UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH
(CDER)

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ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

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MEETING

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WEDNESDAY,
APRIL 2, 2008

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The meeting came to order at 8:00 a.m. at the Sheraton Washington North Hotel, 4095 Powder Mill Road, Beltsville, Maryland, Gregory Townsend, Acting Chair, presiding.

PRESENT:

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

MEMBERS (AIDAC) Voting):

GREGORY TOWNSEND, M.D., Acting Chair

LCDR SOHAIL MOSADDEGH, Pharm.D.,
Executive Secretary

ANNIE WONG-BERINGER, Pharm.D., Consumer
Representative

BERNHARD L. WIEDERMANN, M.D.

CAROL A. KAUFFMAN, M.D.

CENTER FOR DRUG EVALUATION AND RESEARCH
CONSULTANTS, TEMPORARY VOTING MEMBERS

(Voting):

DEAN A. FOLLMANN, Ph.D.

SCOTT DOWELL, M.D., M.P.H.

WILLIAM J. CALHOUN, M.D., F.A.C.P.

THOMAS FLEMING, Ph.D.

KENNETH R. MAKOWA, Consumer Representative

JAN E. PATTERSON, M.D.

JšRGEN VENITZ, MD., Ph.D.

DANIEL M. MUSHER, M.D.

CYNTHIA G. WHITNEY, M.D., M.P.H.

INDUSTRY REPRESENTATIVE (Non-Voting):

JOHN H. REX, M.D., F.A.C.P.

FDA PARTICIPANTS:

JOHN JENKINS, M.D., Director, Office of New

Drugs, Center for Drug Evaluation and Research

ROBERT TEMPLE, M.D., Director, Office of

Medical Policy, Center for Drug Evaluation and Research

EDWARD COX, M.D., M.P.H., Director, Office of Antimicrobial Products, Center for Drug

Evaluation and Research

MARY SINGER, M.D., PH.D., Medical Officer, Office of Antimicrobial Products, Center for Drug Evaluation and Research

SUMATHI NAMBIAR, M.D., M.P.H., Medical Team

Leader, Division of Anti-infective and Ophthalmology Products, Center for Drug Evaluation and Research

KATIE LAESSIG, M.D., Deputy Director, Division of Anti-infective and Ophthalmology Products, Center for Drug Evaluation and Research

RENATA ALBRECHT, M.D., Division Director, Special Pathogens, Center for Drug Evaluation and Research

STEVE GITTERMAN, M.D., PH.D., Deputy Director, Division of Special Pathogen and Transplant Products, Center for Drug Evaluation and

Research

CENTER FOR DRUG EVALUATION AND RESEARCH GUEST SPEAKER (Non-Voting):

DAVID GILBERT, M.D., Chief of Infectious Diseases, Providence Portland Medical Center, Portland, Oregon

RICHARD WUNDERINK, M.D., Professor of Medicine, Pulmonary and Critical Care Division, Northwestern University, Feinberg School of Medicine, Chicago, Illinois

GEORGE H. TALBOT, M.D., FIDSA, George H. Talbot, Talbot Advisors, LLC, 564 Maplewood Avenue, Wayne, Pennsylvania

BRAD SPELLBERG, M.D., Assistant Professor of Medicine, Geffen School of Medicine at UCLA, Division of Infectious Diseases, Harbor-UCLA Medical Center, Los Angeles, California

T A B L E O F C O N T E N T S

P-R-O-C-E-E-D-I-N-G-S

(8:01 a.m.)

ACTING CHAIR TOWNSEND: Good morning, everybody. Welcome back. I don't think we had too many casualties overnight.

Again, a busy day ahead of us, so we are going to try to get started relatively quickly. Again, housekeeping things for those who weren't here yesterday. Bathrooms are out back. If you have a cell phone, please make sure to turn it off or put it on vibrate. I think most of the stuff we talked about yesterday I will bypass and we'll go ahead and start with introductions and then I will read the prepared statement.

I am Greg Townsend. I am the acting chair of the Anti-Infective Drug Advisory Advisory Committee, Infectious Diseases, from the University of Virginia.

Dr. Jenkins?

DR. JENKINS: Good morning. I am John Jenkins. I am the Director of the Office

of New Drugs at FDA.

DR. COX: Good morning. Ed Cox, Director of the Office of Antimicrobial Products, FDA.

DR. SINGER: Mary Singer, Medical Officer, Division of Special Pathogens.

DR. NAMBIAR: Sumathi Nambiar, Medical Team Leader, Division of Anti-infective and Ophthalmology Products.

DR. LAESSIG: Katie Laessig, Deputy Director, Division of Anti-Infective and Ophthalmology Products.

DR. GITTERMAN: Steve Gitterman, Deputy Director, Division of Special Pathogen and Transplant Products.

DR. WHITNEY: Cindy Whitney, Chief of the Respiratory Diseases Branch at the CDC in Atlanta.

DR. FOLLMANN: Dean Follmann, Head of Biostatistics at NIAID.

DR. WIEDERMANN: Bud Wiedermann, Pediatric Infectious Diseases, Children's

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National Medical Center in George Washington University, Washington, D.C.

DR. FLEMING: Tom Fleming, Professor of Biostatistics, University of Washington.

EXECUTIVE SECRETARY MOSADDEGH: Sohail Mosaddegh, the designated federal official for the Anti-Infective Drug Advisory Committee.

DR. KAUFFMAN: Carol Kauffman, Infectious Diseases, University of Michigan and the Ann Arbor VA.

DR. CALHOUN: Good morning. I'm Bill Calhoun, Professor of Medicine in Pulmonary and Critical Care at the University of Texas in Galveston.

DR. VENITZ: Jurgen Venitz, Clinical Pharmacologist at Virginia Commonwealth University in Richmond, Virginia.

DR. PATTERSON: Jan Patterson, Infectious Disease physician, University of Texas, San Antonio, and South Texas Veterans

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Healthcare System.

DR. MUSHER: I am Daniel Musher. I am a Professor of Medicine in Microbiology at the Baylor College of Medicine and the Head of Infectious Diseases at the VA Hospital in Houston, Texas.

DR. DOWELL: Scott Dowell. I direct Global Disease Detection at CDC.

MR. MAKOWKA: Ken Makowka, Patient Consultant, FDA.

DR. WONG-BERINGER: Annie Wong-Beringer, Associate Professor of Pharmacy, University of Southern California and also Infectious Disease Pharmacist.

DR. REX: John Rex, formerly Professor of Medicine and Infectious Diseases. Currently, Vice President, Clinical Infection, AstraZeneca Pharmaceuticals, a non-voting industry representative to the committee.

ACTING CHAIR TOWNSEND: Welcome all. I will read the prepared statement. For topics such as those being discussed at

today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion for these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion.

Also, the committee is reminded to

please refrain from discussing the meeting topic during breaks or lunch. Thank you.

EXECUTIVE SECRETARY MOSADDEGH: Good morning. The Food and Drug Administration is convening today's meeting of the Anti-Infective Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of the Committee's compliance with federal ethics and conflict of interest laws covered by but not limited to those found at 18 U.S.C. 208 and 712 of the Federal Food, Drug, and Cosmetic Act is being provided to participants in today's meeting and to the public.

FDA has determined that members

and consultants of this Committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. 208, Congress has authorized FDA to grant waivers to special government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual service outweighs his or her potential financial conflict of interest.

Under 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular government employees with potential financial conflicts when necessary to afford the Committee essential expertise. Related to the discussion of today's meeting, members and consultants of this Committee who are special government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. 208,

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their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teachings, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussions of new product development and clinical trial design for both mild, moderate, and moderate-severe community-acquired pneumonia. A primary objective for Committee deliberations is to discuss issues relating to the identification of an appropriate non-inferiority margin for active control trials. The issues to be discussed are particular matters of general applicability. The discussions will not have a distinct impact on any particular product or firm. Rather, the discussions could affect all products and firms to the same extent.

Based on the agenda for today's meeting, all financial interests reported by the committee members and consultants, no

conflict of interest waivers have been issued in accordance with 18 U.S.C. 208(b)(3) and 712 of the FD&C Act. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Dr. Brad Spellberg, an FDA-invited guest, would like to acknowledge that Pfizer, Astellas, Gilead, Novartis and Enzon support a research grant or contract project of his. In addition, Dr. Spellberg serves as a consultant to Pfizer, Merck, and Astellas.

Dr. David Gilbert, an FDA-invited guest, would like to acknowledge that he serves as a consultant to Pacific Beach Bioscience, Advance Life Sciences, Merck, Pfizer, Roche, Wyeth, Shering-Plough, and Johnson and Johnson.

Dr. Talbot, an FDA-invited guest speaker, would like to acknowledge that Calixa, Cerexa, Shire, Theravance, PTC, and

Actelion support a research grant or contract project of his. In addition, Dr. Talbot serves as a part-time employee to Talbot Advisors, LLC.

With respect to FDA's invited industry representative, we would like to disclose that Dr. John Rex is participating in this meeting as a non-voting industry representative, acting in behalf of regulated industry. Dr. Rex's role on this committee is to represent industry interests in general and not any one particular company. Dr. Rex is employed by AstraZeneca.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvements and their exclusions will be noted for the record.

FDA encourages all other

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participants to advise the committee of any financial relationships that they may have with any firms at issue.

Thank you.

ACTING CHAIR TOWNSEND: Thank you, Sohail.

EXECUTIVE SECRETARY MOSADDEGH: If I could make just a housekeeping announcement. There are apparently three vehicles parked outside that will be towed if not moved immediately.

(Whereupon, the Chairman identified the make, model and license plate numbers of three cars.)

Thank you.

ACTING CHAIR TOWNSEND: All right. I think, Dr. Musher, if you are ready, Dr. Musher will start off today's proceedings with a clinician scientific approach to pneumonia.

DR. MUSHER: Good morning and thank you very much for asking me to speak

today. It has been a very interesting day yesterday. It will take a second to load up. Thank you.

EXECUTIVE SECRETARY MOSADDEGH: Hold on one second.

DR. MUSHER: I think I was -- I pushed the wrong button before. Okay. Thank you. Thank you very much.

EXECUTIVE SECRETARY MOSADDEGH: You're welcome.

DR. MUSHER: Okay. So, let's talk about evaluating treatment for pneumonia. And I have called these philosophical problems. That's really -- they are medical and scientific problems but they are kind of deep and they are worth our commenting on.

Because of the natural history of infectious diseases, there is a varying proportion of patients who respond spontaneously, that means they respond without treatment. In the modern era, there has generally been a very high success rate of

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existing therapies for common pathogens. Now, of course, that could change with emergence of new pathogenic organisms causing disease or with newly resistant organisms. It is already changing, ladies and gentlemen, it is constantly changing. The recommendations for "empiric therapy" of "community-acquired pneumonia" are already problematic if staph aureus is prevalent, which staph aureus has become. And that is just an example.

There is a problem with empiricism. In many cases, we don't know what infection we are treating. We, unfortunately, live with empiricism. We can't always establish the cause of the diseases that we are taking care of, but we must continue to recognize that this increasingly pervasive approach, being satisfied with empiricism or encouraging empiricism, as in again, this empiric therapy for so-called community-acquired pneumonia, this is antithetical to scientific study of medicine.

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I think patients get better care when we study their cases scientifically and humanely. I promise you, I am a humane doctor. I am a decent and a good doctor, but I think a scientific approach makes a big difference. And I was delighted they picked that title for my talk. I didn't know that was the title, a scientific approach to caring for pneumonia. I am delighted with that.

Now, without a correct diagnosis, we are not certain whether, if a patient gets better on treatment our drug is responsible. Stated very simply and that is just common sense. If you don't know, it could have been one of those diseases that responded spontaneously, unrelated to our therapy.

True cases of the disease are diluted by those that might not respond to or get better without regard to treatment. If you have got ten patients with pneumonia and nine of them have pneumococcal pneumonia and you treat with penicillin, and there is a

certain rate of improvement, then you probably can attribute that to the penicillin. If you have got ten patients with pneumonia and nine of them have viral pneumonia and you treat them with penicillin and they get better, you can't attribute that to penicillin. And it makes all the difference in the world. And if you don't know what is in your group, then you really don't know and you don't know if your treatment is effective or not and it makes a big difference.

Even if we know what we are treating and we develop criteria to recognize therapeutic success or failure, can we design studies that are large enough to provide meaningful results but are still practicable?

Let me show you these next couple of slides just for a moment. It gives you an idea about the size of studies. And it is from an area relating to pneumococcal vaccine, which is an area I have been working in especially for the last few years. The study

that showed that so-called multivalent pneumococcal vaccine, a vaccine that has four capsular polysaccharides, that showed a drug like this could be effective, required 17,000 healthy young adults to participate. And they had a vaccine that had polysaccharide from type one, type two, type five, and type seven pneumococcus and didn't have type four and type twelve. And they observed the numbers of cases of pneumonia in the controls and in the vaccinated group. And with this enormous study, they were able to show that the vaccine was effective in type two pneumonia and type seven pneumonia. They couldn't even show it was effective in type five or in type one. And that is a huge study and that is what it took. And you didn't have statistical significance when it was all done.

This is one of the most important studies, a magnificent study, in my lifetime in medicine, the Kaiser Permanente study that led to the development of the valent protein

conjugate vaccine. Thirty-eight thousand infants and I am going to show you, this slide I am going to use as a prelude to show you why you have to know exactly what it is that you are treating in order to evaluate the efficacy.

If you were vaccinating to prevent invasive pneumococcal disease, that is absolutely provable infection. You get a blood culture or a cerebral spinal fluid culture, you grow pneumococcus. That is invasive disease. You know the kid has it or you know the kid hasn't got it.

Now, the non-vaccinated subjects, there were 49 cases. Notice, you had 38,000 infants to do this, there were 49 cases of invasive pneumococcal disease, compared to four in the vaccine group. That is a 90-plus percent reduction. And that is what you get when you specifically make a diagnosis.

Otitis media, middle ear infection, the major cause is pneumococcus.

So you might say, well, gosh, we can show a major effect of this vaccine on otitis media. So, we should be able to do that. You can only do that if your diagnosis is absolutely correct and reliable.

A little tiny child, a doctor's office, parent trying to hold the kid down. Everybody is motivated to diagnose otitis media because then you give an antibiotic and everyone feels better. And it is very hard to see that tympanic membrane but maybe it looks a little bit red. And that is what happens. And otitis media is diagnosed by that maybe it looks a little bit red, not by a really good diagnosis of otitis media.

As a result, if you look at the efficacy of the vaccine, it reduces otitis media by only nine percent. That is because the diagnosis wasn't reliable. You have got to have a reliable diagnosis. If you look at otitis media, when you have proven that there is a vaccine-type pneumococcus in the middle

ear fluid, that is a 65 percent reduction. That is getting to be more like it.

If you are just treating some gemischt of patients, you are labeling them all community-acquired pneumonia, you don't know what it is, you are going to have a lot of problems in interpreting whether your medication is efficacious. I hope that is clear. It should be, yes.

The goal for studying any new drug should be to eradicate disease for which the etiology is established. That should be the goal. You can't do it all the time, but that has got to be a major part of the treatment.

So, what that means is that, if you are going to set up -- maybe you remember from my comments yesterday, I think it is very important if we are going to design studies, you have got to design them so that, in some determined proportion, you have established an etiologic diagnosis.

And then you can say, well, I

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think the rest of the cases in which I couldn't establish it looked like the ones in which I did. And you can probably check that by some statistical analysis. And then you say, therefore, the whole lot of them probably had bacterial pneumonia, or most of them did, and this is the effect of my antibiotic in treating it. And if you haven't got that kind of analysis, then you can't be sure what it is you are treating.

So, some clinicians object. And I am a clinician. That is what I do. Some clinicians say it is not a real-life scenario. So actually, if we only, if our profession were only prescribing antibiotics to patients who really needed them, the proposed approach would be much closer to a real life scenario. Unfortunately, we are giving a lot of antibiotics to patients who don't need them. So it is a different situation.

Now, some clinical criteria to evaluate therapeutic success. Now we are

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talking about therapeutic success and therapeutic failure. And of course, it is really the same thing. I am just separating them out for the purposes of discussion.

So, I am going to look at the time to defervescence, the mean rate of fall of the temperature. You can use a Kaplan-Meier analysis or some other kind of thing. And of course, I would turn to my statistical, my statistician colleagues and I say help me design the ways to demonstrate this. But there was some talk yesterday about the fever is like an epiphenomenon. That's not an epiphenomenon. You can reduce fever by giving some other drug. You can give Tylenol. You can remove the fever and maybe some antibiotics have an anti-inflammatory effect and maybe they reduce fever independently of their ability to cure an infection, but the rate of fall in temperature, that is what we clinicians look at.

The time to clinical stability --

and I will show you some things we might use. They relate to how rapidly the oxygen saturation in the blood stream rises and how rapidly the pulse falls and the respiratory rate falls. There are good ways to evaluate patients and that is what doctors look at all the time. A symptom questionnaire is something reasonable. I will show you that, also, in just a moment.

This is one way to look at the median time to defervescence and you can compare whether the patients in one group become afebrile more rapidly than in another. This was an open label study. The data are unacceptable. I am going to talk about open label studies in a few minutes. Even if you think you are measuring something objective, it is unacceptable in open label study. I will come back to that. But this is, I just used it because it was a picture that I had of a way in which you might evaluate such data.

Now, when you are measuring the

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time for defervescence, you could ask, does a day or two of lower body temperature really matter? I think it really does and I think that the clinicians all say that it does.

First of all, you know, more rapid is more rapid. The patient feels better. The patient feels better without fever than he does with fever. And our goal is to treat human beings and make them feel better. Fewer days in the hospital. Doctors don't like to send patients home when they are still febrile. There probably are going to be fewer complications in proportion to the number of days in the hospital. The more days you are in the hospital, the more complications you get. Everybody knows that. And as a result, I think that the rate of defervescence is a goal. It is something that should be looked at.

Now, I mentioned already that defervescence could be due to some property of the antimicrobial agent. That would be a

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separate issue altogether. And I have here as a footnote, obviously a failure to defervesce is consistent with a clinical failure, although other causes could be possible. The patient could develop something altogether different, and that is a separate issue.

Time to clinical stability. Here are just some of the things that doctors look at all the time. Take for example, oxygen saturation. Patients have pneumonia. There is shunting. There is blood that goes through the lungs and doesn't get oxygenated and the percentage of oxygen in the bloodstream, stated very loosely, is oxygen saturation -- falls. So, how many days does it take for that oxygen saturation to return? So here you see, this tells you the number of patients in this particular series that had an oxygen saturation below 94 at the baseline and the median number of days to have it return to greater than 94 was four days.

Just, for instance, this is useful

data. This is how a doctor looks at a patient. You look at the respiratory rate. You observe it every day and how rapidly does it return to an acceptable respiratory rate? The pulse. I have already commented on the temperature. Is the patient able to eat? Does the patient look better? Ladies and gentlemen, a good doctor can tell you if a patient looks better. And if you have got a double-blinded study where you are comparing drug A and drug B, and that is what your goal is, then the doctor's observation, my patient looks better today or doesn't, is a fair observation and it is, in its way, objective. You know, you don't have a number applied to it, but it is the way doctors do and doctors are trained to do that.

Symptom questionnaire. This was reported by Lamping, et al. It is perfectly reasonable. You ask the patient whether he or she has chills or sweats, cough, sputum production, chest pain, shortness of breath,

et cetera. These are the symptoms for which the patient came into the hospital and over a period of two or three days, they get better.

In a comparative study of three antibiotics, the questionnaire was easily administered and was well-accepted. They showed it to be reproducible and reliable to give valid results. And I propose again, in a double-blind study, you can accept these responses and these should provide reliable data on how effective your antibiotic is.

In an open label -- now I am going to comment on open label studies. Good morning, Mrs. Smith, how are you doing on this wonderful new antibiotic that we have you on? Oh, doctor, I am just so much better. That is fine.

Good morning, Mr. Jones, how is your shortness of breath today? Well, if it's not so good, that is okay. You write it down on the questionnaire. You tell us how it is doing. Ladies and gentlemen, nobody should be

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doing these open label studies. My professional journal of clinical infectious diseases, produced by the Infectious Disease Society of America published this thing. I can't believe it.

This is not a problem with the questionnaire. This is a problem with the design of the study. It is inexcusable to have an open label study to measure things like this and to report it. And I feel the same, by the way, even with temperature. How can you be unobjective about temperature? I can tell you how. I am making rounds in the afternoon and Mr. Brown over here, he is on my drug that I don't think is so good and he feels a little bit warm. Nurse, would you mind just checking the temperature on Mr. Brown this afternoon? I would like to see how he is doing. He feels a little febrile to me.

One patient here and one patient there and the number of days to defervescence. It is not honest stuff, guys. It is not

honest.

Anyway, so this is the problem. This happened to be, although I believe that you can ask patients their symptoms and look at the rate of decline, if it is an open study, you can't begin to use the results the way these are done. So these data illustrate two points, the possibility and the lack of validity. This is weakness and cough, sputum quantity and sputum color. And the statisticians have done their analysis, except it is not valid data.

All right. So, this is another thing. It is astonishing. The duration of hospitalization in that particular study, was shorter in the group that received moxifloxacin, but you can't give ceftriaxone orally. So how on earth could you -- you had to choose to stop the antibiotics. You can send your moxifloxacin patients home on the drug. You can't do it with ceftriaxone. So, of course the comparison is misleading.

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There are studies like that, comparing. You compare, it is in one of those backup slides. Vancomycin and oxazolidinyl, lenazolid, in treating soft tissue infection and the duration of hospitalization is longer in the vancomycin group, statistically, it is longer. Amazing. There is no oral form of vancomycin. You have got to keep the patients in the hospital long enough to treat them. You can't send them home. The guys who get the lenazolid, they can go home because they can take it orally.

So, a lot depends upon your study design. And I am going to comment on study design again at the end. Note that in the study that I am talking about, that I am objecting to, nevertheless, the overall cure rate was identical in the two treatment groups. This has been a remarkable theme overall in a lot of the studies on pneumonia in the last couple of decades. The overall cure rate, that is, the doctor looks at the

patients at some time along the way. Ten days later, fourteen days later, and says, this patient is cured. There is a little box on those forms. You check the box, the patient is cured and remarkably similar in the two.

And that is why you could say, if you wanted, well does a day or two less of the fever make a difference or not? And you can open that up for discussion. But if you want to show that a new drug is as good as an old one, these are some of the ways that you might go ahead and do it.

So, I've already talked about open label studies. Now let me talk about clinical failure of treatment for pneumonia. Death; persistent bacteremia and that means the bacteria in your blood cultures stay positive; develop a complication; if there is progression of the pneumonia; delayed defervescence, I've already talked about; duration of hospitalization, I will comment on when I discuss that issue in the next slide.

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So, you can look at death and the question is, what time point do you take? This is important, but you have got to understand this. You can say well, if a patient dies, then your treatment is obviously not as good as if your patient didn't die. So there are nice data to suggest deaths in the first two, three, four days in the hospital, are unrelated to treatment. Patients who are that sick when they come into the hospital, your treatment isn't going to be able to turn the thing around.

And there is a very famous graph that was shown, figure that was shown yesterday. It is shown at a lot of scientific meetings. Let me show it to you again. This is when Austrian and Gold took patients from the pre-antibiotic era untreated, from also the pre-antibiotic era treated with antiserum, and from the early penicillin era, and they plotted their survival each day of hospitalization, these days in the hospital.

And what they showed was that the death rate in the first four or five days in the hospital was the same whether they were treated or whether they were untreated. A lot of immunologists call this cytokine storm. All the things that happen in the body that are triggered by a serious infection, they keep going even if you give a really good antibiotic. So you probably shouldn't take death in those first few days in the hospital and you should probably exclude those.

Interestingly, our patients now who get pneumonia, many are older and debilitated and they have got what are called co-morbidities. They have got underlying diseases. And after a couple of weeks in the hospital, they are dying of these other things that happen to them. And therefore, death after 15 or 16 days probably shouldn't be considered either.

So, if you say I'm going to look at the death rate in my pneumonia patients at

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60 days or 90 days, you might get an overall death rate that is pretty substantial, but a lot of those deaths might be, in fact, unrelated to your treatment. And you probably should take a time like something between five days and 15 days and use that to evaluate the efficacy of your antibiotic therapy.

Now, the total numbers aren't going to be as big so you might not think it is as robust, but it is going to be better. It will be more reliable data so it really will be more robust and that is the way I would interpret looking at the rate of survival.

So the patients, let me see, if you are going to study death as an endpoint in pneumonia, of course, the patients have to be sick enough for that to be something to observe. I have already commented more broadly, we cast our net in order to increase our numbers, the greater dilutional affect of death to the other causes and I have already

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commented on that.

So, that is a point about death and obviously death is an objective point and even then you have got to be careful which days, which figures you use.

New or persistent or recurrent bacteremia. If you are treating a patient for pneumococcal pneumonia and he didn't have positive blood cultures at the start and then after three or four days his fever persists, you repeat the blood cultures and now they are positive, that is not a good sign. Also, if he has persistent blood cultures that are positive or they recur afterwards, that suggests a failure of therapy.

The thing about this is this is very rare, except in gram negative rod, pneumonia, and severely immunocompromised patients, you might see it in staph aureus pneumonia. This is very uncommon. So, as I said, obviously if bacteremia recurs, it is a failure but the percentage in which this is

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going to be seen is going to be very small. So, it is not going to be terribly useful unless you have huge studies.

Appearance of a complication on treatment is the same kind of a thing. The complications, usually, are recognized at the time of admission to the hospital. A complication is the presence of infection in the pleural space and empyema, in a joint, in the bone, in a heart valve. These things are usually seen in patients who have serious pneumonia. You see them at admission or they appear really immediately afterwards. So, it is not a failure of therapy.

If they did appear after a week of treatment, you would say, oh my goodness, I have got a problem with my treatment. But that is a very rare event. So, again, I think it wouldn't be too useful to follow it, unless you had a huge patient sample.

The rate of resolution I have already commented on. The progression of a

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pneumonia, you know, I haven't really. There is data on the resolution, the radiologic resolution of pneumonia. That means how rapidly x-rays clear and that is kind of a slowish process. And I don't think that most people believe that it is too closely related to antibiotic efficacy.

Now, I have commented on what clinicians use and I emphasize it again on this slide. You could study any of those variables in the PORT score, the blood pressure, the temperature, the respiratory rate, the serum sodium, there are all kinds of things that clinicians observe every day. And you can take any one of those and you can observe them and see how rapidly they return to normal. And that would indicate, these are all parameters that might indicate the efficacy of your antibiotic treatment.

It is very complicated and it depends upon the intensity of treatment and the skill of the physicians. In a blinded

study, the skill the physician should average out because -- by the way, when you do these studies also, you have to be sure that you don't have one group of physicians or one medical center providing a hundred patients and then ten others providing four or five patients, because then you get too much variability. You, ideally, would like to have every single physician or participating group provide the same number of patients, so that the thing all averages out. Now, it doesn't happen that way, but that is the way you like it to do.

At any rate, there are things you can follow for clinical failure and clinical success.

Here are some other considerations. Number of days in the ICU for those who require ICU care; number of days of intubation, if they have been intubated; the number of days of IV therapy, if there is a protocol where a switch to oral therapy is an

option. Obviously, and I say obviously, you can only use these in blinded studies. And I am telling you, I can cite the numerous studies, I can cite numerous -- and there are lots more I can't remember to cite, where people have used these things and they haven't been blinded studies. Well, the FDA should only endorse blinded studies. Anything else is used for only the purposes of advertisements. And the doctors shouldn't do it, the journalists shouldn't publish it, and the FDA shouldn't endorse it. That is my opinion as a scientific clinician.

Total days in the hospital, which may sound, from a common sense point of view, oh my God, they have got that poor patient, getting out the hospital who has pneumonia for three months, that is too much dependent on those comorbidities that I mentioned earlier. So I don't think it is actually very useful, even though it might seem to a lay person, intuitively, that it would be.

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I am now going to comment briefly on what constitutes a bacteriologic cure. So, first I have got to consider bacteriologic diagnosis. There is extensive -- blood cultures are positive in pneumococcal pneumonia in something like a fourth or a fifth of cases. In Haemophilus influenza pneumonia, it is a lower proportion, maybe it is an eighth of cases. In Morexella pneumonia, it is rare. So, when you get a positive blood culture, you have got a bacteriologic diagnosis. The rest of the time, you are dependent upon some other technique. And there really aren't very many. You heard mention of the urine pneumococcal antigen test yesterday, which I think is a reliable test, when it is positive. Otherwise, you are left with a traditional method of a sputum gram stain and culture.

So there is extensive literature on it, most of which literature states that this test is unreliable. And I would like to

show you the results of a study that motivated me to do a study that was published a few years ago in Clinical Infectious Diseases. One hundred and five patients who had proven pneumococcal pneumonia, that means they pneumonia. They had cough, fever, sputum, a chest x-ray abnormality that we doctors call a consolidation. And they had pneumococcus in their blood stream. That, ladies and gentlemen, is unquestionable pneumococcal pneumonia. Now, the gram stain, which is the clear bar, and the culture of the sputum in these patients, look how terrible it was. Only 30 percent, 35 percent by gram stain, only 45 percent by culture had a positive. That is the small number in which they were positive. That is what the literature says.

Now, watch this analysis. Of these 105 patients, 31 of them couldn't cough up a sample. There was no sputum. Well, if you are evaluating the validity of a technique, you don't consider the people in

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whom the study wasn't done. So you exclude those. And then another 16 of them coughed up a sputum that the laboratory sends back a note saying, not interpretable. Mainly, it was saliva, it wasn't sputum. So, you can't use these at all, either.

So, you only had a test in 58 of them. And now you are getting to have a culture result that is 80 percent positive and a gram stain that is 60 percent positive. That is getting better. That is more what it looks like.

Now, look at this next slide. These are the guys who had no antibiotic at the time the specimen was submitted, 90 percent positive culture, 80 percent positive gram stain. You know, as clinical studies go, that is pretty good in this world. And actually, it wasn't bad if they had antibiotics for six hours or even up to 24 hours.

For reasons that always escape me,

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a bunch of the residence send sputum after the patient has been on antibiotics for a day or two or three, and you those you can't make a diagnosis. So, the point is, the gram stain and the culture of sputum are useful but you don't get a whole lot of patients who can provide them promptly, and it is problematic.

Now, if it is hard to make a diagnosis when they come in, think about a microbiological cure. A lot of your patients couldn't provide a sputum when they came in. Well, three or four days later, when they are getting treated for their pneumonia, they are certainly not going to be able to provide a sputum then. And that is what the problem is.

And so it is very difficult to demonstrate a microbiologic cure. Most of the people who think they can provide a specimen after several days, provide a poor or useless sample. And if we encourage, if we require people who participate in clinical studies to give us this bacteriologic cure, then it

encourages us to give bad data.

The same thing. Mr. Jones, I know it is hard for you to cough now, but I need some kind of a sample. Just cough and put something in that cup for me. I will send it down to the lab. That is when you get saliva. You get a non-valid specimen. So, that is the problem. Also, cultures can detect colonizing organisms like, I'm sorry, I have got some old literature for you on this and the slides in the back have more of that stuff.

The point is, is that it is not so easy to establish that bacteriologic diagnosis of sputum and a bacteriologic cure is just a very difficult kind of a thing. We shouldn't do it. So I have already commented about that.

Now, placebo studies. I don't even know what to say. They are simply unacceptable. Anybody who signs a consent form either hasn't been fully informed or he is not competent to sign. It is just that

simple. It is not even a discussion. I am going to skip the slides.

(Laughter.)

DR. MUSHER: I'm going to summarize. I'm going to have like two moments of comments after my summary slide. I think that there are good ways of evaluating clinical responses to patients whom you are treating for pneumonia. You can use symptom questionnaires. You can use time to defervescence, time to clinical stability, which uses a whole lot of different findings that we physicians use all the time. You can look at mortality between 72 hours, see, look, I wrote ten days when I made the slide. A couple of weeks ago, I think 15 days is fine. Stay in the ICU, days of intubation. If they develop a complication while they are on treatment, that indicates, probably, a failure or it certainly isn't a good sign.

Emergence of resistant bacterium, you have got to show it is the same strain,

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the same organism, but that certainly isn't a good sign, either. And persistent bacteremia, of course, is bad. There are ways of doing it and they can be done.

Now, I would like to comment about the process, if I might for just a moment. I sat and listened yesterday. I did the best I could trying to understand the issues as they were being discussed and I thought about it last night. I didn't sleep at all well last night, so I did a lot of thinking, and my problem is this. I have designed many studies of all kinds over many years. I have done in vitro studies. I have done animal studies. I have done human studies, case reports. I have written hundreds of papers. I raise the questions scientifically. I try to design a study. I have worked closely in my career with two statisticians who have been of tremendous help to me. They clarify my questions for me. They help me clarify my questions and they show me how I can obtain

data that are going to be meaningful.

But, ladies and gentlemen, I am the one who frames the questions, because I am the doctor. I am the one who is taking care of the patients. I am concerned. I looked at those questions that I am going to be asked to answer later today. I don't know how I am going to answer them. I don't think I can understand those questions and I don't think I can answer them.

And we are talking about a disease that I take care of all the time. I round on the infectious disease service. I see every consult in the hospital three months a year. And two months a year, I run a general medical ward. That means whoever comes in. I am a clinician. I should be the one asking the questions. The statisticians shouldn't be the ones asking the questions. I should say, guys, these are things I can observe as a doctor. Please help me with the statistical instruments that I can objectify the

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responses, but this is what we have got to measure.

Thank you very much.

ACTING CHAIR TOWNSEND: Dr. Musher, I think we will wait until the question and answer session to have questions for you.

The next speaker will be Dr. Gitterman on consideration in the design of CAP studies.

DR. GITTERMAN: Thank you very much. Good morning, Dr. Townsend, members of the committee, colleagues and invited guest.

What I would like to discuss in my brief presentation is what I see are key points for the subsequent discussions. As part of my talk, I would like to highlight areas where I see there is likely to be agreement and similarly, areas where I believe more discussion is needed. My hope is that everything I will address will dovetail with the broader questions the committee has been

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asked to address.

And actually, in an irony, I think I will be addressing some of the points that Dr. Musher has just addressed, even though I hadn't looked at his slides until this morning.

Now, this slide attempts to basically distill down what I see are the most important issues in studies of CAP and are likely the most important issues in any experimental study, and the issues are obviously intertwined. Obviously, the inclusion criteria largely define the study population. A non-inferiority study can only be designed on a specific given endpoint or outcome. And to narrow it down, I will be focusing on the items in yellow but obviously, it just as easily could have been the items in white. They could have been reversed.

And one approach or the approach I am going to take to my concerns is simply to fill in this table, to put some specifics into

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what I think has been presented earlier and possibly serves as a bridge to the discussion that is going to occur later today.

You know, it is important to note, and I have to be absolutely explicit about this, I do not have the answers and I am not meaning to provide answers. What I am simply trying to do is provide some ideas. And some concepts, I think can be reasonably gleaned from what has been discussed earlier today, what has been discussed yesterday and what was discussed earlier at the, IDSA FDA symposium.

But this also somewhat reflects my belief that the primary concern facing the committee is what is in this slide. And that is, really verbatim, that although challenges exist for both inpatient and outpatient studies, that the more difficult issue may be identifying an appropriate non-inferiority margin for drugs that only have oral formulations. And I will explain that as I go through filling out the table through the next

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slides.

Now what are the concerns that I would like to discuss and we could start with inpatient studies which I am making synonymous to some extent with parenteral studies. And this was the right side of the table that I showed earlier.

Obviously, to belabor the obvious, there is the implied assumption that the inpatient studies reflect patients with a worse prognosis. This is evidence explicitly cited in the IDSA ATS recommendations where the severity of scores are recommended as level one evidence for contributing to the decision to admit a patient. I am sure Dr. Rex could read it to us verbatim if we need to, but it is level one evidence in the document.

For study design, you know, there has obviously been much discussion and Dr. Musher had made the point rather emphatically during his last talk. But I think we don't

really need to discuss it further, certainly, for the case for inpatient studies.

Study population is obviously intertwined with the issue of study design. But we could also take from the discussions of yesterday and from the earlier discussions that the effect of antibiotics was greater in more elderly patients or older patients. And that is, I think, we could all agree could be reasonably inferred from that data that we have seen earlier.

Similarly, we can use the data again, stretching a little bit, but to argue that bacteremia patients who are more ill, are likely to have greater benefit from the use of antibiotics. However, and as you can see as I put up PORT scores criterion, the severity scores or PORT Scores or CURB scores are really a recent development and certainly post-date the historical data on which we are basing the issue of severity.

I recall and again, this is very

important and this, of course, came up at the IDSA FDA symposium, that PORT scores are only for treated patients. They only discuss -- you know, they do not tell you anything about prognosis in untreated patients.

So the question, in discussing and filling out the table image in four of these study populations are, are PORT scores appropriate for use in clinical studies and how do these relates to historical studies. Further, if such a scale is adopted for use in inclusion criteria, what should that specific criterion be? And people have mentioned specific suggestions yesterday.

And I think the answer to this is somewhat provided by the data discussed yesterday by Dr. Singer. If we reasonably conclude that there is a quantifiable benefit from the treatment of antibiotics for patients who are over 50 who were treated again in the 1930s and, since a PORT score of two generally reflects patients older than 50, I can't go

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back to my slides, but I wish I had another slide of the PORT criteria that Dr. Alexander showed yesterday, a PORT score of two gives us a reasonable link to the previous historical studies.

The PORT score has the advantage, as was noted by Dr. Fleming and others yesterday that it doesn't reflect age solely but it adds additional risk factors, albeit not all the risk factors but it's assumed. I mean, it gets us out of the oddity that a 30-year old who is incredibly ill by the judgments perhaps Dr. Musher made earlier, would not be, you know, would not be PORT four or PORT five, or would likely be someone that most people would believe needed antibiotic therapy and is likely, in comparison to historical studies, to have benefitted from antibiotic levels.

The bottom line that I am saying is that, in consideration of the study of populations, the PORT score can be used as a

link to the historical data by the way it is written. I am not using it for any other purpose in this regard and I want be clear that we are not using it for the issue of prognosis because again, the PORT score is based on treated patients.

We all saw yesterday how antibiotics back, even in the '30s, flattened, the biggest risk factor, flattened outcome for the biggest risk factor, which was bacteremia.

I would also say, too, that even though I have put on this slide as my second bullet that a PORT two or three could be a minimum, it is also true -- and I don't mean to argue against myself -- is that we have greater certainty that the studies reflect a higher risk group or, perhaps, have a greater link to the 1930s as the PORT score goes higher. And the committee, of course, is going to be asked to address this question, if a PORT score is appropriate and what a PORT score should be. And again, as we heard

yesterday, there was substantial discussion on what a PORT score represents.

I have this in my notes. Again, I don't want -- but Dr. Musher, again, yesterday gave us some inkling about what hospitalization represented or may have represented in the early 1940s or in the 1930s at the time these patients were admitted. I don't mean to suggest that Dr. Musher was there, but it was close. And I think just he was at the hospital with Dr. Bullowa who collected a lot of this data with the same institution. I don't know if he was there at the time that Dr. Musher was there. But again, I am saying this with a smile on my face. You know, those in the back who can't see it, I mean, it is a little bit tongue-in-cheek.

I would also mention, too that Dr. Nambiar presented some data yesterday which I will get back to again which is recent data which shows that a certain study was unable to

establish a non-inferiority margin, even though PORT five was completely excluded from that study, a study that enrolled patients only in categories two to four and I will mention that in a second.

For the third major bullet, which is analysis populations, again, the committee is going to be asked to discuss this. And we have heard again, only because of the recency effect, Dr. Musher also addressed this, as did other speakers yesterday, is do we require patients with microbiologically confirmed diagnosis, as that of course does give us some additional, I would say confirmation for lack of a better word, or rigor in the way that we approach the studies.

Now, I would also say, too, and it is a very important point that I think has been stressed by every speaker, is that any basis for non-inferiority of margin has to be based on solid prior information. And the data available to us as people have spoken is,

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primarily, from pneumococcal pneumonia.

As Dr. Nambiar also mentioned yesterday, you know, perhaps half of the patients on the recent studies had a microbiological diagnosis and, of course, a fraction of those were pneumococcal pneumonia. But this is balanced, I think, by the important paper that Dr. Alexander had showed yesterday about the fact that, for most patients without a diagnosis who are very ill, a procedure we are not going to do, which is a transthoracic tap, did appear to pneumococcal pneumonia when further investigation was done.

Now again, there is obviously cohort affects. Whether this will be true in the study of increased vaccinations, et cetera, is uncertain but there is some evidence that in the ill patients there is a link by diagnosis. I would also mention, too, is that this again was somewhat alluded to by Dr. Musher, is that FDA traditionally and

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prior to 2008 has used pneumonia as the diagnosis, as the criteria for enrollment in these studies rather than actually microbiologically confirmed diagnosis even though all of this data was looked at at the time of analysis of various subgroups.

Just jumping ahead and digressing slightly, and I make this point again in the discussion of oral studies, but when we talk about analysis populations, we really have three populations and I think it has to be very careful. We have to be careful. We have bacteriologically confirmed, I just make the point in this context of whether for parenteral studies or inpatient studies one could conceivably exclude microplasma if they believe that had a different prognosis and didn't belong because of the same non-inferiority margin. But we have bacteriologically confirmed patients. We have patients without bacteriological confirmation and that is the patients that I mentioned in

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the Ruiz-Gonzalez study.

And we also have patients without bacterial infections, people who we have confirmed, to some extent, do not have a bacteriological cause for pneumonia. Patients with a lot of rapid diagnostic tests, which are becoming increasingly available. If somebody has influenza, we would exclude that patient. There has been a lot of discussion, and I think absolutely valid, of the point that some of these patients are mixed populations or that we can make a mistake by enrolling a patient with influenza. But I think it is important to, and obviously we can discuss it, is we do have mechanisms to exclude these patients. So there really are three categories. And patients with, you know, we will increase the likelihood that patients do have a bacteriological pneumonia because we will be able to exclude patients with an obvious, non-bacteriological pneumonia in some cases.

Going to, just finishing up on filling out the table for inpatient pneumonias, going to clinical endpoints. And this is going to be a difficult point for me to articulate. So, I notice in the schedule they have left a full hour after I speak for questions and clarifications. I didn't take that personally and I think it is a coincidence.

But, although mortality has been discussed as the link to studies and again, I can't emphasize this more, that the regulations specifically state studies have to be adequate and well controlled, I think Dr. Fleming described very well what that means in the context of coming up with a non-inferiority margin, we do have clinical endpoints. You know, we obviously have to have some clinical endpoints and as Thamban had mentioned yesterday, mortality in 2008 is a confounded endpoint because we don't want people to die in our studies and we usually

use an ethical grounds criteria by which we believe we could intervene, criteria of quote failure, by which we could intervene before somebody is likely to die, so we could put them in what we believe to be effective therapy. Obviously, ethical mandates, you know, ethical mandates would obviously require that we do this. And so to some extent and again, I hope I could articulate this well, we have moved beyond a mortality endpoint, except endpoints other than mortality in these studies. We are accepting the definition of failure, which is a clinical endpoint, rather than one that goes back to the historical controls.

Now, to some extent again, when we do this, we are using a clinical endpoint that we believe is clinically reasonable or one that has been determined on clinical criteria, not based on historical evidence or directly that can be gleaned, I believe from historical evidence.

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Now, I have to mention in this point, I think the daptomycin study, that was discussed to some degree by Dr. Nambiar yesterday, is very, very important in this regard because that study did not show -- and I have to say this right -- did not -- showed, perhaps, that daptomycin was not non-inferior to ceftriaxone, if I have gotten my double negatives correct. Further, the differences between daptomycin and the other arms were greater for the failure endpoint than they were for the mortality endpoint. There was a difference, I believe, it is 4.6 versus 2.8 percent for mortality. But the non-inferiority margin, which was based on clinical failure, which was on clinical endpoints, some of which had face validity, did show a bigger difference in that regard.

And, I would also add, and I don't want to push this too far because these are points for discussion later, all the subgroups that had clinical plausibility, what I would

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say biological plausibility, all fell out, at least as reported in the paper, in the direction consistent with those results. Even though Dr. Musher, I thought, again, give us a presentation before, how difficult the microbiological endpoints were, this was a study which, at least as reported, purported to show a difference in microbiological outcome, which did show greater persistence for strep pneumoniae in the group, that the group that got the daptomycin versus the group that got the alternative antibiotics.

And again, and we can all discuss this and I know there will be other points, too, I am just reporting what is in the paper, when you took what one or some folks might consider the purest subgroup, which is the group that did not get prior antibiotics, the difference is more magnified in that regard. Again, I don't want to push it too far and again, these are points for discussion.

As regards, and I should also note

too, and that is why I have written my comments out verbatim, so hopefully I don't miss much, this was a study, as I mentioned in the previous slide, where PORT five was not enrolled. They were explicitly excluded. These were PORTs two to four, and I believe Dr. Nambiar can correct me, that there were 40 percent of the subjects with PORT four, which meant 60 percent of the subjects had less than PORT four. And again, it is at a broader range than perhaps some of the enrollment criteria that was suggested yesterday.

Let me read what the definition of clinical cure was, at least in the paper, clinical cure was defined as the absence or improvement of clinically significant symptoms and signs such that no additional therapy was required. Clinical response was defined as clinical failure. If symptoms and signs persisted or progressed, the patient died, of course, or the study therapy was stopped because of an adverse event.

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Again, in the slide there, to some extent, that is why I have listed mortality as, at best a secondary endpoint or, of course, being part of the co-primary endpoint.

So, trying to put this all together a little bit, it may be possible, and again, I don't have the answers, I can't be more emphatic about this and I am not trying to suggest these are my answers or FDA's answers, but we can perhaps fill in some of this table, which would say PORT criteria are one possibility for criteria and it is possible that two or three, or some minimum criteria for parenteral IV inpatient studies, whatever synonym you want to use.

The study design, again, I don't want to go into it. Non-inferiority, might be appropriate, the analysis of microbiology as we, again -- non-bacterial etiologies to the limit of our present technology can be excluded. Again, there is a point for discussion, whether microplasma should be

included in that group is certainly a consideration.

I think it is fair to say, and again, Dr. Nambiar or Dr. Singer or others can comment far better than I, that in-patient parenteral studies in 2008, microplasma per se, is not that common a microbiological diagnosis. Clinical endpoints, as we have discussed, for a lot of reasons, have to include -- have to be to some extent, clinical failure, including mortality as death.

And I do want to make the point that I am not talking about attributable mortality. We are talking about all course of mortality. And a non-inferiority margin that might be possible based on, you know, again, some recent papers that have been presented and some of the data we can glean from the 1930s are potentially justifiable non-inferiority might be ten percent.

I'd like to go through the same exercise -- am I doing okay on time? I'd like

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to go through the same exercise for outpatient oral studies. And again, I have to say throughout this discussion, the regulatory definition is adequate and well-controlled studies and I think, again, it has been brought through what the criteria are. But for the study design, the issue of placebo controls is, again, identical for in-patient studies.

I would also just like to make the point, and I think this very much relates to the point we made earlier regarding PORT scores and, of course, I thought it was well brought out, I think by Dr. Cox, the ideas at the CAP symposium, although patients with PORT one may be less ill, and I say that with a tremendous, I have to say that I have to be very careful when we say less ill because as a doctor, what we can say is the PORT scores, they have a better prognosis. What being less ill or not for a 30-year old who is breathing at a very high rate or is at a very high

temperature, that is more, but we could certainly say they have a better prognosis treated. We don't know what the individual prognosis is for any individual, other than, I think, for treated mortality. There really is no good data on progression for an individual that we can say, that we can take from the past.

Doctors Nelson and Goldkind, I think very well addressed the ethical issues. I thought it was an outstanding presentation yesterday, in placebo-controlled studies. I would just like to add one point, perhaps to emphasize it a little differently than Dr. Musher did, but I thought Dr. Nambiar presented information that was directly relevant to this. We do not know at enrollment if somebody does have pneumococcal bacteremia.

Dr. Nambiar presented a slide summarizing the recent studies based again on Dr. Higgins excellent presentation at the

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workshop. But that, I believe, and correct me if I am wrong, that up to two percent of patients in studies had pneumococcal bacteremia at enrollment. One has to consider, you can't rule those patients out at the time of enrollment, one has to consider the ethics of a placebo-controlled study where the potential that two percent of your patients have pneumococcal bacteremia when we know, to some extent, what the outcome of pneumococcal bacteremia could be, based on the studies from the early 1930s. I just want to make that point, which I think perhaps is consistent with some other points but again, is a point, you know, with our issues the committee needs to discuss.

Regarding study populations, I think the same criteria exist. Should a PORT criteria be used? And if so, what the criterion again, what the specific criterion for enrollment ought to be, is again a discussion for the committee, should these be

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the same as intravenous studies. It is difficult.

I certainly don't have, you know -- I could certainly say that Dr. Nambiar did present in her summary what the expected distribution might be in patients who were to present an oral outpatient studies in the year 2008. And obviously to some extent, I won't say obviously, but the issue of placebo controlled studies becomes more difficult as PORT scores increase.

Regarding bacteriology, I think the same issues I discussed earlier should be obvious. We again have the issue of bacteriologically confirmed. If we do wish bacteriologically confirmed, we also have the issue of pathogen requirements.

And this really gets to the point of whether we treat CAP as a unified entry, or we treat it as separate entries. If we treat it as a unified entry, then we say you can enroll anyone in such a study, we would then

have to decide whether we want to power separately from pneumococcal pneumonia, or we would power just for CAP, but if we treat it as a unified entry, then you would have to discuss the issue of whether there should be minimum number of pathogens would be appropriate within that. Because again, just belaboring the obvious, we would not probably want to have a study that involved only mycoplasma pneumonia.

I would state, though, that powering separately for each pathogen has substantial issues, which again, I suspect the committee will address. And I do want to raise the point that, similar to the in-patient studies, there would be the assumption, I would make that assumption, and the committee can discuss it, that whatever diagnostic technology is available, one would use that to enrich the population as much as possible by excluding non-bacteriological infections, which may be more common in a

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population of outpatients.

Regarding clinical endpoints, obviously, we believe mortality may be a less relevant endpoint for oral studies, given the outcome by -- the prognosis by PORT classification that was presented earlier. However, the consideration of endpoints for oral studies really yields a conundrum that I thought was very well discussed by the FDA statisticians yesterday is that, to some extent, we as FDA recommend PROs for clinically meaningful endpoints.

What we're talking about, to some extent, with the patient reported outcome, and recognizing that there is obviously signs in this case, I mean, you know, it will be very, very difficult for somebody intubated to fill out a patient reported outcome. I don't want to get into issues with that, but assuming these are all patients who can do some of the things Dr. Musher suggested earlier, we're talking about, in our PRO, using a well-

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defined mechanism to to some extent, validate and quantify points Dr. Musher made earlier.

However, this yields the conundrum that we brought up yesterday is that, even though a PRO may be a preferred endpoint or means of measurement, the fact is, we have absolutely no historical data on which to base a non-inferiority margin for a PRO. So, how we get around this issue that every endpoint in a non-inferiority must be based on existing evidence, which leads us to the, you know, again, the argument of how we use, what we would like to use as an outcome, is one, I think, that deserves further discussion, and I suspect there will be.

If we cannot use a PRO, then we have to go to separate systems. One approach I think is re-examining the data that Dr. Singer, I think, well presented for microplasma, yesterday, you know, particularly can be looked at more carefully. Failure, of course, should be a part of any clinical

endpoint, you know, similar to inpatient studies. But of course, failure -- well, we suspect failure is to be less likely in this situation. We have seen it from the studies that were discussed yesterday that, overall, the responses are very, very high.

And I would also raise the point, which Dr. Temple brought up yesterday, and I think it was presented again in a different context by Dr. Musher, that other endpoints may be useful, for example temperature, even though they do raise concerns that Dr. Fleming, I thought, brought well.

I had a longer discussion of this in an earlier draft of the talk. I just wanted to make the point that there is no prohibition against using state of the art diagnostics in clinical trials, to some extent, assuming they are double-blinded, et cetera, and randomized. And one would encourage, if there are state of the art diagnostics, to enrich populations. There's

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no prohibition against doing that, obviously.

And I would just mention, perhaps as a plug, FDA just had a relatively new biomarker qualification process for approving the use of diagnostic tests. That is absolutely the wrong word. It is not approval. So please, if we can retract that from the transcripts, I would do so. But they do have a process whereby FDA will review the proposed use of biomarkers in clinical trials in a process that is wholly separate from labeling, or clinical use.

Regarding non-inferiority margin for oral studies, this is difficult. This is predicated on a specific endpoint, and we have to have, obviously, the non-inferiority margin, as I have said repeatedly, has to be based on historical information, and it has to be adequate and well-controlled. And of course, it is predicated on the specific endpoint. That's done.

I will mention again, there is

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something perhaps to be taken from the previous studies that Dr. Singer had said, you know, Dr. Singer had cited, the Kingston study, and some of those other studies. And I would mention in passing that the ideas and recommendations were suggested yesterday. And Dr. Fleming, I believe, also had some recommendations. And some of the various documents that have been presented have good recommendations, and there have been previous FDA recommendations, as well.

So, going back to the filling out the table, I have put in bold, perhaps IV, because again, going back several slides, I think perhaps it is likely there may be easier or less challenges faced by the committee in discussion of IV studies. That's not to say the answers are, and it is not to say that discussion would not be invaluable. That is why we are all here. But perhaps it may be slightly easier to come to some consensus.

But again, this is what I have

listed before, and each point in the questions is a subject for discussion. Oral studies are difficult. One could, you know, report what the PORT criteria should be. If a PORT criteria is appropriate is an issue of discussion. Non-inferiority versus superiority, I think it has been emphasized that non-inferiority, you know, that superiority studies do not have to be against placebo. Again, as I mentioned earlier, an active controlled superiority study does present different issues in this context. I think Dr. Talbot had mentioned that a little bit, but by no means it's a point for discussion. Again, what the endpoint should be, whether these should be confirmed, or by pathogen.

And I just want to make a point of what I describe as clinical criteria, and I want to put on my quasi-clinician hat at this point, is to some extent when patients are ill, they are ill, and to some extent, where

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they go from being very ill may not matter as much how they got there as it does in patients who are less ill.

And when I say something like clinical criteria, we all want bacteriological confirmation. That would be ideal, and I think everybody has said that. However, to some extent, people who are more ill, who you don't have a bacteriological confirmation, one may accept that the fact is their prognosis may be worse as a fact of the, that they're more ill, and may not be as demanding of a bacteriological confirmation as it would be for patients who are less ill.

And again, I have also mentioned in the oral studies of whether bypathogen analyses are necessary, or how that might be approached. Clinical endpoint, again, I am just citing clinical failure. That is a point for more discussion. For clinical endpoints here, we have PROs, we have clinical failure. I omitted separate symptoms are also a

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possibility. And of course, mortality is part of this. I only do not mention that because we accept that mortality may be very, very low.

And whereas it's easier to throw out a number, and again, these are ideas being thrown out, I certainly think any number I would throw out for a non-inferiority discussion would be worthless the second I threw it out, so that I'm not even broaching any possibility at this point, since it is a subject for discussion.

I think that's the end of my slides, and I very, very much appreciate everybody's attention. Thank you.

ACTING CHAIR TOWNSEND: Thank you very much, Dr. Gitterman. We now have time for questions for Dr. Musher, Dr. Gitterman, or opportunities for clarification.

Dr. Wong-Beringer?

DR. WONG-BERINGER: I wonder if Dr. Gitterman could expand on his point about

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the FDA's position on biomarker qualification process.

DR. GITTERMAN: Absolutely. That's an advertisement, but let me tell you what the relevance is. And I have to think this is a tremendous step by the Agency. There is not uncommonly, and I have to say in absolute honesty, I do not think this is directly relevant to this meeting. So just let me, I don't want to digress on this too much.

But we are always faced with the idea that there're studies that can be done that either may not be approved, or not approved for a specific indication, but are invaluable in certain situations. I could cite the example of the early studies with PCR for HIV, which were invaluable at a time that nothing was marketed for that indication. But under certain controlled conditions, as reviewed by microbiologists et cetera, et cetera, they gave invaluable insight, and

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could be very very useful in that.

FDA now has a process where any interested group, sponsors, individuals, et cetera, and I believe Dr. Rex may be familiar with my closest study group actually has just done this where measures that are believed to be invaluable in clinical studies for which the data exists, can submit these to FDA. It is not a approval process, but they can get through a very well described process a review, and it is a, I could show you, it is a very sophisticated flow diagram, which I don't quite understand, but can then perhaps get, and I cannot use what I, I do not want to use the word -- I will say, listing, that use of this measure, in this particular way, in this particular sense, may be possible, even though it's not approved for that use, so that it's of value in clinical trials, so that every sponsor coming in afterwards does not have to re-justify that use.

I'm so -- there are obvious

examples, which I could share with you privately. I would hate to say this in public, because then I'll be on the record, let's say, Steve Gitterman said blank could be used. But there's good examples of that. But I don't think it's necessarily, in 2008, there is nothing on the table, to my knowledge, right now.

What I do want to point out is that it is important because FDA really is committed that, as better diagnostic tools can come along, even if they are not necessarily of clinical value, but they are of value in experimental studies, I think there is a route available for their use. But wipe it out for this discussion.

ACTING CHAIR TOWNSEND: Dr. Dowell.

DR. DOWELL: I just had a question, a clarification, for really anyone from FDA. So it seems like we are categorizing the approvals under oral versus

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IV. The question is, is it possible that a drug would get approval with, let's say, less stringent criteria under oral, but then end up being used for a more severely ill patient in the future, or what are the safeguards against that?

DR. COX: Yes, so typically, you know, oral drugs have been labeled as for mild and moderate community-acquired pneumonia, reflecting the disease population that they are usually studied in. You know, IV drugs typically studied in sicker patients, you know, then end up getting an indication it is not qualified as mild to moderate. So, we try and reflect the population in whom we have information, who we have data on. You know, where safety and efficacy has been shown. And to your question is, you know, could somebody under the practice of medicine use a drug that was approved for mild to moderate community-acquired pneumonia in a sicker patient? And, you know, under the practice of medicine,

physicians may, with their individual patients, you know, decide to do so.

But we do try and describe, you know, in the label, the types of patients in whom the drug has been studied.

DR. DOWELL: I guess, if I could follow up on that, and I apologize if everybody else knows the answer to this, but so if a drug has an oral and an IV formulation, how does that work?

DR. COX: So usually labels for drugs that have both an IV and an oral formulation, it would just say, community-acquired pneumonia, and list the microorganisms that were included in the study program in sufficient numbers.

So it wouldn't have the qualification of mild to moderate. It would just say, community-acquired pneumonia. There are probably some instances where the label does in fact say mild, moderate, and severe, also. So, it would list that full range, but

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it wouldn't be a qualified indication in the sense of the oral drug just specified mild moderate.

DR. DOWELL: Can I do one more follow up on that? I'm sorry.

ACTING CHAIR TOWNSEND: Follow up on that same question?

DR. DOWELL: Same issue.

ACTING CHAIR TOWNSEND: Sure.

DR. DOWELL: Just to make sure I am understanding it. So, if we set up criteria with different non-inferiority margins and so forth for oral and IV formulations, and I've got a drug that has both an oral and an IV formulation, wouldn't I use the less stringent criteria for the purpose of approval, and then my IV formulation could be used for severe patients, or what's the check and balance on that?

DR. COX: Yes, I'm not sure I'm completely following your question, but the non-inferiority margin that you set would be

something that would be done during the stage of protocol development, and, you know, as we have talked about over the course of the day, there are certain factors that are going to impact upon the size of the treatment effect that you would expect in the population that you are studying. You know, age has been brought up, bacteremia. So, the margin is going to be something that will be determined by who you are studying. So I don't know that, you know, the way you are describing it it is almost that you are trying to figure out is there some way that somebody would be able to have an inappropriate margin. And I think it really is derived from the types of patients you are studying would be determined early during the protocol stage.

Does that help, or could you restate your question?

DR. DOWELL: I'm sorry if I am being -- here is -- I will try and restate the question.

So, if we set up criteria for enrolling patients for IV formulations and oral formulations, the IV formulations, let's say, require a PORT score of three and higher. So it's really hard to find those three and higher patients. But it's easy to find patients with a PORT score one, and two, and so forth. Then it makes sense that I am going to enroll patients with mild illness, and get the approval, which would then apply for oral and IV formulations, and the drug could then be used for patients with more severe illness. Or am I getting that backwards?

DR. COX: Well, I think that, you know, the types of patients that you enroll, I mean, if you are enrolling just patients who have very, very mild disease, then in order to have an informative study there, you will need to understand what the treatment effect is in that group.

That sounds like a group of patients with milder illness that you would

study in an oral study. I mean, if you are going to do an inpatient study of patients using an IV drug, presumably, you are going to be enrolling patients who are sicker, who have more severe disease. And in that setting, the non-inferiority margin will be different than what you would have in an oral study, because there should be, from the data we've seen, a larger treatment effect there.

And in essence, what you study is how we would label the drug. So if you only studied really mild patients, that would be reflected in the label. And we talked about the difficulty of understanding the treatment effect in that group, so it wouldn't be an easy thing to do.

DR. TEMPLE: I mean, these are some of the things that are going to get discussed, but most of the data that have been presented are on people showing a clear effect of antibiotic treatment are on people who are relatively ill. So one of the big questions

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is whether it is going to be possible to do a credible study in mild disease at all. Can you define a non-inferiority margin, and if you do, is it so small that the study will have to be of immense size?

So, I think the expectation is that the easiest thing to study is going to be people who are fairly severely ill, which will get a claim for pneumonia. And it's going to be hard to think of how to do that in products that don't have both an IV and oral form. Now, after a drug is then approved, could somebody take a very sick person and treat them with only the oral drug? Well, yes, people are allowed to do things in practice that aren't the best therapy. They could do that. But one thought is that the labeling would say, for community-acquired pneumonia, and it would reflect, the demonstration of effectiveness would be in very severe people, but you would also believe that people who have lesser illness would be improved by the

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same drug. Maybe those people would just get an oral form to start, but the product would be available in both forms. Does that help?

ACTING CHAIR TOWNSEND: Does that answer your question?

DR. DOWELL: I'm not totally clear, but I think I will be by the end of the day. I am going to wait awhile.

ACTING CHAIR TOWNSEND: Okay. Dr. Calhoun.

DR. CALHOUN: So, can I ask for some clarification on the Agency position? Because I heard something that maybe I misinterpreted, but I heard Dr. Gitterman say that every outcome, and I'm presuming that you meant for primary outcome for the studies, must be based on pre-existing data. And so the question is, the bulk of the data that we saw yesterday and this morning have been mortality data.

So is it the Agency's position that the only outcome on which non-inferiority

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study could be based is mortality, and if so, I think it goes to the matter that Dr. Temple was talking about, this defining a non-inferiority margin when the event rate is so low is a difficult thing to do, and may not be a clinically relevant question to ask.

DR. GITTERMAN: I think I will defer to Dr. Cox and Dr. Temple, perhaps, to address that.

DR. COX: The question about what is the correct endpoint based on what we know from historical data is actually one of the questions that we're posing to the Committee here today. You know, you've seen the data, you've seen what's out there. And one of the things we are asking you is, is given some of the uncertainties, how can we use that information to inform endpoints that might be appropriate for a current day trial. Would it be mortality? Would it be patients who get urgent rescue? You know, folks who might have, in the days gone by, you know,

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progressed to die, patients with complications, and then, you know, in that list of possible endpoints, are things of lesser severity.

So that's one of the issues I think we are trying to get some clarification. We use sort of the scientific basis for what we know from the past data, and how that might translate into a current day endpoint that would be appropriate, and be informed by what we know from past data.

DR. CALHOUN: So the Agency is amenable to outcomes other than mortality?

DR. COX: Yes, that's one of the things that we are trying to, you know, hear from the Committee on. You know, is there a justifiable endpoint, other than mortality, that can be based on that information?

DR. CALHOUN: Okay, thank you. I misunderstood the context, then.

DR. TEMPLE: Well, I just wanted to add something, and ask maybe Tom to

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comment. A very low event rate for, say, death, doesn't mean the study is not informative. If you believe the event rate in the absence of treatment, which is what we're talking about here, is 30 percent, and in your treated groups, it's zero, that's okay. That rules out a difference of 30 percent, or 10 percent, or anything you like.

You don't have to have bad events in the treated population. In fact, if the drug is very effective, you won't. That's okay. That doesn't mean the study can't be done. You are looking at the difference between the treatments. And if there are no events, which could be because you put the wrong population in, but we will ignore that for the moment, if there are no events, you rule out that difference pretty readily. Tom? You don't have to have any deaths in this trial to show if you believe you know what would have happened in the absence of treatment, which is the whole point here, you

don't need any events of those kinds. That's okay.

DR. CALHOUN: But the point is, for the reasons that Dr. Musher mentioned, we're not looking at placebo controlled trials. We are looking at trials in which effective therapy is being compared to a new potentially effective therapy, and therefore, you would expect that the event rate in both arms would be low.

DR. TEMPLE: That's what I said. That's okay. That is not an impediment to reaching a favorable conclusion. That's all right. In fact, if drugs are very, very effective, then the event rates are low. What you need to know, as best you can without measuring it, because nobody is going to leave people untreated, you need to know what the event rate would have been in the absence of treatment. That's what your margin is, or some fraction of that margin, because you don't want to have all of the deaths.