]

The applicant attributed this to the fact that in the European sites there were fewer patients with

ventilator-associated pneumonia and the European patients tended to have lower APACHE II scores.

[Slide]

These are the findings for the groups with ventilator-associated pneumonia. It is expected that the cure rates would be lower in patients with ventilator-associated pneumonia. Then, the cure rate is broken down by baseline APACHE II scores.

[Slide]

This shows the all-cause mortality in the intent-to-treat group broken out by various study intervals. This is during IV study therapy, the first 28 days of the study or during therapy and the succeeding 30 days. What you can see here is that there was a somewhat higher relative risk of mortality in doripenem patients during the IV therapy period, which evened out by day 28 or 30 days following therapy.

[Slide]

I would like to move now to DORI-10. The inclusion criteria were mechanical ventilation for more than 24 hours or patients who had been weaned within the preceding 72 hours. Also, the clinical pulmonary infection

score for this trial was greater than or equal to 5, new or progressive infiltrate on chest radiograph and fever or white blood count abnormalities.

[Slide]

The microbiology was similar in this trial in that lower respiratory tract cultures were to be obtained before enrollment. Again, for intubated patients these specimens could be endotracheal aspirates or bronchoscopy specimens, and the acceptability was according to local guidelines. There are very few non-intubated patients in this trial but the sputum criteria were the same as what they were for DORI-09. Again, blood cultures were obtained from the patients in this trial.

[Slide]

This study compared doripenem infused over 4 hours versus imipenem infused over either 30 or 60 minutes. Randomization was stratified by geographic region, duration of ventilation and APACHE II score. Adjunctive therapy in this trial again included amikacin. For doripenem patients amikacin was permitted at the discretion of the investigator for potential carbapenem-resistant Pseudomonas.

For imipenem patients amikacin was recommended if

Pseudomonas aeruginosa was suspected. Vancomycin was also permitted if methicillin-resistant Staph. was isolated or suspected. There was no option for an oral switch in this study and the total duration of therapy was 7-14 days.

[Slide]

The primary endpoint was the clinical cure rate at the test of cure visit 7-14 days following completion of all therapy. In this study there were no blinded evaluators or a blinded evaluation committee.

[Slide]

The co-primary populations were the same as for DORI-09, clinical MITT and the clinically evaluable. Once again, non-inferiority was determined if the lower bound of the 95 percent confidence interval of the difference in success rates was greater than minus 20 percent.

[Slide]

These are the demographic and baseline characteristics of the patients in DORI-10. The patients in this study were a little bit younger than the ones in DORI-09.

[Slide]

The distribution of patients geographically, about

half of the patients were from North American sites. The remaining patients were from Western Europe and most of the others were from Australia. Forty percent of the patients had early onset ventilator-associated pneumonia. Baseline APACHE II distribution is shown here. The median score was 16.

[Slide]

These are the applicant's determinations of evaluability for DORI-10. About half of the patients were clinically evaluable.

[Slide]

Looking at the clinical pulmonary infection scores from DORI-10, 35 percent of the MITT patients in the doripenem arm and 41 percent in the imipenem arm had clinical pulmonary infection sores of less than or equal to 6, which could be considered unlikely to represent pneumonia. In the clinically evaluable groups these percentages are 39 percent in the doripenem arm and 36 percent in the imipenem arm.

[Slide]

Again, radiologists generally were not part of the study personnel. The applicant subsequently identified

patients who did not have new or progressive infiltrates consistent with pneumonia based only on the radiologist=s report and excluding patients with missing reports. At this stage in our back and forth with them, they identified 68 patients in the MITT group and 38 in the clinically evaluable group that fell under this. Now, this does include some who had missing reports.

[Slide]

They stated that many sites in Europe, as you heard, did not have formal radiology reports of chest x-rays and that investigators= interpretations of films were entered on worksheets. There were also some patients for whom a Anote to file@ was provided and the information was entered directly onto the case report form rather than on a worksheet. These worksheet interpretations were considered equivalent to x-ray reports and part of the source documentation, and were the only documented interpretation at those sites.

At one stage, and this is what was in your briefing package, when the applicant identified all patients who had no formal radiology report, meaning that it was either not available, or one of these worksheets, or Anote

to file,@ there were over 100 patients in the MITT group.

[Slide]

Now, since the packages were prepared, the applicant has provided some information in which they went back to the sites and requested a review of the original films by an independent radiologist who provided either a summary form or a formal report. Of the 133 or so from earlier, they got 122 replies, nearly all of which were on a one-page summary sheet, and the radiologists identified infiltrates that could be pneumonia in 97 percent of these patients. When comparing those films with films that had been obtained 24 or more hours earlier, the radiologists stated that 2 of the screening films were improved; 15 showed no change; the remainder showed either worsening or new infiltrate or there was no previous film available.

[Slide]

So, combining those patients with the ones that the applicant previously identified who didn't meet strict radiologic criteria for pneumonia, if we look at the patients who did not have formal radiology reports, there are 60 patients in the MITT group and 35 patients in the clinically evaluable group.

[Slide]

Once again, the results of gram stain examinations of screening lower respiratory tract specimens were not recorded on case report forms and not included in the data sets. The applicant also obtained gram stain reports from local laboratories from expectorated sputum specimens from 6 patients. One of these specimens was adequate by semiquantitative criteria. But there were no supporting gram stain data for other specimens. In the MITT analysis set most of the patients had specimens that were obtained by endotracheal aspirate.

[Slide]

In DORI-10 the protocol stated that if Pseudomonas aeruginosa was suspected, and giving the examples of patients hospitalized for more than 7 days or who had received prior broad-spectrum antibacterial therapy, adjunctive amikacin was permitted.

In the doripenem arm it was recommended that it should only be added at the discretion of the investigator if carbapenem-resistant Pseudomonas was a concern, using the examples of patients who had received previous carbapenem therapy or an ICU carbapenem-resistant rate of greater than

15 percent.

For patients in the imipenem arm amikacin was recommended if Pseudomonas aeruginosa was suspected, regardless of susceptibility. If Pseudomonas aeruginosa was not confirmed by culture, generally within 48 hours, amikacin should be discontinued. If Pseudomonas aeruginosa was confirmed, for patients in the imipenem arm it was recommended that they continue amikacin for a total of 5-7 days. In the doripenem arm it was recommended that amikacin be discontinued if the isolate was not resistant to meropenem and the patient was stable or improving.

[Slide]

This is similar to the slide that I showed you earlier. I am pointing out the bottom 2 rows here where patients were given 3-5 days or more of adjunctive aminoglycoside therapy. You can see that in DORI-10 only 13 percent of the patients received 3-5 days or more of adjunctive amikacin therapy. There were relatively few patients who had Pseudomonas aeruginosa isolated. None of the isolates in the clinically evaluable group were resistant to doripenem based on tentative breakpoints.

[Slide]

If methicillin-resistant Staph. was isolated or suspected, the use of vancomycin was permitted at the discretion of the investigator. Vancomycin was recommended to be discontinued within 48 hours if the respiratory specimen and blood culture were negative for MRSA.

[Slide]

Somewhat higher numbers in DORI-10 received adjunctive therapy for methicillin-resistant Staph., but you can see here that most of the patients who received more than 5 days also had MRSA isolated.

[Slide]

These are the clinical outcomes at the test of cure that were presented by the applicant.

[Slide]

These are the clinical outcomes in some of the clinically evaluable subgroups by geographic region. You can see that North American patients treated with doripenem did a little bit better. This is not a statistically significant difference. The situation is somewhat reversed in Europe.

[Slide]

Looking at the days of ventilation at baseline,

patients with late onset pneumonia had higher cure rates than patients with early onset pneumonia, which is a little bit of a surprise. Then, these are the clinical success rates based on APACHE II scores.

[Slide]

This is the all-cause mortality in the intent-to-treat population, again, broken out by IV study therapy period, days 1-28 and during therapy and the following 30 days. You can see that the risk was similar across all 3 time periods.

[Slide]

In evaluating this trial there were significant issues that limit our ability to conclude that doripenem is non-inferior to its comparators. Both of these studies were open-label studies. There was lack of gram stain data for the assessment of adequacy of lower respiratory tract specimens; the use of low clinical pulmonary infection scores in an inclusion criterion for ventilated patients; the lack of independent confirmation by radiologists, particularly in DORI-10, of investigators= interpretations of screening films and, especially in DORI-09, the excessive use of adjunctive therapies, especially aminoglycosides.

I think that part of the reason that these are important, particularly with the clinical pulmonary infection scores and questions about some of the x-rays, is that, you know, in a non-inferiority trial we really need to be sure that patients have the condition of interest. And to the extent that there are patients with ambiguous findings that are included in these trials it will bias the trials toward a finding of non-inferiority.

We consider that having radiologic confirmation of an x-ray film gives us a little extra assurance that patients really have the condition of interest and, also, that having some kind of gram stain criteria, even though the science may be controversial in this area, gives us additional assurance that the specimens were, indeed, reflective of lower respiratory tract samples and could be considered valid for assessing the microbiology.

I think we would like the committee to consider these issues in our discussions later this morning. I think now we will move to Dr. Sorbello who will talk about the safety data.

Clinical Safety of Doripenem

DR. SORBELLO: I am Alfred Sorbello.

[Slide]

I am going to give a brief summary of the safety data from the FDA's review.

[Slide]

In terms of overview, I am going to touch on several issues. First, I am going to just briefly describe some of the safety information from the doripenem Phase 1, Phase 2 studies and the Phase 3 complicated urinary tract and complicated intra-abdominal infection clinical studies which were part of the original NDA, as well as some of the spontaneous postmarketing reports that were looked at as part of that NDA.

Secondly, I will provide some comments on the safety data in terms of the Phase 3 clinical trials for nosocomial pneumonia, including ventilator-associated pneumonia.

Third, I will discuss some of the limitations of the safety experience and some of the difficulties we had in making some assessments of this data. Lastly, I will have a few points in terms of the safety of doripenem in relation to other carbapenems.

[Slide]

So, first I would like to just provide some comments about some safety issues related to the original NDA which included Phase 1 and Phase 2 studies and the complicated intra-abdominal infection and complicated UTI experience.

In terms of the Phase 1 studies, there was a negative QT study performed, indicating that doripenem had no effect on either heart rate or other electrocardiographic measurements. Studies were conducted in patients with renal impairment and in the elderly. And, there was a safety and PK study conducted in healthy adults using aerosolized doripenem, doripenem by inhalation. But as some of the subjects developed an acute pulmonary inflammatory reaction, after about 7 or 9 days that study was terminated.

In terms of the Phase 2 and Phase 3 clinical experience, there was a single Phase 2 study of hospitalized patients with complicated urinary tract infections, and then 2 studies in complicated urinary tract infections, and then 2 clinical trials in complicated intra-abdominal infections.

In brief, I wanted to make a couple of comments. First, in terms of adverse drug reactions that could be plausibly associated with doripenem exposure, these included

findings such as nausea and diarrhea, rash, headache and phlebitis.

But we also did find some imbalances in some of the treatment-emergent adverse events for which we didn't have sufficient evidence to make conclusions about causality but we did find imbalances. One was in terms of renal events where there were 16 pooled patients from the doripenem experience compared to 1 comparator-treated patient who had either acute renal failure or renal impairment.

But assessment of those cases was problematic because many of the patients had abnormal baseline renal function, either mild or moderate renal impairment. Approximately 40 percent had received concomitant nephrotoxic drugs in terms of vancomycin or aminoglycosides. A number of the patients, particularly in the doripenem arm, had either prerenal azotemia or intravascular volume depletion, which could be due either to vomiting or diarrhea, or the use of diuretics in treating conditions such as congestive heart failure.

There were also indication-specific treatment-emergent adverse events in terms of asymptomatic bacteriuria

being only reported amongst patients in the complicated urinary tract infection studies, and anemia which was seen both in the clinical trials for complicated UTI and complicated intra-abdominal, but to a larger degree amongst patients with complicated intra-abdominal infections.

But, again, assessing this type of imbalance in terms of anemia was difficult and we didn't have sufficient evidence in terms of causality because many of the patients were anemic at baseline. Although there was the suggestion that perioperative blood loss may have accounted for some of the anemias, there was no prospective quantitative data collection regarding perioperative blood loss for any of the patients in the complicated UTI study.

There was also limited data collection in terms of a very small number of patients out of that experience who had direct Coombs testing performed. We did not find any definite cases of immune-mediated hemolytic anemia in that experience but we did find an imbalance.

Lastly, I just wanted to comment that in terms of convulsions and seizures none of the doripenem-treated patients experienced a seizure in any of the Phase 1, Phase 2 or Phase 3 studies for those indications compared to only

1 in the comparator arms.

[Slide]

In terms of spontaneous postmarketing experience, this was basically derived from spontaneous postmarketing reports originated from Japan where the drug had previously been approved. Some of the reports included Stevens Johnson syndrome, toxic epidermic necrolysis, seizure and interstitial pneumonia. But, again, the data was limited and it was insufficient for us to make any conclusions regarding causality.

[Slide]

I would like to move on just to make some comments about the safety experience related to the nosocomial pneumonia and ventilator-associated pneumonia clinical trials. I wanted to focus on four issues. One is pneumonia and pneumonia-related serious adverse events and deaths. Second is seizures. Third, imbalances that were noted in either treatment-emergent adverse events or the frequency of laboratory abnormalities. Lastly, some limitations of the safety database.

[Slide]

This slide summarizes the frequencies of

treatment-emergent adverse events, drug-related and serious treatment-emergent adverse events and deaths for the treatment arms in both of the clinical trials for nosocomial pneumonia and VAP.

As you will note, most of the patients in both studies experienced at least one treatment-emergent adverse event. The frequency of serious adverse events was in the range of about 25-30 percent. The incidence of death was about 12-13 percent in the DORI-10 study which was less than that in DORI-09 which was about 17-20 percent.

[Slide]

Focusing on pneumonia-related serious adverse events and deaths, this table summarizes those serious adverse events and deaths in which pneumonia was cited as the cause, and it compares the treatment arms in DORI-09 compared to DORI-10.

What you will note is that the frequency of pneumonia-related serious adverse events and deaths was markedly higher in the doripenem arm of DORI-09 compared to the comparator arm in that study, piperacillin/tazobactam, but also compared to the 2 arms in the study DORI-10.

When these cases were further investigated, they

revealed that all these patients who had pneumonia-related serious adverse events and deaths were clinical failures either at end of therapy, or test of cure, or relapses at late follow-up, indicating that these safety-related experiences and events that were reported actually were reflective upon an efficacy issue and lack of efficacy of the study drug and treatment in those patients.

[Slide]

In terms of patients who experienced seizures, whereas there were no seizures in the Phase 1, Phase 2 and Phase 3 studies that I described earlier related to complicated intra-abdominal and complicated urinary tract infections NDA, in the patients with nosocomial and ventilator-associated pneumonia there were 6 doripenem-treated patients compared to 6 pip/tazo and 10 imipenem-treated patients who experienced seizures.

However, when assessing the patients treated with doripenem who experienced seizures, many of them had a history of a predisposing central nervous system condition. This was primarily either a cerebral bleed of subarachnoid hemorrhage. Three of the 6 patients seized post end of therapy, after they had already completed their course of

doripenem, and 1 had a negative rechallenge where the drug was continued despite the seizure and the patient did not have any further seizure episodes.

In terms of imbalances and either treatment-emergent adverse events or laboratory abnormalities, just a few observations. There were no marked imbalances in terms of either hepatic or hematologic laboratory test abnormalities or renal events, and there were no marked imbalances in terms of patients who fulfilled Hy's rule for hepatotoxicity.

There was 1 imbalance identified in DORI-10 in which there were more patients who were doripenem-treated compared to imipenem-treated who experienced a serum CPK that rose to greater than 3 times normal from a normal baseline. But, again, in investigating those cases a bit further, half of the 12 doripenem-treated patients had a negative rechallenge and they remained on the drug and did not have further increases in CPK.

The remaining 6 had other concurrent predisposing issues, including extensive surgeries and traumatic brain injuries. So, there was really no supportive evidence that this observation of the CPK abnormality represented a true

safety signal.

[Slide]

I would like at this point to comment on some of the limitations in reviewing the safety database for this indication.

First, there was missing safety laboratory data from study DORI-09 and this primarily involved sites in Eastern Europe. When looking at the frequency of the missing data, and this would either be hemologic, chemistry or urinalysis data, most of the missing data was screening data. Primarily, about 43 percent of patients from the pooled sites were missing either 1 or more screening lab test results. But when you look at visits which are beyond the screening point, the next peak that you find is about test of cure where about 26 percent of the patients were missing at least 1 test of cure result.

Second would be the oral switch option. This was alluded to previously. Approximately 45 percent of patients in DORI-09 were able to be switched from intravenous to an oral regimen, and this did contribute to heterogeneity in the experience in DORI-09 and made it problematic in some instances to sort out attribution from IV to oral therapy.

In terms of safety between the 1-hour infusion and the 4-hour infusion regimens for doripenem, again, we already talked about the finding with pneumonia in DORI-09 which used the 1-hour infusion. But in terms of DORI-10 where you are looking at patients who received 500 mg over 4 hours, there was a suggestion of some cross-study differences such as oral candidiasis or elevated hepatic enzymes being somewhat more frequent in that group.

However, again, it was very difficult to otherwise make any conclusions specifically related to that 4-hour infusion because, although there were cross-study differences, the frequencies of those events within each study when you are comparing treatment arm to treatment arm were comparable. Overall, the frequency of adverse events was low and the sample size, particularly for the 4-hour infusion experience, was small, which was limited only to DORI-10 of 262 patients.

Just as important was that there are disparities in the demographics of the patients in each trial, considering that in DORI-10, which were the patients with ventilator-associated pneumonia, they tend to be younger, have a higher APACHE score and, obviously would be

mechanically ventilated, compared to those who were in DORI-09. So, there were some demographic differences in terms of whether you can really compare these 2 populations well.

[Slide]

Then, finally, some other difficulties in trying to sort out and interpret safety laboratory data were 3 sources. In general, we are dealing with very ill patients so there were a number of concurrent medical illnesses, abnormal baseline organ function, multiple concurrent medications and, obviously, age which I alluded to. There was some age differential between the 2 groups.

In general, there was a lack of routine testing for hepatitis, CPK isoenzymes and, in some instances, medical imaging studies of the liver or the kidneys in patients who had some abnormalities. As was seen in the original NDA experience, there was some limited data collection in terms of Coombs and attempts to try to sort out some findings related to anemia, although we did not see an imbalance in the nosocomial pneumonia and VAP experience that we did in the previous.

[Slide]

Lastly, I just wanted to make a couple of comments

regarding the safety of doripenem in relation to other carbapenems. First, there are some similarities in adverse reaction profiles in terms of gastrointestinal effects such as nausea or diarrhea; other findings such as rash, either phlebitis or injection site reactions, or transient hepatic enzyme elevations.

Second is the issue of seizure potential. Whereas imipenem seems to have the highest incidence of the carbapenem group, doripenem appears to have a very low propensity to induce seizures.

Finally, an issue that is still under study is the potential for a drug-drug interaction with valproic acid, which is an anticonvulsant. In terms of other carbapenems, there have been case reports of an interaction with meropenem or ertapenem in patients who are on valproic acid where the serum levels of valproic acid are reduced in patients who are on those drugs. However, this issue is still to be evaluated in a Phase 1 study which I think is ongoing, being conducted by the applicant. Thank you.

Questions from the Committee

DR. TOWNSEND: Thank you, Dr. Sorbello. We have time for questions for Dr. Smith and Dr. Sorbello.

DR. M. SMITH: I guess I will ask this first question. Could you tell from adverse events, people specifically in the DORI-09 group, if they were the individuals that had the CPIS scores that were higher than 6 or lower?

DR. SORBELLO: I did not specifically do an analysis stratified by CPIS scores. [Inaudible; sound system not working.]

DR. TOWNSEND: Dr. Rehm.

DR. REHM: I have a question. Is there any postmarketing data available on seizures related to doripenem that possibly relates to [inaudible.]

DR. SORBELLO: There are some additional spontaneous postmarketing safety reports from patients that seized who had a previous experience. These are all patients that have multiple underlying problems that could predispose them to seize. Again, I could not make any clear conclusions regarding a relationship to seizure related to doripenem. [Indaudible]

But a lot of these were patients that have central-nervous-system problems from early bleeds. But I think, even though the data that is available suggests that

the propensity [inaudible]. We need to monitor postmarketing as the use of the drug continues and we can get a better feel for what is happening with continued use in the U.S. [inaudible].

Now that the drug is marketed, we should have a broader postmarketing experience in the U.S. which may help us to sort the seizure data out.

DR. TOWNSEND: The mikes are out and we are not recording right now so this might actually be a good time to take a break. So you can save your questions.

I want to remind everybody not to discuss this at all while on lunch break. We should be back here by one o'clock.

[Whereupon, at 11:57 a.m., the proceedings were adjourned for lunch, to reconvene at 1:00 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. TOWNSEND: Let's take our seats, get settled and we will get the show on the road. We are going to finish up with questions. Dr. Rehm had a question. Any other questions for Dr. Smith and Sorbello? Then, if we have anybody who is interested in giving voice for open public hearing, that will be the time. Then we will move on from there. Dr. Rehm?

DR. REHM: Thank you, Dr. Townsend. My second question was with regard to the potential differential of reporting of pneumonia on the adverse events reporting. You mentioned that a number of the pneumonia events and AEs were on the DORI side. I wondered if you were able to determine, in looking at both of the studies, whether there was differential reporting of pneumonia as an AE in patients who failed.

DR. SORBELLO: Sorbello, for the FDA. I don't know that I can really comment on that. I don't really think that there was any way that I could really make any firm conclusion about reporting. It certainly crossed my mind because the frequency of serious adverse events and deaths which were considered related to pneumonia was higher in the

DORI-09 study, especially in the doripenem arm, but I don't know that I can specifically cite any follow-up data or analysis that could support that. You know, this is kind of the observation from what the data was. Again, with the caveat that even though these were being reported, or reported more frequently in DORI-10 than in DORI-09, there were patients whose clinical outcomes were poor.

DR. TOWNSEND: Dr. Ohl?

DR. OHL: I guess this would probably be directed to Dr. Smith. Two questions referring to the chest radiograph issues that you had reported on. You had mentioned that the applicant was asked to submit a review of the original films by an independent radiologist for DORI-10 and you received 122 replies, most of those in summary form. Were the summary form reports conclusive enough or detailed enough so that you could surmise what was actually going on in the film?

And, there had been some mention in the briefing book that many of these were exactly the same wording that was in the case report form, I believe. I may be mistaken. But if you could elaborate on that.

Then, part two of the question is if you take the

60 patients in the clinical intent-to-treat analysis and the 35 patients in the clinical evaluable analysis and factor these patients out of the final analysis, did it make an efficacy difference in the outcome data?

DR. SMITH: Yes, the applicant provided those reviewed forms to us. They did that on their own and submitted those fairly recently. Most of what they submitted was a single sheet where the radiologists would check off whether there was an infiltrate that could represent pneumonia. There was a line underneath there for any additional comments. Then there was a box underneath that that asked them to look at any previous films and to check off whether the infiltrate was, you know, improved or the same, or whether there were no previous films. So, you know, most of the forms had boxes checked.

Regarding your other question, we have looked at some of that in terms of the efficacy results and it doesn't seem really to make a substantial difference. I think that the 60 and 35 that I mentioned would fairly similarly overlap the ones that the applicant presented in their summary slide for DORI-09 and 10.

DR. TOWNSEND: Dr. Calhoun?

DR. CALHOUN: Thank you. I have two questions for Dr. Smith. The first turns on the clinical pulmonary infection score. If I understood your position, and you are representing the FDA's position on this I presume, the lack of gram stain and the lack of quantitative culture data then gives zero points to the CPIS if you were trying to make a conversion to the 12-point scale from the 10-point scale. Is that fair?

DR. SMITH: Well, I think I would say that there is no basis for assigning a score for that variable if you don't have that information. The information that we had to deal with was the variables for the 10-point scale and, in fact, there are no gram stain data or semiquantitative data that were submitted by the applicant even to look at that issue.

DR. CALHOUN: As I understood the applicant, and perhaps one of them can talk to this, they had qualitative culture data but not quantitative culture data.

DR. SMITH: That is correct.

DR. CALHOUN: The second point is a clarification on the chest x-ray interpretation in which, for DORI-09, you indicated that when the investigator=s description and the

independent radiologist's description were at variance the investigator=s was considered to be more definitive.

I was just looking for a little clarification on that because of two matters. Number one, the radiologist=s profession is to interpret chest radiographs. That is number one. Number two, the investigator wasn't blinded.

DR. SMITH: No, I agree. That was what the applicant told us, that when those were discrepant that they took the investigator=s as the more definitive.

DR. CALHOUN: And was there any return guidance from the agency to the applicant to review those data and perhaps clean them up?

DR. SMITH: No, we just would take that into account when we were doing our review.

DR. CALHOUN: Thanks.

DR. TOWNSEND: Dr. Edwards?

DR. EDWARDS: I wanted to ask Dr. Sorbello if the missing data, if there was any distribution in terms of one arm versus another, or whether missing data in general was across both arms of the studies, the 26 percent missing data.

DR. SORBELLO: It was across both arms. The number

of patients who were enrolled differed amongst the four countries from the eastern sites. For instance, for Russia there were 116 patients, 29 from Georgia, 20 from Ukraine and 6 patients enrolled from Belorusse. There was some variability in terms of the pattern of missing data for those sites. For instance, for Georgia the bulk of the missing data was the test of cure but that only involved 29 patients, whereas the screening data was primarily out of Belorusse and Ukraine which was 46 patients together and from Russia which was 116. So, there was some variability in terms of the site country of origin as far as what study visits were involved.

But overall the bulk of the data was screening data, part of the patients having been exposed to study drug although there was some data later on. The biggest would be at test of cure. Again, as far as those four countries, it was primarily the data out of Georgia where most of the missing data was at the test of cure.

DR. TOWNSEND: Dr. Stoller?

DR. STOLLER: A question for Dr. Smith and perhaps a little guidance from the agency, in the context of multinational studies such as this where many of the

patients are contributed from abroad, how do you look at the data when there are discordances between outcomes in North America and the United States, for example as in DORI-09 on slide 25, where actually the clinically evaluable subgroup from North America and the United States in particular did worse in contrast to the overall better outcomes in non-U.S., non-North American sites? How do you, as an agency, kind of interpret that, or what other information do you put around that as guidance to us in thinking about this?

DR. SMITH: Well, that is a concern that we had. We do try to identify whether there are any differences in the patients in Europe versus the ones that were studied at the other sites. As the applicant stated I think for DORI-09, you know, for one thing, there weren't as many patients in North America so it is a little hard to know what to make of those figures. There were fewer of them percentage-wise. I mean, I should say there were more in the North American sites that were ventilator-associated pneumonia at higher APACHE II scores. So, it is conceivable that that played some part in the difference. I have to say that we were a little surprised to see such high cure rates in the European sites.

DR. STOLLER: But absence of a clear methodologic difference, some process of care difference or some recruitment difference that is identifiable, is there a default preference for North American, U.S. data in the context of this study without some clear-minded line of reasoning as to how the populations differ?

DR. COX: Yes, for data from foreign countries one of the questions we are always faced with is, is this applicable to the U.S. population? You know, is it generalizable? Is it relevant? That is oftentimes a question, you know, that we search for answers. If there is a difference we always try and understand why.

As Dr. Smith has mentioned, some of the numbers there are smaller in the United States but certainly, you know, any thoughts or advice that the committee may have on the issues of, you know, where may these differences come from or things along those lines will help us as we look at that data. But, yes, we are looking at the data in the context of what it means. You know, I mean, are there differences in the foreign data and the U.S. population? You know, we are looking at the data to try and understand how the drug will work in the U.S. population.

DR. TOWNSEND: Any other questions? Dr. Dowell?

DR. DOWELL: I am confused on this critical question about the chest x-rays and I am trying to get a sense about how worried we should be about whether the study population was badly diluted by patients who may not have had pneumonia.

In the first presentation this morning it seemed to me like it was maybe a couple of percent in each study that may not have had pneumonia. In some pages in the FDA presentation there is 34 percent and 39 percent. I am still feeling like I am not clear about your estimation. What is your best guess of the range of patients who might not have had pneumonia in these two studies or, to clarify, who did not have chest x-rays that were consistent with pneumonia?

DR. SMITH: Part of that was a concern because in DORI-10 in particular there were all these films that were interpreted by the investigator and hadn't been read by a radiologist. That is why I included that information in there, which is not in your briefing package, about the subsequent review that the applicant had radiologists carry out at the sites. So, it does appear that in the majority of those patients, you know, the radiologists did check off

that there was an infiltrate that was consistent with pneumonia. So, that would bring the estimate of the numbers of patients who may not have had pneumonia based on strict, you know, radiologic criteria to 60 or so and 35 that I showed in one of the last slides.

DR. DOWELL: Sorry, I was following you until you said 60 and 35. Can you clarify again what does the 60 and 35 mean?

DR. SMITH: Sorry, that was in one of the last slides that I had shown. I don't have the slide number handy.

DR. FLEMING: You said it was the number of patients who didn't meet strict radiologic criteria for pneumonia.

DR. SMITH: Right.

DR. FLEMING: It was 60 in MITT and 35 in CE.

DR. SMITH: Right.

[Slide]

That is the correct slide.

DR. DOWELL: Thanks. That is helpful. I was saying, you know, is it 2 percent or 40 percent? It sounds like for DORI-10 it is about 12 or 14 percent who might not

have had pneumonia. And for DORI-09?

DR. SMITH: For DORI-09 it was a smaller percentage. In the equivalent slide for DORI-09 that I showed I think there were only 18 patients in the MITT and 6 or so in the clinically evaluable. So, it is less of an issue for DORI-09 than for DORI-10.

The other thing to keep in mind though with this issue about the radiographs is that it is not simply the radiographs but also clinical pulmonary infection scores too that might need to be considered.

DR. TOWNSEND: Dr. Ohl?

DR. OHL: Just to follow up on that, that was exactly what my question was. So, the CPIS score that you presented earlier in the presentation then was based on the data acquired before the additional radiology reports were found? Or, does that include this additional data? If it does not include it, do you have a rough estimate then how those scores might change the distribution?

DR. SMITH: Those were the data that were submitted with the original NDA so I am not sure we really have a way to go back and correct that.

DR. OHL: But one could surmise that if you added

the additional films that were provided in this slide and the one previously that those CPIS scores might then go up. Is that correct?

DR. SMITH: No, because they would already have had a score that was assigned by the investigator for the infiltrate, and those investigators made the diagnosis of pneumonia. So actually, if anything, if a patient didn't have pneumonia the scores might go down.

DR. TOWNSEND: Dr. Fleming?

DR. FLEMING: In the 09 trial there is a very clear signal for excess of pneumonia deaths, 9 against 1, which is about a z-value 2.5 or 2-sided p-value of 01. In addition to that, there is the excess mortality seen during IV treatment, which also crosses statistical significance at 21 against 9. I wonder how much overlap there is or, to be specific, in these pneumonia deaths, 9 against 1, where 9 of these deaths that were pneumonia, 7 of the 9 were only pneumonia as the cause of death, how many of that 9 versus 1 occurred during the IV treatment phase? Is there overlap between these 2 excesses?

DR. SORBELLO: Sorbello for FDA. I am not sure that I have that readily available. Any information that I

have here should be looking basically at study day of death compared toB-I know I have looked at that but I don't know if I have that data specifically with me, but I will look.

DR. TOWNSEND: Any other questions?

[No response]

Is there anyone in the public who would be interested in making a comment in the open public hearing?

[No response]

Thank you. Then we will move on to Dr. Coderre from FDA.

Microbial Resistance

DR. CODERRE: We have heard from Dr. Sorbello, Komo and Smith regarding the non-inferiority margins, the clinical efficacy and the clinical safety.

[Slide]

I am Dr. Coderre and I am going to talk about the microbiology aspect of this submission. Specifically I want to talk about decease in doripenem susceptibility that occurred in patients during therapy.

[Slide]

We are concerned that the decreased susceptibility in the doripenem MICs from patients in the nosocomial

pneumonia trials may lead to treatment failure. We are particularly concerned about the transmittal of these bacteria with increased resistance or decreased susceptibility, depending upon how you want to look at it. We see this as a safety concern, and we derive this from observations from our review of the data, particularly the large MIC increases that occurred during therapy, the Monte Carlo simulation data, resistance selection data performed in vitro, elevated MICs for doripenem among cystic fibrosis isolates, and also the surveillance data that span 2003 to 2005.

[Slide]

We are particularly focused on Pseudomonas aeruginosa here. Just as sort of a refresher, when Pseudomonas aeruginosa was granted for the previous indications, the complicated intra-abdominal infections, complicated urinary tract infections, the breakpoint MIC for susceptibility was an MIC of less than or equal to 2 mcg/mL for what was considered susceptible to doripenem. However, no breakpoints were made for intermediate or resistant isolates. So, we wanted to know what the consequences of this decreased doripenem susceptibility would lead to.

[Slide]

We first looked at the analysis of nosocomial pneumonia isolates with doripenem MIC increases that had at least a 2-step or greater increase. What you see here, on the left-hand side is the trial arm of the study and a couple of columns over you see the organisms. These are all organisms that had these large doripenem step increases. In the doripenem arm of DORI-09 you see 2 organisms, Staph. aureus and Pseudomonas aeruginosa. Both were clinical failures here. The doripenem MIC increases here range from 4-5 step increases. Keep in mind that these are the non-intubated nosocomial pneumonia patients that were treated with doripenem.

If you look at the piperacillin/tazobactam arm you see that, interestingly, none of the patients having these organisms resulted in clinical failure.

[Slide]

We next looked at the doripenem arm of the doripenem-09 study. Look at the MIC increases among these. It was very interesting. You see here, in the green, these are all patients that had isolates of Pseudomonas aeruginosa. If you look on the right-hand side you see the

doripenem step increases ranging anywhere from 2 to 5 step increases. These now are intubated patients in DORI-10. What is also interesting is that the meropenem step increases tend to mirror the doripenem step increases.

[Slide]

We next looked at the doripenem 10 study. We looked here at the imipenem arm and we see once again several Pseudomonas aeruginosa isolates from patients. We see 3 clinical failures here. Doripenem step increases, again, are 4-5 steps, meropenem step increases mirroring doripenem step increases again.

[Slide]

We next decided to look at clinical failures and tried to get a sense of what are some of the characteristics of patients who were clinical failures in this study, here. Over on the left you see several colored boxes. These are patients that had more than 1 organism infecting them so these are patients with polymicrobial infections.

You will also see here, in the green, Pseudomonas aeruginosa isolates from patients in the doripenem 09 study, the doripenem treatment arm. You also see Staph. aureus isolates indicated in the gold.

Also, you will see on the right some of the initial doripenem MICs, indicated in orange next to these. Over on the right you will see the doripenem step increases and meropenem step increase.

[Slide]

In the doripenem-09 arm when we looked at the comparator, piperacillin/tazobactam--these are clinical failures--we see that again we have several polymicrobial infections among the patients. We have several Pseudomonas aeruginosa isolates. Again, over on the right-hand side are highlighted the doripenem step increases and meropenem step increases.

[Slide]

This is a continuation of the piperacillin/tazobactam arm of the doripenem 09 study, an analysis of the clinical failures. Again, you see several polymicrobial infections indicated among patients over on the left-hand side. Staphylococcus aureus isolates among some of these patients are indicated in the gold.

[Slide]

In the doripenem 10 study we looked at the doripenem treatment arm. You will see several polymicrobial

infections, indicated over on the left; several Pseudomonas infections, indicated in the green, with some of the corresponding doripenem MICs.

[Slide]

This is a continuation of the doripenem arm of the DORI-10 study. Again, you see a number of Staphylococcus aureus isolates. Staphylococcus aureus isolates with an asterisk are indicative of a methicillin-resistant Staphylococcus aureus. Again, over on the left-hand side we see a number of patients that had polymicrobial infections and you can see some of the step increases in the doripenem and the meropenem over on the right, in the orange.

[Slide]

Next we analyzed the MICs among clinical failures in the doripenem 10 arm among the comparator arm of this study, the imipenem arm. Polymicrobial infections are indicated on the left by the different colors, with patient IDs.

[Slide]

This is a continuation of the imipenem arm. Again, you see a number of patients that had polymicrobial infections. Here we start to see a number of Pseudomonas

aeruginosa isolates among some of these patients. You see some large step increases on the right-hand side in doripenem and meropenem.

[Slide]

This is a continuation, again, of the imipenem arm. You see more Pseudomonas aeruginosa isolates and several Staphylococcus aureus isolates. Again, the methicillin-resistant Staphylococcus aureus is indicated by asterisks. Over on the left-hand side you see the multi-colors and the patient Ids, again indicative of patients with polymicrobial infections. Over on the right-hand side step increases, large step increases are indicated in the orange.

[Slide]

So, looking at these clinical failures among the patients receiving either doripenem or a comparator, what we see is that most of these patients had one of several characteristics or more than one characteristic. These include patients infected with polymicrobial infections; baseline doripenem MICs of 1 mcg/mL or greater; infection with methicillin-resistant Staphylococcus aureus; infection with Pseudomonas aeruginosa; or at least a 2-step or greater

increase in drop MIC during therapy.

[Slide]

We next looked at some of the in vivo data from the pharmacodynamics. We looked specifically at Monte Carlo simulations. What we examined was the species-specific target attainment values that were calculated to determine the probability of attaining a particular target at a selected dose of doripenem against a particular pathogen.

The applicant has indicated that the time above MIC is the best pharmacokinetic parameter or predictor of in vivo efficacy. The next table is a summary table and will show you the species of bacteria of interest at both the 1-hour and 4-hour infusions for nosocomial pneumonia pathogens.

[Slide]

This table shows the probability of target attainment and it is broken out by individual organisms or groups of organisms. Over on the left-hand side most of these organisms are organisms that were in the indication desired by the applicant. Across the top you will see the 25 percent time above MIC, 30 percent time above MIC and 35 percent time above MIC values in both the 1-hour and the 4-

hour infusions.

If I could draw your attention to the orange writing and orange numbers and red boxes, what you see here is when you look at target attainment values for Pseudomonas aeruginosa and for Acinetobacter species you see that at the most conservative value of 35 percent time above MIC both organisms fall below the 90 percent level, which is the level indicative of in vivo efficacy.

However, when you look at the 4-hour infusion, now Pseudomonas aeruginosa goes above the 90 percent target attainment value and Acinetobacter species continues to stay below the 90 percent value.

[Slide]

We next looked at some resistance development studies. Studies were conducted where Pseudomonas was serially passaged with doripenem with or without gentamicin. When you look at the doripenem MICs among organisms that were passaged-Bthis is Pseudomonas nowB-in doripenem alone 3 isolates had 8-fold increase or greater; 1 isolate had a 2-fold increase; 2 isolates remained unchanged.

However, when you passage the organisms through doripenem and gentamicin you see that MIC increases a little

bit here where you only have 1 isolate having a 4-fold increase, 2 isolates having a 2-fold increase, and 3 isolates had no change. So, obviously, there were fewer doripenem MIC increases occurring when it is combined with gentamicin during passage.

[Slide]

This is the data from a Pseudomonas aeruginosa multiple passage study. What you have here is the organisms passaged through 3 different carbapenems, a doripenem passage, a meropenem passage and an imipenem passage. MICs for the 3 different antibiotics are indicated across the top row, second to the top row, there. If you look at the orange numbers you see doripenem MIC values when the organism was passaged through doripenem. You see that the MIC increases from 0.06 at the first passage to 4 mcg/mL in the eighth passage. Also, what is indicated here too is that the drop in MIC increases were fairly similar to both meropenem and imipenem.

[Slide]

Next we looked at the doripenem MIC90s for a number of multi-drug resistant isolates. More specifically, we looked at Acinetobacter baumannii and Pseudomonas

aeruginosa. The different drug resistance is indicated over on the left-hand column, and across the top you see the number of isolates and the MIC90.

If I could draw your attention to the orange numbers and text, you see that, for instance, in Acinetobacter baumannii, ceftazidime non-susceptible isolates had a rather high MIC90 of greater than 16 mcg/mL. Amongst Pseudomonas aeruginosa when you look at cystic fibrosis isolates, both mucoid and non-mucoid, again you have rather higher MIC90s of 32 and 64 mcg. As expected, carbapenem-resistant isolates had MIC90s anywhere from 8 to greater than 32 mcg/mL, depending upon the study. And, also isolates of Pseudomonas aeruginosa containing metallo beta-lactamases have rather high MIC90s. In one study it was greater than 32 mcg/mL. In another it was 64 mcg/mL. Now, keep in mind that in some cases here these were not true MIC90s, obviously, because there are not 100 isolates in the study.

[Slide]

We next looked at some of the surveillance data supplied by the applicant. Particularly, there were 17,000 organisms provided over a period of 3 years, from 2003 to

2005. These were taken from North America, Latin America and Europe. There were 20 sites per region. What I will show you now is a table of the MICs from North America. They are shown for the organisms that are pertinent to the nosocomial pneumonia indication.

[Slide]

Here is the surveillance data for 2003, 2004 and 2005. What is indicated here are the MIC90s and the MIC range for each year for each of these organisms. The organisms on the left here, some of these organisms are sought for the nosocomial pneumonia infection and some of these are organisms that were sought or granted for the previous indications for doripenem, the complicated intra-abdominal infections and complicated urinary tract infections.

If I could draw your attention to the orange text and numbers, we see that the MIC90s for Staphylococcus aureus, particularly Staphylococcus aureus that is methicillin-resistant, are quite high at 8 or greater than 98 mcg/mL. Also, if you look here, Pseudomonas aeruginosa and Acinetobacter species had MIC90s of 4 mcg/mL. These are values that are at least 3 steps higher than the next

pathogen listed in this.

[Slide]

To summarize, we looked at an analysis of the doripenem MIC increases. When we looked at the DORI-09 study, these are the non-intubated patients, doripenem MIC increases associated with clinical failure in the doripenem arm. We see in the DORI-10 study, the intubated patients, that Pseudomonas aeruginosa was the most common organism that had a 2-step or greater increase in doripenem MIC. These, however, were not necessarily clinical failures in every case. Between both studies we also noticed that meropenem MIC increases tend to follow or mirror the doripenem MIC increases.

We did an analysis of the clinical failures, and what we see here is that the majority of patients had one of the following traits, or more: polymicrobial infection; a baseline MIC of 1 mcg/mL or greater; a MRSA infection; a Pseudomonas aeruginosa infection; or pathogens that had a 2-step or greater increase in doripenem MIC during the course of therapy.

[Slide]

We looked at in vivo data, the pharmacodynamics

using Monte Carlo simulations, the probability of target attainment fox Pseudomonas aeruginosa and acinetobacter species. The range here was considered relevant, that the in vivo efficacy was below that of efficacy, below 90 percent.

We looked at the resistance studies. We looked at serial passage studies with Pseudomonas aeruginosa. When isolates were treated with doripenem alone they had greater MIC increases than doripenem plus gentamicin. When the organism was passaged in doripenem it was similar to meropenem and imipenem when we looked at the MICs during those passages.

Multi-drug resistant cystic fibrosis isolates had elevated MIC90s. Also, Pseudomonas aeruginosa that had metallo beta-lactamases also had rather high MIC90 values.

Finally, when we looked at the surveillance data over 3 years doripenem had some of the least activity against methicillin-resistant Staphylococcus aureus, Pseudomonas aeruginosa or Acinetobacter baumannii. Thank you.

Questions/Clarifications

DR. TOWNSEND: Questions?

DR. REX: John Rex. If you go back to your slide 17, you pointed out to us that the target attainment rates for Acinetobacter and Pseudomonas were not very good. I infer from these numbers that the population against which you have done this includes a lot of high MIC isolates. Is that correct?

DR. CODERRE: Well, I did not do the simulations but these were data provided by the applicant.

DR. REX: They have a different table. Rather, this particular summary gets at the question of against a population but if I already know that the isolates have a high MIC, then knowing that I can't get target attainment against that isn't instructive. I already know that I am unhappy with that. So, that is what I am getting at.

There is a parallel table in the applicant's briefing document where they look at the target attainment by specific target MIC and that analysis seems to me to answer another useful question and I just want to be sure that I understood what you meant by this. Because I think this answers only one possible question. The other question is what is the inherent variability in exposures from one person to the next. If the two of us are infected with an