UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH
(CDER)

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ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE

MEETING

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TUESDAY, APRIL 1, 2008

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

Chairman, presiding.

PRESENT:

GREGORY TOWNSEND, M.D. Acting Chair
LCDR SOHAIL MOSADDEGH, PHARMD, Executive Secretary

CAROL A. KAUFFMAN, M.D. Member
BERNHARD L. WIEDERMAN N, M.D. Member
ANNIE WONG-BERINGER, PHARMD, Consumer Representative
KENNETH R. MAKOWA, Temporary Consumer Representative
WILLLIAM J. CALHOUN, M.D., F.A.C.P.

Temporary Voting Member
SCOTT DOWELL, M.D., M.P.H., Temporary Voting Member

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PRESENT: (CONT.)

THOMAS FLEMING, Temporary Voting Member
DEAN A. FOLLMANN, PH.D., Temporary Voting Member

DANIEL MUSHER, Temporary Voting Member

JAN E. PATTERSON, M.D., Temporary Voting Member

CYNTHIA G. WHITNEY, M.D., M.P.H., Temporary Voting Member

JšRGEN VENITZ, MD., PH.D., Temporary Voting Member

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

EDWARD COX, M.D., FDA

STEVE GITTERMAN, M.D., PH.D., FDA

JOHN JENKINS, M.D., FDA

KATIE LAESSIG, M.D., FDA

SUMATHI NAMBIAR, M.D., M.P.H., FDA

MARY SINGER, M.D., FDA

ROBERT TEMPLE, M.D., FDA

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C-O-N-T-E-N-T-S

P R O C E E D I N G S

(8:00 a.m.)

CALL TO ORDER AND OPENING REMARKS

DR. JENKINS: Good morning. Welcome. Appreciate everybody being here so early in the morning.

I'm Greg Townsend. I'm the acting chair of the Anti-Infective Drug Advisory Committee.

Just by way of apology before we get started, this is my first time doing this. So I may stumble along the way. Please bear with me. But, Sohail, I hope you keep me on track.

A couple of housekeeping things before we get started. Bathrooms out the door, left-hand side of the hallway, if anybody needs them.

In the green folders for the folks sitting up here there are menus. Please circle what you want on the menu, put your name on it, and those will be picked up at the

break.

When you are speaking - most of us have done this before - please turn the microphone on, and also, to use your name. This will be recorded, so we need to make sure that we know who is speaking when you speak.

When there are times for questions, if you just want to raise your hand so Sohail will write your names down, and then you can put your hands down, so you don't need to keep them up for 10 minutes or so.

We have, as I'm sure you've been aware, a lot of things to discuss over the next two days. This is going to be, I think, a very exciting couple of days. As Ed Cox reminded me several times on Friday, this may be the most exciting two days that this committee has ever had. Actually, I'm not sure exciting was the word he used, but something along those lines.

We have a lot of interesting things to talk about, and I think some fairly

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groundbreaking material to go over.

So we have a lot of things on the schedule that we'll need to get through, so we'll try very hard to keep on schedule.

I think we'll go ahead and go with the introductions. Then there'll be a couple of more housekeeping things to take care of, and then I'll turn it over to Sohail.

So I'll get things started again.

INTRODUCTION OF COMMITTEE

ACTING CHAIR TOWNSEND: I'm Greg Townsend. I'm at the University of Virginia in the Division of Infectious Diseases.

Dr. Jenkins?

DR. JENKINS: Good morning. I'm John Jenkins. I'm the director of the Office of New Drugs at FDA.

DR. COX: Ed Cox. I'm the director of the Office of Anti-Microbial Products at FDA.

DR. SINGER: Mary Singer. I'm a medical officer in the Division of Special

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Pathogens at FDA.

DR. NAMBIAR: Sumathin Nambiar, medical team leader, Division of Anti-Infective and Ophthalmology Products.

DR. LAESSIG: Katie Laessig, deputy director of the Division of Anti-Infectives and Ophthalmology Products at FDA.

DR. WHITNEY: Cynthia Whitney, chief of the respiratory diseases branch at CDC.

DR. FOLLMANN: Dean Follmann, head of biostatistics at NIAID.

DR. WEIDERMANN: Bud Weidermann. I practice pediatric infectious diseases at Children's National Medical Center, George Washington University in Washington, D.C.

DR. FLEMING: Thomas Fleming, professor of biostatistics at the University of Washington.

EXECUTIVE SECRETARY MOSADDEGH: Sohail Mosaddegh, the designated federal officer for FDA's Anti-Infective Drug Advisory

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Committee.

DR. KAUFFMAN: Carol Kauffman. I do infectious diseases at the University of Michigan and the VA Hospital in Ann Arbor.

DR. CALHOUN: Morning. I'm Bill Calhoun. I'm a professor of medicine at the University of Texas in Galveston.

DR. VENITZ: I'm Jergen Venitz, clinical pharmacologist at Virginia Commonwealth University in Richmond, Virginia.

DR. PATTERSON: Jan Patterson, infectious disease physician at the University of Texas, Health Science Center, San Antonio, and South Texas Veterans Health Care System.

DR. DOWELL: Scott Dowell with CDC.

MR. MAKOWKA: Ken Makowka, patient consultant for the FDA.

DR. WONG-BERINGER: Annie Wong-Beringer from the University of Southern California School of Pharmacy. I practice as infectious disease pharmaco-therapist.

DR. REX: John Rex, vice president,

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infection, Astra-Zeneca, and also relevant to today, I am a board-certified internist. Infectious disease is my specialty. I have practiced infectious diseases for more than 15 years.

DR. MUSHER: Sorry to be late. I'm Daniel Musher from Houston, Texas, a little jet lagged.

ACTING CHAIR TOWNSEND: Thanks for being here. Thanks, everybody, for making it.

I have a prepared statement that I'm going to read, and then I'm going to turn over the proceedings to Sohail.

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 of these issues, and that individuals can express their views without interruption.

Thus, as a gentle reminder,

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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.

A press conference will be held in the Washingtonian Room immediately following the meeting today.

Also the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch.

Thank you.

CONFLICT OF INTEREST STATEMENT

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EXECUTIVE SECRETARY MOSADDEGH: Good morning. I'd like to first remind everyone to please silence your cell phones, if you already haven't done so.

I'd also like to identify the FDA press contact, Christopher Kelly, if you are here, to please stand up.

We'll get hold fo him and introduce him at a later time.

The Food & Drug Administration is covering today's meeting of the Anti-Infective Drug Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972.

With the exception of the industry representative, all members and consultants are special government employees or regular government 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 the

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Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 USC 208 and 712 of the Federal Food, Drug & Cosmetic Act, FD&C 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 USC, 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's 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 USC 208, their employers.

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

Today's agenda involves discussion of new product development and clinical trial design for both mild and moderate severe community-acquired pneumonia.

A primary object 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 discussion could affect all products and firms to the same extent.

Based on the agenda for today's meeting, and all financial interests reported by the committee's members and consultants, no conflict of interest waivers have been issued in accordance with 18 USC 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.

Brad Spellberg, an FDA-invited guest speaker, would like to acknowledge that Pfizer, Astellas, Gilead, Novartis, and Enzon-supported research grant or contract project of his.

In addition, Dr. Spellberg serves as a consultant to Pfizer, Merck and Astellas.

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

Dr. George Talbot, an FDA-invited guest speaker, would like to acknowledge that Alexa, SorexaShire, 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 Advisers, 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 on behalf of regulated industry.

Dr. Rex's role on this committee is to present industry interests in general, and not any one particular company.

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Dr. Rex is employed by Astra-Zeneca.

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

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue. Thank you.

The press conference room that Dr. Townsend mentioned is incorrect. If there is one tomorrow, we'll update you tomorrow. But there is no press conference scheduled today.

Thank you very much, Dr. Townsend.

FDA INTRODUCTORY REMARKS AND REGULATORY BACKGROUND

DR. COX: Good morning. I'm Ed

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Cox.

And I first want to start out by welcoming everybody here today to our meeting. We really do appreciate the committee members coming to join us and to meet with us here today to provide advice.

I'd also thank all the members of the audience who have come to join us, also.

The topic for discussion today is discussing clinical trial designs for community-acquired pneumonia.

And, really, we are here today to get advice from the committee about informative, safe and ethical trial designs that will allow us to evaluate new drug therapies for their safety and efficacy in the treatment of community-acquired pneumonia.

We hope that, over the course of this two-day meeting, that we will be able to work through some of the key parameters in the design of a community-acquired pneumonia trial.

We are also very interested to hear the scientific rationale in the discussions, the evidence relied upon, and the reasoning in arriving at recommendations for clinical trial designs that may be possible trial designs for studies of community-acquired pneumonia.

And I thought it would be helpful just to back up for a minute and think about some of the background, some of the history of sort of how we got to where we are here today.

And, no question, anti-bacterial drugs provided really a major advance in medicine. They were discovered many years ago, and have been incorporated into clinical practice, and have been a very important advance that save lives in the treatment of infectious diseases.

Clearly they are a standard of care for community-acquired pneumonia, and have been so for years.

And some of the information,

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because anti-bacterial drugs have been adopted and used for so long, some of the information that we need to look at to try and understand the effect of drugs for community-acquired pneumonia comes from literature from many years ago. And you'll see that this information, although old, is really very valuable information in helping us to understand what anti-microbial drugs do in community-acquired pneumonia.

As we look, too, at new drug applications and the science of clinical trials and NDAs, we've seen that over time there has an advance in the clinical trials that support indications for respiratory tract infections.

And if we look to the early drugs, we can see that the labels in earlier drugs are typically microbiologically focused, so they may be focused against a particular organism within the body site being secondarily. And then as we look forward in

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time, clinical trials advanced to include more homogeneous populations of patients. So patients with a particular infectious disease condition located at a particular organ site - and this is important, because having patients with similar types of conditions allows for appropriate evaluations, and for the natural history of disease that is the same across the studies.

So we moved from microbiologically focused labels to the broader indication of respiratory tract infections, which is a composite of upper respiratory tract and lower respiratory tract infections, to an indication of lower respiratory tract infections that typically included patients with both acute bacterial exacerbations of chronic bronchitis, and along with patients with community-acquired pneumonia, to the more current indication which we've been awarding more recently, and that is an indication for community-acquired pneumonia.

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And these trials are all specifically patients with community-acquired pneumonia. The studies that we've seen in the recent past have been noninferiority designs with margins of 10 to 15 percent. And typically the margin choice was based on convention, rather than a clear justification based on the evaluation of available data.

And within the community-acquired pneumonia indication, we've also, for oral drugs, when there is just an oral preparation, have modified the indication to clarify that it is just for mild to moderate disease severity, reflecting the types of patients that are typically enrolled in these types of studies.

I thought it would be helpful just to put out sort of a prototypical indication for community-acquired pneumonia. Typically the indication is, the drug name is indicated in the treatment of infections caused by susceptible strains of the designated

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microorganisms and the conditions listed below, with the community-acquired pneumonia indication, including a list of the prototypical pathogens that we associate with community-acquired pneumonia.

This slide, it's not meant to - I don't mean for you to read through it all. But it provides, again, the progression over time from microbiologically focused labeling to the broader indication of respiratory tract infections to the lower respiratory tract infections indication to the current-day community-acquired pneumonia indication.

Listed beneath each of the indications are a number of drugs. I don't expect you to read through that. But if you'll look at just a couple, you'll notice the microbiologically focused, we start with penicillin G and penicillin V, and you almost see a progression over time as you move down the list toward the community-acquired pneumonia indication that we currently grant.

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Again, if you look at the types of drugs here, you will see that some are IV drugs or drugs for parenteral administration. Some drugs are both available in IV or oral forms, and some of the drugs are available just as oral compounds.

Just to talk about the importance of what we're here to talk about today, clearly there is a public health need for new therapeutic options. Anti-microbial resistance limits our current therapeutic choices, and also, we can expect that it will chip away at the therapeutic options that we have in the future.

We also need informative trials to characterize the safety and efficacy of new drugs that are being studied. This allows us to weigh the risks and benefits of these therapies.

So really, as I think about these two things, these two elements, they do, in essence, go hand in hand; that is, the

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importance of having new drugs in this area also supports the importance of having adequate characterization of safety and efficacy.

And this provides quality information that allows health care providers to have the information that they need to use these drugs appropriately.

One of the things that makes this particularly challenging is the disease that we are talking about here today, and that is community-acquired pneumonia, a disease for which there is a risk of progression or extension of infection. So this makes this study of disease particularly challenging.

The clinical trials for community-acquired pneumonia need to be informative, need to not expose patients to significant risks, need to be ethical and acceptable, and there are some strategies that can be used to minimize risk, and some of these strategies we are already using, even in current day,

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previously conducted noninferiority studies, because there are a number of therapeutic options that are available today, if a patient is failing therapy, typically that patient will receive alternative therapy to try to prevent progression of disease in the setting of failing study therapy.

Other things that can be done to minimize risk include patient selection, and that's reflected in part in that typically what we're doing with oral drugs is, we're studying patients in the outpatient setting with oral drugs, whereas inpatients, patients who are more severely -- are typically getting IV therapy.

Just a few comments on drug product approval. In 1938 the Federal Food Drug & Cosmetic Act was passed, and required clearance of drugs for safety and pre-marketing, but did not require evaluation of efficacy.

In 1962, the FD&C Act was amended

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to add a requirement for demonstration of effectiveness based upon substantial evidence. The Act goes on to further define substantial evidence a evidence consisting of adequate and well controlled investigations, including clinical investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved on the basis of what could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the labeling, or proposed labeling thereof.

And the regulations go on to further describe adequate and well controlled studies. And I'll just read from these. I think they really do provide meaningful information on adequate and well controlled studies and their purpose.

The purpose of conducting clinical investigations of a drug is to distinguish the

effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation.

And then, within the different types of adequate and well controlled trials, one of the types of trials is described as an active treatment concurrent with a control trial. And the regulations talk about when you might use such a study, and the test - this is a situation where the test drug is compared with the known effect of therapy, for example, where the condition treated is such that administration of placebo or no treatment would be contrary to the interests of the patient.

And then the regulations also go on to describe one of the things that is particularly important to understand if you are doing a study where you are trying to show that a test drug is similar to an active drug. 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 detect the difference between treatments.

Similarity of the test drug and active control could mean that either both drugs were effective, or that neither was effective.

The analysis of the study should explain why the drug should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies, the active control drug.

And on this slide, this is sort of an oversimplified version to try to illustrate the concept that I just read from the regulations.

You will hear this described in more detail from other speakers, who will go into more detail, but just the basic concept here.

If you are doing a study where you

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are comparing a test drug to an active control drug, if the two appear to be coming out about the same with regards to the response rate, in a study where you only have a test drug and an active control drug, one of the other pieces of information that you need to know is, if a placebo had been included in the study, how would it have performed.

Well, in this case where there is a large treatment effect we see that an inactive or placebo drug would not have had much effect. So the finding here of the test performing about the same as the active is informative.

And this is contrasted with the other pole, the spectrum, where you have a test drug performing the same as an active control drug, but in this situation, there is a high spontaneous resolution rate of the condition, so that if you had had a placebo included in the study, the placebo would not have performed that much different from the

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active control and the test drug, making it difficult to discern that the test drug or the active control had an effect in this study.

And obviously, these are just two examples, two poles of the spectrum here. There are all sorts of variants that you can imagine of intermediate cases. But I present them, and you will hear a lot more discussion on this today.

So, one of the real challenges of community-acquired pneumonia trials is to try and quantitatively estimate the effect of the active control drug over the placebo. In a study that we would do in the present day, based on what we know from previous information - and another topic that we'll be talking a lot about today is treatment effect. And I think one of the important things to keep in mind as we talk about treatment effect is that treatment effect reflects the types of patients that are enrolled in the study, the severity of the disease they have, the

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endpoints and timing of their assessments and other factors. So really the historical information informs us about treatment effect, but also provides, in essence, some conditions or factors describing what that treatment effect could possibly relate to.

And as we go through the information, you'll see that the types of information that we have obviously doesn't match exactly the situation that we have in the current day. So one of the issues for discussion, too, will be how to address uncertainty, given that the data, much of the data that we have on treatment effect is from an era of the past.

And so, in looking at this data, it is important to account for uncertainty. And one way to do this is through discounting, and obviously judgments have to be made. And it's important to understand the rationale and the reasons for judgments that we're making.

The ultimate goal here is to have

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informative trials.

When we talk about new drug applications, typically we see studies in in-patients, in situations where there is an IV formulation available for the drug. If there is also an oral formulation, the oral formulation may be used for step-down therapy, and may also be used in additional studies where the oral formulation is used as initial therapy.

The indication in this setting is typically described as community-acquired pneumonia.

And then the other type of study that we typically see in new drug applications are outpatient studies of community-acquired pneumonia, and in this setting, typically, we are seeing studies of oral anti-bacterial drugs, so this is when an IV formulation wouldn't be available.

And the indication is typically modified with mild to moderate CAP to reflect

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the type of population that's usually studied.

So key topics that we will try and cover over the couple of days that we have to meet and discuss this. We will review what we know and don't know about community-acquired pneumonia and issues in clinical trial design.

One of the key things will be getting at this issue of treatment effect based on available data. And as we think about treatment effect, we need to think about what population we're talking about, what disease severity, what types of conditions they have, and then also what endpoints are we looking at. How does that relate to the historical information?

Also, there are other key parameters that we'll touch on, too, as we get to the questions.

So we'll be trying to address key issues and clinical trial designs for community-acquired pneumonia and describe possible informative CAP trial designs for

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both studies of IV drugs and studies of oral drugs.

We'll talk about endpoints, populations, ask questions about non-authority studies and in what settings they can be done, and also in what settings superiority studies might be able to be done.

So over the course of the two days we've tried to provide a number of presentations that I think will help inform the discussion.

First off, as folks may know, we recently had a co-sponsored workshop with the Infectious Disease Society of America in January. It was a very productive discussion and provided an opportunity to move the science forward here about clinical trial designs and community-acquired pneumonia.

So we'll be reviewing some of the discussion from that workshop. Then we'll be moving on. We'll be hearing from the Infectious Disease Society of America, and

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also, the American Thoracic Society and the American College of Chest Physicians.

We'll have a presentation on ethical considerations in community-acquired pneumonia trials. We'll hear about non-inferiority trial design for community-acquired pneumonia.

We'll move on and talk some about the historical data; again, very valuable information, but information from years past.

Then we'll move on and talk about contemporary trials, describe what we've seen in recent application so that people have a feel for the types of information that typically comes in in the trials that we have been seeing recently.

We'll hear a presentation on the approaches to setting a non-inferiority margin, some discussion of exposure response analysis and how this might inform treatment effect.

And then we'll hear discussion of

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considerations in CAP trial designs.

We'll take a break after what should be a fairly full day of presentations, and on the second day, come back and hear a clinician's scientific approach to pneumonia, and considerations in design of CAP studies.

And then we'll have time to move to the questions and discussion period. And I think we'll come to it in just a minute. I'll go through the questions just so folks know where we're going, but we've got a lot of ground to cover.

And I think the questions in the discussion period will be very helpful to hear folks' rationale and, when they are providing advice or recommendations, to understand some of the underlying rationale and/or evidence to support that will be very helpful.

Then I was going to go to the questions next, because I thought it would be good to. I thought it would be helpful just to run through the questions so folks know

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where we're going.

The stem here is applicable to both questions one and two, and I'll just read through them.

To rely on noninferiority studies for new drugs to treat CAP, we must be able to estimate the effect size a control drug would have on the primary endpoint used in the current trial.

The agency has presented information, or actually we will present information, on the historical experience to suggest a reduction in mortality with point estimates ranging from 18 to 25 percent in the observational studies, and from approximately 10 to 19 percent in control trials.

These data are derived from patients with pneumococcal lobar pneumonia.

So the first question we'll ask is, can these data be utilized to select a noninferiority margin for a contemporary CAP study for an IV drug in hospitalized patients.

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And then, if the answer to that question is yes, then we'll work through and try and understand the particular population at endpoints that that might apply to.

So the first subquestion asks, to what severity of pneumonia or type of patients would it apply, and how should severity be defined.

And then, should a microbiologic diagnosis be necessary for inclusion in the primary analysis population for the trial? And if so, what organisms should be included?

Should strategies be utilized to enrich the population?

And then we'll ask a question about endpoints. And this reflects that, in early studies when there may have been very few or very limited therapeutic options, there may not have been, in essence, the opportunity to provide alternative therapy, whereas in current day clinical trials, if somebody is failing, typically that patient will get

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additional therapy in order to try and salvage a situation where the patient is not responding.

So this question asks, please discuss whether the evidence which shows a treatment effect based on mortality can be linked to endpoints which are used in current noninferiority CAP trials; for example, clinical success or failure; and if so, how.

And then the typical endpoints that might be included in a clinical failure endpoint could include things such as mortality, patients receiving rescue therapy because of progression or complications, lack of resolution of clinical signs or symptoms such that additional anti-bacterial therapy is administered, or lack of resolution in signs and symptoms at the time the primary endpoint is assessed.

And then a question about appropriate comparators. The historical evidence for treatment effect is based on

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studies which evaluate penicillin, sulfonamides and tetracyclines. Given the need to preserve the treatment effect, the effect of the comparator agent over placebo or no treatment in a future study, what are the appropriate choices for comparator agents? We're interested in hearing the committee's thoughts and advice on this issue.

And then, in a setting where a noninferiority margin can be - if, in fact, the committee believes that a noninferiority margin can be defined for this population, we are interested in hearing what that particular margin would be, based on the types of patients that have been described in earlier parts of the questions as being appropriate for this type of study.

So this question asks, what is your best estimate of the treatment effect size that the historical data support for treatment of hospitalized community-acquired pneumonia reflecting the severity from the

earlier part of the question in a future CAP trial, and what is your recommendation for a noninferiority margin that preserves a portion of the treatment effect for a CAP trial in this population with the endpoints discussed above.

And through the course of the two days here we'll have more chance to talk about M1 and M2.

The second question asks a series of questions related to studies of what typically would be oral drugs. It's sort of a corollary set of questions directed at oral therapies.

So given the information presented mostly from historical data on the treatment effect of drugs for CAP in patients with penumococcal or lobar pneumonia, please address the following questions on trial of outpatient CAP.

So studies using an oral drug. Can a treatment effect be reliably quantified

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for a noninferiority study of outpatient community-acquired pneumonia? And then if so, to which patient populations would this information apply with regards to disease severity and microbiological etiology? What endpoints should be utilized, and what is the supposed noninferiority margin? And the data to support the proposed noninferiority margin.

We then go on and ask, can placebo-controlled trials be carried out in less severely ill patients with community-acquired pneumonia. And if yes, how can the risk be minimized? What patient population should be enrolled? And what endpoints could be evaluated?

And then also, if there are other suggestions about potential study designs that would allow for an informative trial of outpatient CAP, we'd certainly be interested in hearing those.

Question three gets to the issue of, if you have an IV therapy and you are

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studying that, what role might that have in informing about the effect of oral therapy.

So in a setting of hospitalized CAP as described in question one above, one could study therapy with an intravenous formulation administered initially with subsequent step-down therapy to an oral formulation as a means to support the use of the oral and IV formulations for severe disease.

This leaves the question of whether the finding of efficacy for severe CAP would provide evidence of efficacy that could be used to support efficacy of the oral formulation for less severe; for example, mild to moderate CAP.

So do you believe the finding of efficacy in more severe CAP supports the drug's effect in less severe CAP, even though the drug has not been directly studied in less severe CAP?

And then the final question: if

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the available evidence for setting a noninferiority margin in current CAP trials is derived primarily from studies of patients with CAP due to streptococcus pneumonia, should noninferiority studies include patients with other etiologies of CAP?

And then if no, what additional studies are needed to include other anti-bacterial drugs, or show that the drugs work for other anti-bacterial organisms typically associated with the CAP? And we've listed some of these here.

So those are the questions. I just thought it'd be helpful to run through those so folks know, as we're going through the discussions, some of the things that we'll be trying to address when we get to the discussion and question portion, and I look forward to the committee's discussion and advice. I think it'll be a very full two-day meeting.

And I thank you all.

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ACTING CHAIR TOWNSEND: Thank you very much, Dr. Cox.

All right, next presentation will be from John Alexander on key issues from the FDA IDSA workshop that Dr. Cox mentioned.

KEY ISSUES FROM FDA-IDSA WORKSHOP

DR. ALEXANDER: Good morning.

I'll be presenting a summary of some of the key issues discussed at the recent FDA-IDSA workshop.

So this public health workshop was held on January 17th and 18th of this year. The goals of the workshop were to examine critical issues in the design and conduct of trials of the safety and effectiveness of anti-bacterial drugs and the treatment of CAP; the implications of emerging scientific tools that assist in the diagnosis of the etiology of CAP; and to discuss clinical trial design and statistical considerations in demonstrating efficacy in clinical trials of CAP.

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On each day of the workshop, a clinical scenario was described as a focus for the day's presentations and discussions. The day one presentation was of a patient with CAP not requiring hospitalization, a 35-year-old male with a three-day history of URI symptoms with a sudden increase in cough of one day with purulent sputum and fever. On physical exam, his temperature was 38.3 Celsius; his respiratory rate was 18; and exam findings included crackles at the right base.

A chest X-ray was obtained that showed bilateral lower lobe infiltrates, right greater than the left side.

The day two presentation was of a patient hospitalized for CAP, but not requiring ICU care. A 65-year-old female with mild COPD diabetes who was taking an oral hypoglycemic agent; hypertension with one previous hospitalization for congestive heart failure; and a smoker who had a 35 pack-year history.

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Her symptoms included increased sputum, increased dyspnea, and fever of one day's duration. Her temperature on exam was 39.2 degrees Celsius. Her respiratory rate was 24. And O2 SAT was 89 percent on room air; went up to 92 percent on two liters of oxygen.

Her physical exam findings included definite left-sided crackles, and no rubs. After looking at her history and physical exam findings, she was given a PORT Class IV score, and a CURB 65 score of two.

Her chest X-ray showed a left lower lobe consolidation with an air bronchogram and a large heart.

So I thought it important to describe these scenarios for a couple of reasons. First, they describe the types of patients typically enrolled in studies of oral anti-bacterials for the patient in day one, or for intravenous anti-bacterial studies for the patient who was described on day two.

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Though some might argue that the patient with a PORT score of four, and a chest X-ray that showed clear left lower lobe consolidation is kind of rare for our IV studies as well.

Second, I think these scenarios are important as a useful reminder of the patients treated in clinical practice, which is something to keep in mind as the advisory committee hears over the next couple of days the presentations that are given.

Third, I wanted to use these cases to illustrate an important point about the primary purpose of clinical studies of CAP, which is to determine the efficacy of the anti-bacterial.

So let's say that the patient in the day one scenario was treated with an anti-bacterial drug, and had symptoms improve over the course of three to four days. This would be viewed as successful treatment in clinical practice, but how much does it demonstrate the

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efficacy of the anti-bacterial if I told you that his sputum culture grew streptococcus pneumonia?

Then how much would you think the anti-bacterial demonstrated effectiveness if I told you his sputum culture showed no growth but an NP swab was obtained that showed he had influenza?

Similarly for the day two scenario, if the patient showed minimal improvement in symptoms over a week's period of experimental treatment, and then was switched over to another treatment, did that treatment lack effectiveness?

What if I told you that the patient was found to have a bronchial lesion causing partial obstruction of the left lower lobe? How much is the drug actually a part of the failure of this patient?

So moving on to the CAP presentation - the many presentations that were given at the workshop, I'm actually going

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to have a lot of help in summarizing the results of the workshop, because there were a lot of presentations that were given that discussed the issues of noninferiority trials, their clinical importance, the noninferiority trials that had been submitted in the recent past, the historical data on treatment effect, some interesting PK-PD relationships that are attempting to get at the question of what a placebo rate would be, and various perspectives of clinicians, consultants, IDSA and industry that were given at the workshop.

And you are going to hear presentations over the next couple of days at the advisory committee, that offer much of the same information that was discussed, although again, many of these AC presentations are informed by the previous discussions that we had at the workshop, so they are not exactly the same thing.

So from my presentation of some key issues, I wanted to discuss a little bit

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about some discussions that were held at the workshop that focused on diagnostics; their main purpose was discussion of methods to improve clinical and microbiological diagnosis in CAP trials, and I'll go through some of these.

As a reminder, this slide is from one presentation, and it shows the most common pathogens associated with CAP, based on a composite from several studies. Similar pathogens are seen across what is considered to be a continuum of disease from those patients with mild outpatient CAP to those patients who have severe disease requiring ICU care, with pneumococcus as the most common organism.

One of the main points made at the workshop was about - about anti-bacterial testing is that convention methods are limited.

Blood cultures, when they are positive for pneumonia pathogen, are fairly

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reliable, but blood cultures have a low yield.

Sputum testing is also limited, since many patients are unable to produce a sputum sample.

There are interesting results, though, that tell us a little bit about how common pneumococcus is. There was a study that was done of 109 patients with community-acquired pneumonia from Spain. Seventy-seven of those patients were hospitalized, so it included a mix of patients.

The pathogen was identified by conventional methods in 54 out of 109 patients who were tested, with 19 of those being mycoplasma, and nine each being strep pneumoniae and Clamydophila pneumoniae.

What the authors of this publication did was that they then decided to explore further the 55 patients who had no - an unknown cause based on conventional methods of testing.

And they did transthoracic

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aspirates that were obtained for culture, genetic and antigen testing. When they looked at these transthoracic aspirates, they identified strep pneumoniae as the etiologic agent in 33 percent of the patients who had an unknown cause based on conventional methods.

Now, unfortunately, this kind of testing with transthoracic aspirates is not something that we would ever consider as practical for use in clinical trials.

Now we do have another method of identification of patients with streptococcus pneumoniae. The Binax urinary antigen test was approved by the Center for Devices in August of 1999.

The device label includes the results of a prospective study of patients with suspected streptococcus pneumoniae sepsis or lower respiratory tract infection.

In the sensitivity and specificity of 90 percent and 75 percent, or in comparison to blood culture in this cohort of patients.

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The antigen test has also been used specifically in a study of CAP patients. This testing used concentrated urine samples, which is different from just a random urine sample that is obtained in patients. But what they showed was that, for patients with bacteremic pneumococcal CAP, 10 of 13 of them had a positive urine antigen test. For patients who had non-bacteremic pneumococcal CAP, presumably most of these were patients who had pneumococcus on sputum culture, nine in 14 were positive for the urine antigen test.

And then in addition 69 out of 300 patients who had CAP but no pathogen isolated were also positive on the urine antigen test.

Moving on to then atypical pathogens, urinary antigen test for Legionella pneumophila has largely replaced other methods of diagnosis. In the U.S. this is reasonable, since up to 90 percent of Legionella infections are believed to be related to type

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one.

The sensitivity and the specificity of the urine test in comparison to culture for Legionella are shown.

For mycoplasma serologic testing is still the current standard that we have.

For Clamydophila there is a microimmunofluorescence assay that is used for serologic testing, but it has a poor correlation with culture or PCR results.

For PCR assays, there are multiple in-house assays that are used, but these really need standardization. So I do believe there needs to be a lot more development in terms of the diagnostics for atypical pathogens.

For viruses associated with community-acquired pneumonia, there is the xTAG respiratory virus panel which was just recently approved in January of 2008.

This is a PCR system for viral DNA and RNA detection. The device identifies the

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viruses listed here. The use of this is, of course, for diagnosis of viral infections and it's based on testing with a nasal pharyngeal swab.

The question is, then, how do we use this within the settings of clinical trials. Should it be used for exclusion of patients from CAP trials? What about the co-infection with bacteria?

So the use of this clinical test needs further exploration as to how we would actually apply it within the setting of clinical trials.

One of the other presentations of the workshop discussed the use of procalcitonin as a biomarker. Procalcitonin is a hormokine, a hormone that has some cytokine-like responses that is produced by parenchymal cells.

It appears that procalcitonin increases in response to sepsis, but is attenuated by the - is attenuated by cytokines

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related to viral infections.

PCT appears promising as a biomarker for selecting patients more likely to have bacterial versus viral respiratory tract infections. However, the experience with PCT is limited to its use at a few centers. It has not yet been used in trials of drug development, but may become a useful tool in the future.

Another presentation discussed the development of the PORT score, also known as the pneumonia severity index. The PORT score was developed as a prediction tool for short-term mortality in CAP patients. And what I want to do is go over the calculations of PORT scores with you.

So starting with an adult patient who has a clinical diagnosis of pneumonia, you look at the patient age, the presence of these coexisting conditions, and these findings on physical exam. And if none of these are present, then the patient is assigned a risk

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class of one. If any of these factors, you answered yes to, then you move on to assign the patient to risk class II to IV according to the next step of the prediction rule.

The second step involves assigning points for age, and, of course, women get docked 10 points. If you are a nursing home patient, though, you get an extra 10 points. And then you have these point scores that are added for patients based on history findings or findings on physical exam, and these laboratory studies. And you get 10 points if you have an effusion on chest X-ray.

The points that are scored are based on baseline findings. The scores are added up. And then you assign patients to a risk class of I through V based on the scores that they receive. So those numbers for those scores are over here.

Now this table is from the New England Journal article that describes the development of the PORT score, and I wanted to

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make a couple of points here.

The mortality rates that are quoted in association with particular PORT scores are based on the results of the PORT validation cohort, which is here shown in this column.

Especially for risk class I through III you should note that there were very few deaths; so only seven patients who died in over 1,000 patients in risk class I through III.

If you look at the validation cohort and the derivation cohort, that are shown over here in these columns, the mortality rates do vary a bit within a risk class, especially if you look at the PORT score of IV, the PORT score of III, and the point here is that you should understand what the PORT score is, which is, it's a number, a score that is associated with increasing mortality as the risk score increases, but you shouldn't associate necessarily a particular

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PORT score with any particular rate of mortality.

So PORT score is a good prognostic score for mortality. It does include elements that are related to severity, but it's not necessarily a true severity score.

This is one of the points that was made at the workshop presentation.

It is a good tool for reducing unnecessary hospitalization. It's been studied in that manner, so that you can use it as part of a decision-making process to decide when a patient is actually able to be treated as an outpatient.

It is, as was described by Dr. Fine himself, intended to supplement and not override physician judgment.

The other important point that I would make about the PORT score is that this tool was studied in treated patients. So all of those patients that were used to evaluate and validate the PORT score are patients who

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were treated.

We actually don't necessarily know what the PORT scores and what the mortality risks would look like for untreated patients.

And that's important, because there is the question of, would it actually predict mortality in treated patients - I'm sorry, in untreated patients. And I think that the historical data will address some of the questions related to that.

So then, moving on to the workshop discussions, over two days we had two separate discussions looking at these two different scenarios. And overall what I understood was that there were many concerns about the use of noninferiority trials, questions about the selection criteria, the diagnostics being used in current trials, the endpoints and the analyses that are done.

But it appeared to be a consensus that noninferiority trials could be supported for at least some CAP patients.

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We got the clear message from industry participants as well as those who are participating in the workshop presentations that there was a need for clear guidance for CAP trials, and that's part of what we're here with the advisory committee over these next two days to try and get.

For mild pneumonia, there was more debate about the use of noninferiority trials, though most still questioned the ethics of either a placebo-controlled trial or the practicality of superiority.

There were a lot of questions that were raised during the two days of discussions about the ethics of placebo control even for mild patients, and that's one of the reasons that later on in the day we have a presentation fo an ethical framework for, sort of, consideration of those questions.

There was also a lot of discussion about disease severity, because it is not really clear how we classify disease severity.

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The use of a PORT score and CURB-65 were both discussed. And it appeared that most people were satisfied that, with the PORT score, we have sort of got the best that we've got at this moment in terms of looking at the question of severity as it relates to, sort of, the overall prognosis for mortality.

In terms of clinical endpoints, there was an emphasis in the discussion at the workshop on the use of PRO tools for mild pneumonia. And I think that is wonderful that it is objective as a tool. But then the question is, how can we relate the PRO measure to the historic evidence that we have of treatment effect for pneumonia.

There was also a lot of discussion of the use of mortality for severe pneumonia, with the advantage that, also, this is an objective measure, as long as you are not getting into particular causal mortalities.

Oh, I'm sorry, PRO stands for Patient-Reported Outcome tool. And I think

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there will be a little bit more discussion about that later on in the session.

Back to mortality, mortality was considered objective, and appears to be most related to the historical data as you'll see. But the disadvantage is that it's uncommon even in the higher PORT scores. And the question is whether the treatment alternatives that are available now actually prevent mortality to such an extent that it is not really useful as a measure.

There was also the discussion then about how to come up with a composite endpoint, and I think again you will be hearing a little bit more about endpoints later on.

So finally, I'd just like to acknowledge the co-chairs of the workshop, the rapporteur, and all the different participants. These are people who made presentations at the two-day workshop.

I also want to point you to a

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particular website that is available on the FDA website that has the transcripts for the two-day meeting: the different presentations that were given, because I think there is a lot of valuable information that is there about the future of CAP trials.

Thank you very much.

ACTING CHAIR TOWNSEND: Thank you very much, Dr. Alexander.

We are now going to move on to some presentations on the IDSA perspective from Dr. Dave Gilbert and Dr. Brad Spellberg.

IDSA PERSPECTIVE

DR. GILBERT: Thank you.

I'm Dr. Gilbert, and I'm here representing the Infectious Diseases Society of America, and greatly appreciate the opportunity to address the committee.

And we want to thank Dr. Alexander for giving us an extra 15 minutes, as I look at the program, anyway.

As you've heard, we did have a

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very productive workshop in January, and it was a dream of the Infectious Disease Society of America to bring together all the interested constituencies in one room for two days.

We have our physicians, both clinical and academic, who want to - who see an impending disaster. I think everybody in this room has heard of the Infectious Disease Society of America's Bad Bugs, No Drugs campaign. We have this perfect storm of increasing numbers of resistant organisms and fewer and fewer drugs in the pipeline.

Industry keeps telling us that they have attractive new targets; they have improvements on older drugs, but they simply cannot take the necessary financial risk because of unclear regulatory guidance.

As you've heard already this morning, the FDA has a strong and important mandate to approve drugs that are safe and efficacious, and that that approval should

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indicate that the new drug is superior to previous drugs, or if a noninferiority design is utilized, that the approved drug has a substantial treatment effect.

I don't need to repeat most of this. The workshop was jointly sponsored by IDSA and FDA, with participation of industry. The proceedings will be published within the next six months in the Journal of Clinical Infectious Diseases.

And it was after listening to all of the wonderful presentations at the workshop that the IDSA decided to synthesize a position statement that is our consensus on the information as it presently exists.

So I'm going to give the main points that are in the position paper. Several caveats up front; 1) I would hope that the members of the committee would look at the entire position statement. Due to time constraints, we only can present some highlights during the next 30 to 40 minutes.

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Also I want to acknowledge the eloquence of the co-chair - one of the co-chairs - I guess both co-chairs were eloquent. But Dr. Fleming was exceedingly eloquent, raising to our attention the importance of the clinical design - of several clinical design criteria.

Dr. Powers has also spoken and published several documents in this regard.

And the standard has been raised that future trials should be reproducible. The data should be reproducible. The data should be reliable. That we should have quantitative endpoints. We should be able to demonstrate a substantive treatment effect. And we think that all of that is possible.

Another standard which I think is of utmost importance for this group is that future clinical trials also have to be feasible. I think it's easy to generate a clinical trial standard and regulatory requirements that are absolutely perfect in

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design and will totally drive away anybody who is interested in conducting such a trial, because it would be prohibitively expensive and/or take several generations to accomplish.

So the feasibility standard, I think, has to be included in the dialogue and in the considerations.

So placebo-controlled trials; we believe that placebo-controlled trials for community-acquired pneumonia are not justifiable, feasible or ethical.

The previous speaker mentioned that, even in mild community-acquired pneumonia the mortality rate was only seven out of 1,000. Well, but that's seven human beings. If that's somebody you care about, I'd have a hard time asking for informed consent for a placebo-controlled trial for any type of pneumonia.

And furthermore, and we won't have time to go into the details, but Dr. File and Dr. Shintag (phonetic) have data on mild

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community-acquired pneumonia that everybody would say is perfectly feasible for outpatient community-acquired pneumonia treatment, et cetera, et cetera; and the patients progressed over the next several days into severe or more severe pneumonia that required hospitalization, and those patients due to that time relationship, would have been mis-classified initially.

We believe the data demonstrate a substantive treatment effect of anti-bacterial therapy, and hence, there is a strong basis for noninferiority trials.

Dr. Spellberg is going to follow me here momentarily, and will dwell on, primarily, pneumococcal pneumonia because that is where the bulk of the historical data is.

But I think it's also true that there is a substantive treatment effect for every organism that has been studied. And I think that could be strong evidence again for a noninferiority trial design.

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So even though we're talking, just about pneumococcal pneumonia, I think the basic principles apply to all the micro-bacterial etiologies of community-acquired pneumonia.

The regulations require constancy in the study population, and we'll show you data where we think that that is possible to achieve, using the pneumonia severity index that was mentioned by the previous speaker.

And we do think there are quantifiable endpoints in addition to mortality and global clinical assessment that can be used in the patient-reported observations. Time to clinical events are a few examples of that.

One of the problems that has existed in trials over the past several years is identification of the etiology of the pneumonia, and it seems that we should take advantage of the modern tools of molecular biology. The scene is constantly changing.

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We are getting new tools. You already heard about the -- Luminex's company PCR test for 20 different respiratory viruses, and yes, we have to sort out the possibility of mixed infection, viral and bacterial infection, but the ostrich syndrome doesn't make any sense to us.

If you have these tools available to more clearly identify what the etiology is, why would you put your head in the sand and not use them and frustrate the statisticians so that they don't know if a virus is present or not present in a given patient.

We should be able to improve the homogeneity of patients enrolled in trials of bacterial pneumonia.

So I'm the warm-up act, and now Dr. Spellberg will present some of the quantifiable data.

DR. SPELLBERG: Thank you very much, Dave.

I, in the interest of time, am not

going to dwell on the epidemiology of CAP. I think we all know that CAP causes a tremendous burden on the U.S. health care system in terms of the number of cases, economic burden, and number of deaths per year.

But, before we actually get into the data, I do think it's worthwhile pointing out that the viability of CAP as an achievable indication for a drug, is critical to the continued development of anti-bacterials in general.

CAP is a major market, especially in the context of anti-infectives, which generally represent much smaller markets than a lot of other drug types. In previous years, industry has had a clear understanding of what kinds of trials needed to be done to get an indication for CAP.

Those trials were usually successful, and, because the disease is common, it's easy to enroll - or relatively easier to enroll patients into these studies

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than other indications.

If we lose CAP as a viable indication, this will not only eliminate our ability to get new antibiotics for respiratory infections, it will dramatically decrease industry participation in anti-bacterials of all types at earlier stages.

So it's very important that we come to resolution on this issue.

Now we don't have time to go through all six points that were considered in the position paper, so we're just going to summarize the discussion on four of the questions that we considered in the position paper, starting off with the issue of selection of noninferiority versus superiority studies for CAP. We'll also talk about the ability to use disease stratification in order - disease severity stratification in order to fulfill the constancy assumption.

We will talk about the basis of noninferiority margin selection and

appropriate outcome measures.

So starting with the issue of whether we should we doing superiority or noninferiority studies for community-acquired pneumonia, I think there are two subsets to this question. We can focus, A, on the issue of superiority studies; and B, on the issue of noninferiority studies.

With respect to superiority studies we have two questions again. One is, are superiority placebo-controlled studies ethical, And two is, are superiority active drug controlled studies feasible.

When we talk about noninferiority studies, we know from International Congress of Harmonization, E9 and E10 documents, that there are two components that we need to have in order to justify an NI study. We have the historical evidence of sensitivity drug effect, or HESDE standard, which basically means that a prior study has shown that antibiotics -- in this case antibiotics -- are

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superior to placebo or no treatment.

And we have the constancy assumption, which tells us that the trials in which superiority to placebo were established are relevant to modern trials.

So we need to ask the question, have antibacterials been shown to be more effective than placebo or no treatment for CAP. And are these prior studies in which this question was asked relevant to current studies?

So I'm going to start off this group discussion for this whole issue with the issue of, is it feasible to do an active comparator superiority study for CAP.

At the workshop, Karen Higgins gave a nice presentation from FDA showing that all recent registration trials for CAP have been of noninferiority design, and virtually all of them met their predefined, noninferiority endpoints.

Furthermore there are three meta-

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analyses in literature which go through dozens of clinical trials of pneumonia, comparing different antibiotic regimens, either regimens including atypical coverage or not, or regimens comparing short-course therapy to longer-course therapy.

And these three meta-analyses found absolutely no difference in outcomes.

So what we see from the data that are available is that the - it is extremely unusual to actually find a difference in efficacy of antibiotics in modern studies. And this means that there is a high likelihood that if you attempt to do a superiority active control study for CAP that you are going to fail to find superiority, even if the drug is efficacious relative to placebo.

And this high risk of failure makes it fairly infeasible to consider investing in conducting such a trial from an industry perspective.

The other thing I'd point out from

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these sets of data are that -- one of the questions the committee is going to ask to comment on is, if we look at just the historical data, must we use Beta-lactam therapy, sulfa or possibly tetracyclines as the comparator for a noninferiority study.

And the answer is, if we believe - and we'll get into the data in a minute - if we believe that the historical data show that those three types of drugs: Beta-lactam, sulfa and tetracyclines, are superior to placebo, and noninferiority studies subsequently were shown that macrolides and quinolones are noninferior to those comparators, then, by definition, macrolides and quinolones could also be used in future noninferiority studies. So I think that is another important consideration.

Now the issue of placebo-controlled superiority studies has been briefly introduced by Dr. Alexander. At the workshop, there was near-uniform agreement

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amongst the physicians in the room that placebo was unethical for hospitalized patients, due to the risk fo bad outcome.

There was a current of thought that ran through the workshop that you might possibly think that placebo could be ethical in the setting of mild outpatient pneumonia in otherwise healthy patients where the risk of adverse sequelae is lower.

But what wasn't generally appreciated at the workshop, even though Dr. File presented some of the data, is that these trials have already been done, and this really brings me to my key point on placebo control, and IDSA's key position.

Placebo-controlled trials are only ethical if antibacterial efficacy for this disease has not been previously established. And the corollary is if antibacterial efficacy has already been previously established, then placebo-controlled trials are unethical for this disease.

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So let's start looking at the historical data, focusing initially on this population of healthy outpatients with mild atypical pneumonia, where originally it was thought that you might possibly be able to do placebo-controlled trials.

There in fact have been two randomized, double-blinded placebo-controlled trials in exactly this setting in military recruits. There was a focus on serologically confirmed mycoplasma pneumonia, but as we will see, other causes were also included, other microbiological causes were included.

The two trials; one compared tetracycline to placebo, the other was a three-armed study: tetracycline, clindamycin and placebo.

And in addition to those trials, there were three other prospective studies which compared macrolides or tetracyclines to either placebo - to either penicillin or no treatment.

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And in those studies, in two of the studies, comments are made that the control arms are very small, because initial responses seen to the antibiotics were felt to be so significant that they did not feel it was appropriate to continue to offer no therapy to patients with pneumonia.

In all five of these studies, macrolides or tetracyclines were shown to shorten the duration of fever, cough, chest pain, chest X-ray normalization and/or hospitalization.

And I don't have time to go in detail through all fives studies, but I think it's worth going into some detail in the first study, which was published in 1961. You can see 290 military recruits with community-acquired pneumonia randomized to tetracycline or placebo; antibacterial was shown to decrease time to defervescence; resolution of cough, fatigue, malaise, chest X-ray normalization and significantly, hospital

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duration.

Even for mild quote-unquote outpatients, these, of course, were military people in the infirmary.

The magnitude of the effect for these markers was significant. By day three, 30 percent of the treated patients were febrile; whereas 95 percent of placebo patients were febrile.

If we look at one of the data tables in that study we can see that the patients were either serologically mycoplasma-confirmed, they were culture confirmed to have viral infections, or they were - they were not confirmed to have mycoplasma and did not have a microbiological confirmation of disease, and frankly, from recent datasets we know that most of these patients would have had pneumococcus as a cause of their mild pneumonia.

You can see that tetracycline significantly improved markers of morbidity in

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both patients with confirmed mycoplasma pneumonia, and in patients without a microbiological-confirmed diagnosis, but not in patients with confirmed viral infection.

This serves as a useful internal control. This drug is not working by some magical placebo effect; it's working by eliminating the cause of the infection.

And similarly in the other randomized placebo-controlled trial, tetracycline was effective, and clindamycin as you will recall, I told you it was a three-armed study, tetracycline, clindamycin, and placebo - clindamycin was as effective as placebo for atypical pneumonia. And tetracycline was effective.

Yet another useful internal control.

Now in addition to these studies looking at mild outpatient pneumonia in otherwise healthy people, there are 11 other studies identified in the literature that have

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compared antibiotics to no treatment for teens and adults with community-acquired pneumonia. Six of these trials used historical controls, so they prospectively enrolled patients that were all given antibiotics, and outcomes in those patients were compared to historical patients from the pre-antibiotic era.

But there were also five concurrent control trials where patients were prospectively given either treatment or no treatment.

In addition to these 11 studies there were multiple pediatric trials. At last count, I think there were five or six. And these trials are summarized by Drs. Bradley and McCracken in a manuscript that is going to be published in the CID supplement with the position paper.

I don't have time to go through these trials, but take my word for it, as you'll see when it's published, that these findings and these trials were basically

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identical to the trials in teens and adults.

Five of the six trials that used historical controls exclusively evaluated pneumonia caused by a culture-confirmed pneumococcus. One of the trials enrolled patients with culture-confirmed pneumococcus but also had patients in which no microbiological diagnosis could be confirmed, so not pneumococcal confirmation.

All five concurrent control studies enrolled patients that did not necessarily have pneumococcus as the cause of their infection.

And the concurrent control trials, this was in the era before randomized, double-blinded and placebo-controlled trials. These - but they did use rudimentary randomization schemes. These investigators at the time were not completely dimwits, and so they attempted to do the early versions of randomization, and that was either by alternation of therapy by patient, alternation of therapy by admission

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ward - patients admitted to Ward X got drug X; patients admitted to Ward Y got no specific therapy. That was usually a surrogate for admission day, because patients admitted on different days were admitted to different wards, and there were also alternations by day. So those were used in the concurrent controlled trials.

If we look at these studies in aggregate, what we find, as I already emphasized, is that five of the six historical controlled studies did not - or looked at specifically pneumococcal pneumonia, one, did not necessarily isolate specifically pneumococcal pneumonia, and as I mentioned, all five of the concurrent controlled studies included patients that did not necessarily have pneumococcal pneumonia, usually in the context of -- they had lobar pneumonia on chest X-ray.

We know from multiple trials done in the last 20 years that you cannot use the

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chest X-ray appearance to predict what the organism is going to be. Lobar pneumonia does not translate necessarily into pneumococcal pneumonia.

If we calculate a weighted average of these studies, we find that, in the historical controlled studies, the vast majority of these patients of course having pneumococcal disease, the mortality for untreated patients was 38 percent, and the mortality for patients that were treated was 12 percent.

So, by calculating weighted average, the absolute mortality reduction was 26 percent with a 95th percent confidence interval of 24 to 28 percent. This is a rather large mortality benefit.

In the concurrent controlled studies, it's not surprising that the mortality rates are somewhat lower, because these trials included patients that did not necessarily have pneumococcus. Nevertheless,

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we see the weighted average of mortality in untreated patients was 23 percent, and the weighted average of mortality in treated patients was 7 percent, for an absolute reduction of 16 percent, and the lower limit of 95th percent confidence interval was 10 percent; again, quite a substantive reduction in absolute mortality.

Now we can sit here and quibble about the fact that we can't control for internal quality of these studies, and various other factors of meta-analyses. I didn't do a funnel plot for example. These are the data that we have. We are not going to get more data. And you know this is the disease that -- we are not talking here about erectile dysfunction or bladder hyperactivity. We are talking about the disease that William Osler called the captain of the men of death in the pre-antibiotic era. This is a fatal illness.

So we are going to have to do the best we can with the data that are available.

The conclusion, I think, from the historical data is that antibacterials are highly effective for the treatment of community-acquired pneumonia. They reduce mortality by 25 percent absolute for pneumococcal CAP; that's the number needed to treat for mortality of IV.

There are very few interventions in all of medicine that have mortality number needed to treats of four.

If we look at patients from the concurrent studies that included all comers with CAP, not necessarily pneumococcal CAP, the number needed to treat is still seven: a major impact.

So placebo-controlled superiority studies are unethical because we know that antibiotics are effective for CAP, and this is the explanation for why no one has done such a trial in the last four decades.

Active comparator superiority studies have a high likelihood of failure to

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demonstrate superiority, even if the antibiotic is effective compared to placebo.

So if we've met the historical evidence of sensitivity to drug effects standard, the next question is, can we meet the constancy assumption standard to justify noninferiority assumption. And the question is, can we use disease severity stratification to help us answer that question.

Now Dr. Alexander did a nice job of going through the PSI scoring system, and that has actually saved some time for me. The only thing I do want to point out is that it is a scoring system that was derived from a very large database, retrospective database of 14,000 patients, and it was prospectively validated in another large database of 38,000 patients.

Now as Dr. Alexander showed us, the scores are based on age, vital signs, comorbidities, allowed values, and assigning points for each.

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But I think the key concept that I'm going after here is that by far - and anyone who has ever actually calculated a PSI score while admitting a patient to the hospital knows that this is the case - by far the biggest driver of the PSI score is age, because you get one point for each year of life. If you are a female, you subtract 10. But still all the other criteria in the scoring system are worth between 10 and 20 points with two exceptions: cancer and acidemia, you get 30 points.

That means if you are 50 years old you are already starting off with the equivalent of three or more comorbidities or abnormal vital signs. And in fact in clinical trials over the last 15 years, it's been shown repeatedly that age correlates closely with the PSI score.

Now five of the historical datasets break down mortality of pneumonia by age. A couple of them even assign baseline

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disease severity of mild, moderate or severe.

And if we try to separate the mortality by age groups, and we estimate that most patients who are under 30 years old are going to end up in a PSI class of two to three, just by virtue of the fact that they are not going to have enough points to get up to four, because they are young, and they don't get enough points for their age; or if 30 to 59 is probably most of them are going to end up at about three to four; and greater than 60 most are going to end up in the four to five range.

If we break the age apart like that and estimate a weighted average of mortality, we make two observations that are significant. The first is that the overall reduction in mortality is seen across all these age groups. Even in the youngest patients, we see an average mortality reduction of 11 percent on an absolute basis.

And then it goes up to 27 percent

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and 45 percent as the age increases.

The second point that I really want to make here is, focus specifically on the mortality of treated patients in each of these age groups. Less than 30 years, the mortality, one percent with treatment; 30 to 59 years, mortality of 5 percent with treatment; greater than or equal to 60 years, a mortality of 17 percent with treatment. So remember those numbers.

So as I told you, mortality with treatment from the historical dataset: 1, 5 and 17 percent.

If you go to the modern PORT validation cohort and calculate an average mortality for the classes that I estimated were comparable to age, two to three, three to four, and four to five, there is an eerie similarity between the mortality, from the average mortality of these classes in the PORT validation cohort, and in patients that were treated with antibiotics in the historical

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datasets.

And I think in retrospect, perhaps this is not so surprising. The point can be made that medicine in the `30s and `40s is different than medicine today; that the world was different, and how can we compare. The one thing that wasn't different was that 30-year-olds were 30-year-olds, and 50-year-olds were 50-year-olds, and that's still true today;

So if you are using a scoring system that is heavily driven by age, perhaps it's not surprising that that scoring system allows you to estimate similarities between populations from the `30s and populations today.

So we think that this -- the use of the PSI scoring system can allow us to fulfill the constancy assumption to allow us to estimate the benefit of antibiotics in modern studies.

Now what about non-mortality

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historical endpoints? In the pre-antibiotic era there are trials, and there are textbook chapters that tell us that less than 5 percent of patients were afebrile by hospital day three. There were similar rates of improvement, albeit less frequently described, but when they were described similar rates of improvement describing cough, shortness of breath, chest pain, malaise.

Within one year of antibiotic availability the rates of these parameters increased to greater than 60 percent, and in one case was described to be up to 95 percent.

And of course, we've already seen the two randomized placebo-controlled trials and three other prospective studies in young military recruits with mild outpatient pneumonia that similarly show a benefit in clinical morbidity endpoints.

So to summarize where we are with noninferiority rationale, historical studies confirm that antibiotics are effective. For

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CAP, the effect is extremely large and uniformly present in all studies; that's all 11 studies of adults and teens, all five or more studies in pediatric patients, and all five studies using mild outpatient military recruits.

That's at least 21 studies. Every single one of them found the exact same thing. The effect is seen across all groups of age and patient severity, and the effect is not limited to patients with culture-confirmed pneumococcus. Recall the five concurrent controlled historical studies did not exclusively limit their analysis to culture-confirmed pneumococcus.

So we have met the historical evidence of sensitivity to drug effect. And we have evidence supporting the accuracy of the constancy assumption, if we use a stratification system based largely on age.

And so the IDSA position is that noninferiority studies are justified for CAP

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of all disease severity.

If we accept that as a premise, the next question becomes, how do we derive a basis for noninferiority margin selection. ICH E10 tells us that the margin cannot be - the margin for an anti-trial cannot be greater than the smallest effect size that the active drug would be expected to have.

And furthermore, it goes on to tell us that we would like to preserve some of that effect size as well, and that of course, becomes even more important when looking at mortality endpoints as opposed to morbidity endpoints.

If we look at mortality initially, the lower limit of the 95 percent confidence interval of the mortality effect, looking at all patients, or looking at the dataset I showed you broken apart by age, can give us an estimate for the lower limit of antibiotic effect.

And we would, therefore, propose

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in general a 10 percent - a 10 percent margin for mortality, looking across these groups of patients.

Defervescence on the other hand had a much larger effect in the previous studies. Now we can also ask the question, is deferverscence or are morbidity endpoints relevant. I can assure you that, to patients, they are quite relevant. Having a temperature of 102 or 103 is not comfortable, and patients want it to go away.

From a physician perspective of taking care of patients, if the fever goes away, we know that we are successfully treating the pneumonia, and if the fever doesn't go away, we know that we are not, and there are actually clinical studies that validate that you can use morbidity endpoint resolution to show that it is safe to discharge patients to go home, and that they have very low complication rates when these morbidity endpoints are achieved.

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So given the effect size in the historical studies, which you see here, and the fact that this is a morbidity endpoint not a mortality endpoint -- so the imperative to preserve almost the entire effect is not quite as strong for morbidity -- that we propose for defervescence specifically a 15 to 20 percent margin depending on the patient population.

Then we come to the composite endpoint, and this is really the most important one, because nobody is going to do a single endpoint. In general, clinical trials for pneumonia tend to use composite endpoints.

The margin for the composite, of course, depends on which components you include in the composite, and how much you weight each individual component in the composite.

So we have said the data support components including mortality, defervescence, resolution of cough, resolution of dyspnea,

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