chair. Thank you for your cooperation.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationships that you may have with any company or group that may be affected by the topic of this meeting. For example, the financial information may include a company's or group's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The first speaker will be Michael Flavin.

DR. FLAVIN: Thank you and good morning. My name is Mike Flavin. I am chairman and chief executive officer of Advanced Life Sciences. First of all, thank you very much for the opportunity to speak to the committee this morning.

With regard to financial potential conflicts of interest, I will say I am an employee of Advanced Life Sciences. I do have a financial interest in Advanced Life Sciences with stock options, given the fact that I have been an investor in the company. In addition, the company has paid my expenses to attend this meeting.

Advanced Life Sciences is a

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

biopharmaceutical company located near Chicago that has 35 business and technical and scientific professionals focused on the development of cethromycin, which we believe could be a very effective respiratory tract infection antibiotic for the treatment of CAP.

One of the reasons I wanted to address the committee this morning is because we believe we have recent experience in conducting pivotal phase three clinical trials in community-acquired pneumonia, having just completed a two year program a couple of months ago in which we reported the results of our trials that were conducted on a global basis.

In terms of -- I don't have a way to change my slides but if I could, go to the first slide. Thank you.

In terms of community-acquired pneumonia, let me say a few words about our team to begin with. We are a group of scientists and business professionals that

have worked together for over 20 years in drug discovery and development. We have been very motivated in the area of anti-infective drug research and development throughout our careers and through a long-standing work relationship with Abbott Laboratories, we are afforded the opportunity to in-license cethromycin to continue the development of what we found to be a very interesting and promising antibiotic for the treatment of community-acquired pneumonia.

So, we have been motivated then as a team to bring cethromycin forward through pivotal phase three clinical trials to meet what we believe to be a significant unmet medical need and a growing need. CAP, as we have heard in this symposium, is very common. Five million cases reported annually in the U.S. and 80 percent of those cases are mild to moderate. So there is a great need to treat patients that have CAP, that are sick and that are looking for treatments.

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

In fact, if CAP is allowed to progress, it is the sixth leading cause of death in the United States. We believe cethromycin was a drug designed to prevent the progression of mild to moderate CAP into more severe CAP and thus, offer patients and physicians an opportunity to keep patients safe from the downstream, deleterious affects of pathogens like streptococcus pneumonia. In fact, as resistance rates to strep pneumo and other important pathogens continue to rise 40 to 60 percent in some regions of the world, the need for new antibiotics like cethromycin continues to grow.

And because other antibiotics have become weakened through the emergence of resistance, other agents such as fluoroquinolones are tended to be overused, contributing to situations such as clostridium difficile-associated disease and class cross-resistance to the fluoroquinolones in general, which are undesirable problems occurring quite

frequently in the clinic.

It is certainly very important to consider the fact that throughout our history, as we have seen in this symposium, antibiotics have been extremely useful. We have seen great effects throughout history because of the advent of antibiotics. But that doesn't mean we can't improve upon what we already have. In fact, our goals in developing a new antibiotic are those that fill the gaps in current treatments. Can we extend the spectrum of coverage of a new antibiotic? Can we overcome emerging resistance to important pathogens like strep pneumo? And, at the same time, can we have a very safe agent that could be used in a broad population to treat patients that have a need in community-acquired pneumonia?

For a variety of reasons, large pharmaceutical companies have refocused their drug development efforts in favor of chronic diseases. That means that the burden for

coming forward to new antibiotics has, in some respects, fallen to biopharmaceutical companies and biotech firms, stepping in to advance promising antibiotics.

But I think it is important to know that regulatory clarity and consistency, which is what we are discussing today are key factors in the ability of a biotechnology company to develop a new antibiotics under the new paradigm. The new paradigm really is that large pharmaceuticals companies are aiding, are partnering smaller biotechnology companies in bringing new antibiotics forward, in helping to carry the risk. But most of the discovery and development in the new antibiotic field is being carried by biotechnology firms at this point.

It is important to note that the FDA recognizes this new paradigm, that biotechnology companies are getting involved in new drug discovery and development in the antibiotic field and they are working with

firms like ours to help us. They have been very supportive of our efforts to bring cethromycin forward. They have been responsive in answering our questions and they have also been working to elucidate clarity in the regulatory process. And we are very grateful for the workshop that was held in January and the Advisory Committee meeting being held now to help guide us in our future development plans.

We were fortunate enough to in-license cethromycin in 2005 from Abbott Laboratories. I would like to tell you a few facts about our development program because I think it brings for what is required in many respects to conduct pivotal phase three trials.

We selected community-acquired pneumonia because we saw it as the most serious respiratory tract infection. We have been developing cethromycin to treat mild to moderate CAP, in order to have a new agent in

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

the pipeline that prevents the progression to more serious CAP.

Because we wanted to avail ourselves in December of 2005 to the latest thinking and the correct guidelines for the design of clinical trials, we met with the FDA in December of 2005 to confirm non-inferiority trial designs in CAP. So, we had extensive discussions with the Agency, submitted our protocols, went over them. And then, after approval of the protocols for our two pivotal phase three trials, began enrollment in our two trials in early 2006. Over the course of 24 months, we enrolled over 1100 patients at 200 clinical sites worldwide. These two trials, from start to finish, took us two years and cost forty million dollars. Each trial cost about twenty million dollars.

The important thing to note is that clinical trials -- yes?

ACTING CHAIR TOWNSEND: About two minutes.

DR. FLAVIN: Thank you. Clinical trials need to be looked at on the whole. And I think Dr. Rex started to get at that just before my presentation. Clinical trial data in phase three is only part of the application. Extensive pre-clinical animal studies, phase one and phase two trials go into laying the groundwork for a successful phase three trial program. One needs to look at pathogen coverage, clinical benefits, the safety profile, not just the margins of non-inferiority, although they are important.

We found, in our efforts, that non-inferiority trials are a practical method for capturing a wealth of information to demonstrate antimicrobial effectiveness and safety in CAP. We generated much data, a variety of endpoints, clinical cure, fever, all the other clinical signs and symptoms that we have talked about, as well as a variety of safety parameters as well, and have this available for analysis.

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

Remember this, that if we were asked to do a placebo controlled study, it would be extremely difficult. From personal experience in our program, it would be difficult to line up the regulatory agencies worldwide, ministries of health, insurance companies to ensure your clinical trial against the liability of some unforeseen event. Physicians, who often have a mind of their own as investigators, and patients who may or may not want to participate in such a placebo controlled trial when they feel miserable in going to the clinic.

So we believe then that the non-inferiority margins that are currently set up have worked in the past. We have gotten significant and helpful antibiotics. And while it is important to refine our thinking, every time we raise the bar in making it more difficult, even in mild disease to bring a drug forward, it disincentivizes the industry that much more. Because if you think about

it, it is like the carnival game, and I will leave you with this thought, where you take a shot at the basket, you pay three dollars and take one shot. If you make it you win. If you don't, you lose. You have one shot. If you shrink that basketball rim to half its size, I ask you, will you decide to take that shot? As the bar continues to rise, more and more firms shy away from even making the attempt by investing a hundred million dollars to bring an antibiotic to market, because of what lies at the end in terms of phase three suitability.

So, I ask you to consider the whole picture, safety, clinical benefit, and pathogen coverage that is generated by phase three clinical trial data in making a decision about the approvability of a new drug.

Thank you for your attention.

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

The next speak will be Dr. Echols.

You have twenty minutes, Dr. Echols.

DR. ECHOLS: Good morning, since it is still morning, not afternoon. I would like to thank the Committee for the opportunity to present an industry perspective on clinical trial design for community-acquired pneumonia, specifically for those subjects not requiring hospitalization, what I will refer to as mild to moderate CAP.

As an employee and officer of Replidyne which pays for my travel expenses and formerly of Bristol Myers Squibb and Bayer, my perspective is based on my experience in conducting numerous clinical trials to support NDAs for this indication.

I will begin by summarizing the main points I would like the committee to consider. First, CAP represents a continuum of disease from mild to severe. Infection severity is not based on bacterial etiology of the pneumonia but rather the combination of the progression of the infection and the

underlying host factors which include patient immune defenses and comorbidities. While the PORT or Fine classification was developed to predict 30 day all-cause mortality, the score is based more on patient age and comorbid conditions than on physiologic perturbations caused by the infection.

Its utility is to identify patients who can be treated as outpatients with oral antimicrobials. I will show you data from recent clinical trials that clearly show that strep pneumoniae is an important pathogen across all PORT classes.

While there is no contemporary study on the natural history of untreated streptococcus pneumoniae pneumonia, one has to interpret historical data to estimate what the outcome would be. While survival in an otherwise healthy patient might be expected, their clinical course would not be as rapid as provided by effective antimicrobial therapy.

The second point I will demonstrate

is that non-inferiority margins can be established through statistical reasoning and clinical judgment using clinical response, not just mortality, as the outcome demonstrating efficacy. Through a combination of historical data and contemporary studies, a sufficient treatment benefit relative to no treatment can be established.

Finally, I would like the committee to consider that if the treatment benefit of antibiotics for bacterial pneumonia is large, then the real question in establishing an NI margin for future studies is not M1 but M2. In other words, how much less effective can a new antibiotic be, relative to the standard of care? This determination is based on clinical judgment.

This is not the first time this issue of non-inferiority study design has been considered by the FDA. In 1992, in a points to consider document explaining why non-inferiority studies were expected for the

approval of new antibiotics, the Agency made the following statements. With regard to use of placebo, it is "ethically unacceptable not to treat infected patients when therapy is available." And regarding active controlled superiority design, "high cure rates make it nearly impossible or impractical for a new microbial drug product to demonstrate statistical or clinically relevant superiority to an improved comparator agent." At least with regard to community-acquired pneumonia, most clinicians and medical ethicists would agree with these statements today.

Notwithstanding that statistical reasoning that places such inherent value on superiority trials, I think it is important to share with you real world experience regarding placebo controlled superiority studies in indication such as AECB and acute bacterial sinusitis. It has taken Bayer four years to complete a placebo controlled study in ABS in North America. Our own placebo controlled

trial in AECB has been enrolling subjects for more than two years. As difficult as patient enrollment has been at the site level, we have been sobered by the resistance to placebo controlled trials by international ethics committees and ministries of health. These organizations which function under the same ICH guidelines as the FDA have a far different view on the need for superiority trials. The most common reason for rejection is the fact that the placebo controlled studies contradict established treatment guidelines for the indication being studied.

In addition, some European countries, while accepting the rationale for establishing definitive efficacy versus placebo, nevertheless find a study without an active control of no value and, therefore, unethical. Imagine what their response would be for a placebo controlled trial in CAP.

Several years ago, I was directly involved in a large clinical program for an

antibiotic which ultimately was not approved for marketing. This program included seven CAP trial conducted globally, which enrolled over 2100 subjects. All trials characterized patients at baseline by Fine score. Two trials included only Fine class one and two treated with orally administered drug in ambulatory subjects. Two trials involved only hospitalized subjects initially treated with intravenous therapy and the other trials were flexible with regard to location and root of administration.

There was a good recovery of respiratory pathogens, including 1257 typical organisms. The distribution by Fine class in a program where both intravenous and oral formulations were available shows a great preponderance of Fine class one and two, 78 percent.

In 2003, I presented an abstract at the annual IDSA meeting on the analysis of the pooled CAP subjects to determine whether there

was a difference in pathogens defined by Fine class. What we found is that there is very little difference with regards to specific microbial etiology across Fine classes.

Strep pneumoniae was the most common typical pathogen for all groups, followed by Haemophilus influenzae. Among the atypicals, only mycoplasma pneumoniae appeared more frequently in Fine class one relative to the other Fine classes.

We concluded that the etiology of bacterial pathogens was not different across Fine classes and, therefore, the specific microbial cause of CAP was not the reason for differences in mortality observed by the Fine scores. It is also instructive to recognize that of the 353 isolates of streptococcus pneumoniae defined from these CAP studies, 44 percent were from Fine class one.

In order to conduct a scientifically rigorous non-inferiority trial in CAP, we need to establish the benefit of

antimicrobial treatment versus no treatment. While this cannot be achieved through contemporary placebo controlled clinical trials, it is clear to all that antimicrobial therapy first demonstrated with the sulfonamides had a profound impact on patient mortality, due to strep pneumoniae.

Evans and Gaisford, as we have seen before, showed a reduction in mortality from 27 percent to eight percent in two cohorts of lobar pneumonia. Although the study was not randomized in a manner we would find acceptable today, it did have a contemporaneous and well-matched control group.

Using the sulfapyridine dosing recommendations of Evans, Flippin et al reported on a cohort of 100 cases of documented pneumococcal pneumonia. In addition to the low four percent mortality rate, they reported in detail the dramatic clinical response observed by their patients.

Fully 83 percent had a substantial drop in temperature, followed by a prompt, clinical improvement in the first 24 to 48 hours. Their summary at the bottom of that slide, I think, is very informative. They emphasize the dramatic nature in the response to therapy, not just in terms of temperature, but it was followed by a prompt clinical improvement.

It is helpful to illustrate on a patient basis what this means. Cecil's textbook of medicine published in 1942 provides a detailed account of patients who resolved their strep pneumoniae pneumonia spontaneously, with only supportive care. The patient sustained a week of high fever and respiratory distress until the onset of crisis, following which, the patient made a slow recovery.

In contrast, a patient treated with sulfapyridine experienced a dramatic improvement in clinical signs and symptoms

within 24 hours of initiating treatment. It was this dramatic clinical response, as well as the decreased mortality, that made it ethically unacceptable not to treat patients with pneumonia.

While sulfapyridine, chemotherapy, and penicillin clearly had an impact on mortality, using mortality as a primary endpoint in CAP clinical trials for a new oral drug is not appropriate or feasible. Can we ascertain the benefit of antimicrobial therapy based on clinical response from published historical data? While Flippin described clinical response in a cohort of sulfapyridine treated subjects, there was no control group.

In examining the pre-antibiotic era data, we discovered an amazing text of management of the pneumonias written by Bullowa, which details the natural course of clinical resolution in 662 patients with serotype pneumococcal pneumonia. This cohort of survivors received neither serum therapy

nor chemotherapy. From this large dataset, it is clear that even among patients with less severe disease, spontaneous resolution does not occur rapidly. As Dr. Musher explained yesterday, the fact that these patients were hospitalized in the 1930's does not mean they had severe disease.

Crisis, the term used to describe the dramatic drop in fever and clinical improvement, rarely occurs within 72 hours and usually takes seven to nine days. In fully 14 percent of patients, resolution in survivors did not begin before two weeks.

An important controlled study by Agranat et al., was published in the Lancet in 1939. This study included 550 subjects with community-acquired pneumonia treated in four South African Hospitals. Similar to the Evans study, treatment allocation was based on admission ward. Besides showing a difference in mortality, the patients treated with sulfapyridine experienced a much more rapid

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

clinical improvement defined in their study as pyrexia termination. I will show how these data can be used to establish a defined treatment benefit or M1.

Here is the same Bullowa data cohort that was described by Dr. Singer yesterday of the 662 patients with documented pneumococcal pneumonia, showing the day on which they experienced their initial clinical improvement by crisis. By day three, few patients have shown objective clinical improvement. In contemporary clinical practice, a patient who has shown no clinical improvement after several days of antimicrobial therapy would be considered a treatment failure, and alternative antibiotics would be prescribed. In other words, 97 percent of Bullowa's untreated cohort would be considered treatment failures in a contemporary assessment of clinical effect.

The Agranat data is even more

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

compelling, since it includes a control group. By day three, 70 percent of patients receiving sulfapyridine have experienced initial clinical improvement, compared to less than 15 percent of the untreated control group. This difference or treatment benefit is large, 55 percent. The lower boundary of the 95 percent confidence interval is nearly 50 percent. The median difference in time to pyrexia termination is four days. Certainly, a clinically meaningful difference.

All marketed drugs for approval of CAP have been assessed in randomized active controlled clinical trials, where physicians' clinical assessment or, of cure failure was determined at a specified time point post-treatment, often referred to as test of cure. This clinical assessment is global and takes into account early clinical improvement, the normalization of vital signs and laboratory abnormalities caused by the acute infection and the absence of clinical relapse once the

treatment has stopped. Subjects who receive alternative antibiotics with activity in CAP are considered failures.

Physician assessment has been criticized as not being objective. An alternative method of establishing treatment effect, particularly in non-life threatening infections is a patient reported outcome or PRO. The Lamping patient questionnaire has been discussed at this meeting as an alterative method of defining treatment benefit. One must recognize it does meet regulatory definition of a PRO, since it is an administered questionnaire. But more importantly, it represents a new outcome measure and thus, a constancy assumption cannot be verified. There is also no experience using this instrument in a placebo controlled trial from which one might derive a treatment benefit or M1.

This slide illustrates the response curve of the Lamping patient questionnaire

when it was used in a randomized controlled trial called CAP 2000 which compared moxifloxacin to standard of care, which was either amoxicillin or clarithromycin or both. All subjects received oral therapy, mostly as outpatients. And while knowing the time to response may be of interest to both sponsors and clinicians, such an analysis is not suitable for regulatory approval in CAP, since there is no evidence it can distinguish superiority between active therapies and it would be even more difficult to justify a non-inferiority margin and establish a study sample size, based on time to response.

So, can we develop a new, more comprehensive primary endpoint where the M1 benefit established in historical studies is preserved. Call it a composite clinical endpoint that captures early response as clinical improvement within 72 hours, that is supported by objective measures of vital signs and symptoms and that is confirmed by clinical

assessment to document the lack of relapse, once treatment is discontinued. Death related to infection would be considered a treatment failure. A PRO or patient questionnaire could be added as a secondary endpoint for mild to moderate CAP.

There is one contemporary clinical trial, which has been accepted by the FDA as a demonstration of superiority in clinical response. The subjects in this trial were largely defined as having mild to moderate CAP. More than half were treated entirely as outpatients and this meant that half of the cephalosporin group received only cefuroxime.

Based on the FDA medical reviewer's assessment, levofloxacin was superior to the cephalosporin regimen for both clinically valuably and microbiologically evaluable populations.

It is important to note that cefuroxime is not approved for CAP in the United States and the dose used, 500

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

milligrams, is one-third the dose recommended in Europe for the initial treatment of CAP. Thus, while cefuroxime is utilized in this study may be considered sub-therapeutic, it is still likely to be better than placebo. This study is important because it demonstrates the clinical and microbiologic superiority of levofloxacin in a contemporary clinical trial, a study which was carefully reviewed by the FDA and which allowed a superiority claim in the package label of levofloxacin.

The observed difference of 12 percent for the clinically evaluable population and 16 percent for the microbiologically evaluable population underestimates the real benefit of levofloxacin versus no treatment, since the likelihood that the cephalosporin regimen, which included ceftriaxone in half of those patients, had some treatment effect.

The study is contemporary and provides substantial microbiologic

documentation, including pathogens other than streptococcus pneumonia. We believe this study provides one approach for justifying a non-inferiority margin in mild to moderate CAP. Specifically, it supports an NI margin of ten percent for the clinically evaluable population and 15 percent for the microbiologically evaluable population.

For the contemporary treatment of CAP with oral therapy, one cannot derive an NI margin based on previous placebo controlled studies. They simply do not exist. And based on high success rates of available antimicrobials, mortality is not a suitable outcome parameter for NI design.

From the historical clinical datasets, we should conclude that the treatment benefit or M1 is large, even for clinical response in bacterial pneumonia treated with an appropriate antimicrobial drug. To determine M2, the question should be how much less effective than standard of care

is clinically acceptable?

ACTING CHAIR TOWNSEND: Two minutes, Dr. Echols.

DR. ECHOLS: This requires a clinical judgment not statistical reasoning.

It is okay for a new drug to be not much worse than the control drug, since the new drug may have other advantages, such as the ability to treat resistant organisms or having a better safety tolerability profile. It still boils down to benefit-risk assessment, based on clinical judgment.

Before I conclude my comments on NI margins, it is important to understand what population of enrolled subjects is analyzed for the primary efficacy parameter. The FDA prefers two co-primary populations in their analysis. In the past, these have been clinically evaluable and ITT.

Currently, the FDA is requesting the clinically evaluable and mITT, which is the ITT with positive cultures, estimated here

to be about 30 to 35 percent.

A study previously sized to show an NI margin within ten percent with 484 subjects enrolled would now require nearly 1200 subjects, should this same ten percent margin be applied to the mITT. However, if the NI margin applied is 15 percent, the sample size would be 556. Remember that two CAP trials are required for approval of this indication.

Let me summarize what I have tried to present as an industry perspective on clinical trials in CAP.

First, we think the evidence supports the fact that CAP represents a continuum of disease, not separate entities, depending on the triaging of patients able to be treated with oral antimicrobials.

Second, while recognizing the statistical reasoning for superiority trials, neither placebo controlled nor active controlled superiority trials in CAP, even in mild to moderate cap are feasible, even when

one looks at alternative outcomes.

Third, the NI margins for mild to moderate CAP can be justified using clinical judgment and statistical reasoning. A large treatment benefit for clinical response can justify an NI margin, and using composite clinical response parameters, the --

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

The next discussion will be Dr. Goldhammer.

DR. GOLDHAMMER: Thank you very much.

ACTING CHAIR TOWNSEND: Twenty minutes, Dr. Goldhammer.

DR. GOLDHAMMER: Yes, thank you very much.

I have no conflicts to declare, other than the salary and travel paid for by my employer. And I am here to present a perspective from our antibiotic development technical group.

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

We welcome the discussion on the use of non-inferiority trials. These are often required in antibiotic development. We agree that a well-developed guidance will be helpful to sponsors. However, we have concerns with the FDA proposal in two broad areas.

We are concerned about the lack of detail on practical designs for non-inferiority studies, using available assessment criteria. And second, we are concerned about the decision that agreed upon special protocol assessments may no longer be valid. These concerns have been communicated in detail in our comments to FDA on the draft guidance.

Today, my focus will be on the CAP study design. And these issues, of course, are central to the use of non-inferiority trials.

Collaboration among industry, regulatory agencies and clinicians is key to

bringing new drugs to patients. We all understand the importance of having novel antibacterial agents available. Resistance is progressive and already here for some agents.

Generating industry effort and investment in this area requires opportunities for both medical and commercial value. We have heard over the past day and a half about many of the challenges of CAP trial design. These challenges are real. Fundamentally, the data supporting efficacy must be credible.

At the same time, a path forward must offer a feasible approach to CAP. Demonstrating efficacy in CAP will be fundamental to the development of new antibacterials and without this opportunity, the incentives to develop new therapies in this area will be further reduced, something we cannot tolerate.

Thus, clarity is urgently needed on a way forward in CAP. Regulatory uncertainty impedes drug development.

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

PhRMA believes that two different kinds of non-inferiority based approaches to CAP are required. First, we need a route to study the more severe CAP in an inpatient setting. This is the situation in which IV therapies would be developed. Second and perhaps most important, we need a route forward for less severe CAP in the setting of outpatient care, where an oral agent would be developed.

It is important that we have both routes. Not all agents can be developed for both oral and intravenous treatment. Of particular note, given the concerns expressed over the challenges with endpoints and effect sizes in less severe CAP, do remember that oral agents are important in overall cost reduction. Having them available to the community is a powerful tool for physicians and an important option for patient.

New tools may be possible, but it should be viewed as an extension of current

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

approaches, not a replacement. A message that we must spend some months or years trying to develop and validate new tools, before development can proceed on any new drug would be simply unacceptable to industry.

Finally, it should be noted that a feasible trial size and study durations are required.

Regarding the question or superiority studies for new drugs in CAP, we see two principal approaches, neither of which is feasible. First, superiority designs based on withholding active therapy are not feasible because of ethical and safety concerns for patients. There has been a great deal of confusion on this point because of the lack of experience over the past 50 years with the consequences of untreated CAP in general and pneumococcal CAP in particular.

While not a physician, my personal experience with CAP 25 years ago was quite striking. The progression from being in good

health to feverish chill and severe chest pain was striking. Fortunately, the course of my illness did not progress to blood-tinged sputum stage. That an antibiotic will alter the pace and outcome of that process, at least for me, was incontrovertible.

We believe that placebo controlled studies are simply not possible. IRB approval is quite problematic and physicians and patients view these as unacceptable. As noted in the appendix slides that we have provided, we know why antibiotics are able to have such a powerful effect. Our knowledge of the preclinical in vitro activity, the demonstration of activities in animal models of infection and our understanding of the use of pharmacodynamics to predict drug effect are more powerful in infection than any other therapeutic area.

If ever there was a setting of high base in prior probability that the null hypothesis of no difference is false, this is

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

that setting. This point is worth keeping in mind and I will come back to it in just a minute.

For similar reasons, delayed therapy approaches are not acceptable, as this disease can progress quite rapidly. It is not possible to predict those patients who are bacteremic and waiting for deterioration will not be tolerated.

Empiric therapy is a central part of our medical practice for CAP, just as it is for many other diseases. It is sometimes suggested that dose-ranging studies can offer support regarding proof of activity. We do agree that small hints can be obtained here, but the kind of dose ranging done in infection focuses mainly on asking pharmacokinetic pharmacodynamic questions across a narrow range of exposures. None of the selected dose regimens are deemed highly likely to fail and any observed range of response rates will be small. We certainly do not think it is

reasonable to plan to test using a dose that is so low as to be tantamount to a placebo.

The second possibility for superiority is the approach of insisting that a new drug beat an existing drug. While this is a laudable goal, when we have heard the suggestion that we study only resistant isolates and just show superiority, you hear such ideas that if current drugs work, then we don't need new drugs. If resistance is big, new drugs will easily show their value. It is not that simple.

The requirements of good trial design require us to remove a subject from study if the infecting isolate is found resistant to the comparator, as leaving such patients in the study would not only be unfair to the patient, but also create a bias regarding the affect of the control drug that we are going to remove the study the very patients for whom it would be possible to show this type of superiority.

But it is only through developing new drugs that we can prepare for the rising tide of resistance, a critical issue. One of the values of new agents is they will offer reliable empirical therapy. Current drugs don't always fail.

I do note here the burden is not entirely upon the FDA. Sponsors need to implement very high quality non-inferiority trials. Protocol violations must be minimized. A significant effort to prove microbiological etiology is needed and prior therapy should be limited and an adequate safety database must be generated. All of these are critical to a sound data package. We have no choice but to study future drugs in today's context. We must have the tools to continue to make this possible.

Although imperfect, we do see and have heard discussed over the past two days two approaches to endpoints for non-inferiority trials in CAP that I mentioned

previously. For more severe CAP, an approach that combines mortality with clinical response can be pursued. For less severe CAP, mortality should also be studied but mortality rates will be so small, just a few percent, that no meaningful comparisons will be possible or are expected.

We think it is now clear that clinical response is a valid endpoint. This approach has been used for the last ten years and led to the registration of our existing drugs. It is based on a test of cure over a short period of time after the end of therapy. As exemplified in the daptomycin versus ceftriaxone study, this approach can show the difference between two drugs.

And it is not just that study. Exposure-response analyses can also show differences. We welcome the pooled quinolone analyses provided by the FDA in the briefing document are encouraged by the fact that FDA believes that this approach can yet be another

route to estimating placebo size.

However, the FDA felt this analysis was inconclusive because of limited data. We are certain that more data exist and we have provided some datasets in the appendix to this slide set that demonstrate that. And I would recommend you taking a look at these.

We, thus, have every reason to believe that a consensus effect size estimate is possible. The daptomycin-ceftriaxone study gives an absolute minimum effect for that effect size but it is clearly in large a reality going from a 70 response rate with lower AUC/MIC values to a 90 percent response with higher values.

Note that the 70 percent response rate is going to at least be a little better than the effect on placebo, at least for some of the subjects in the lower AUC/MIC cohort that are getting partially effective therapy. It is more like the daptomycin situation than a true placebo.

Finally and as to comparators for future studies, the similarity in efficacy rates for newer agents is striking and encouraging. The Committee is asked to comment on whether or not older drugs for which was have snippets of placebo-based data should be used as comparators. Insisting on this would be like taking skepticism to an extraordinary level. It would create other difficulties, as the FDA briefing document notes so clearly on page 34. There are a number of difficulties inherent in extrapolating from clinical endpoints used in these studies to those used in more modern studies. Thus, we emphasize the importance of really looking at modern data and fully utilizing every bit of it.

We can use what we have learned over the past several decades about microbiology and pharmacokinetics, the predictive power of in vitro susceptibility testing, the correlations between in vivo

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

models and human response. There are multiple drugs with similar and strong efficacies. Ceftriaxone, the respiratory quinolones and newer macrolides all could be reasonably used as comparators. This view is similar to that of the American Thoracic Society and the IDSA in their joint guideline for CAP. When the isolate is susceptible, these are all good drugs.

Severity is a tricky thing and we should not be too quick to draw assumptions based on PORT or CURB categories. These tools can produce very misleading results, especially in young subjects. They are heavily driven by age. When you are under 30, it is very hard, indeed, to get much beyond PORT two.

Of additional concern, the scores don't capture the risk of progression. Pneumococcus in blood, for example, is definitely a risk for negative outcomes. Thus, the approaches to severity should be

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

made less complex, rather than more. We have been using for some time categories or mild, moderate, and moderate severe, based on general clinical judgment. This may be all that we really can do at present and the ATS guidelines do offer a plausible approach for being more systematic here.

Statistical analyses are an important part of medical research but we have been struck in recent years by the ascendancy of quantitative analysis over a combined approach that starts with biological reasoning, works from prior probabilities and adds experimental data and draws meaningful conclusions.

The numbers do not speak for themselves. They must be placed in context. Traditional non-inferiority statistical approaches that employ arbitrary targets, such as 50 percent effect retention are very conservative. These are also increasingly coming under criticism because the approaches

can lead to logical inconsistencies. They also take us away from the real goal demonstrating efficacy relative to a placebo.

We do understand the importance of providing adjustments for uncertainty and appreciate the use of effect retention as an approach to this. But it is important that we step back and remember the message of Thomas Bayes, who points out ever so clearly that the inductive process by which we analyze experimental data requires us to think carefully about the context, about prior probability, about plausibility, and about biological logic. If ever there was a therapeutic area where Bayes's and prior probabilities work in our favor, this is it.

We do not believe that alternative ideas such as effect retention likelihood can be usefully employed here. And there are two slides in the appendix that cover this.

We do need flexibility in the guidance to permit the use of such techniques,

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

where appropriate.

In a recent anonymous Lancet editorial, a comment takes us back to the big picture where we started a couple of minutes ago. "The practicalities of running trials and encouraging industry participation in antibiotic development should not be forgotten in the desire of theoretical perfection."

We could not agree more. It would be possible to announce perfect rules. These rules would yield infinitely conservative estimates and produce perfect demonstrations of activity. However, these would work slowly but surely to reduce the pace of work in this area and ultimately reduce development and production of new anti-infectives.

On the other hand, practical routes to non-inferiority CAP studies would maintain industry momentum in antibiotic discovery, provide convincing support for registration and provide convincing support for the validation of new tools, such as patient

reported outcomes. We can't make progress unless we make progress and we won't see any further work on validating new tools, unless we have a reason, and that includes industry sponsorship to validate these tools.

Failure is not an option here. Drug discovery and development takes years. Once the epidemic of drug resistance is fully upon us and it is clear in certain drug classes that it is already here, there won't be any time left. We will need ten years to develop new drugs and we have to start now to study future drugs in today's context. The lack of feasible development paths for CAP will further remove resources from antibiotic development.

And there are those who have responded to our concern about such issues having a chilling effect by saying that surely we have misunderstood and surely we will be happier with a new approach. Well, I can tell you quite frankly, among our task group, we

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

have not misunderstood. We understand the new approach and unless it includes the elements mentioned previously, routes for study of inpatient and outpatient CAP, routes that permit reasonable sample size, and routes that do not require placebo-based studies, then there will be even less effort put into this are as in the past.

I come to my last slide in this brief presentation. I have tried to convey a sense of overlapping concerns on the part of industry sponsors who drive and fund antibiotic discovery and development. The level of anxiety around this issue right now is enormous within the sponsored community and this is a pivotal moment for us all. It is critical that we get this right. And we must not decide from a single viewpoint. We must not make the road forward too narrow. Voltaire said it well. "Perfect is the enemy of the good."

And the tools that we need here,

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

the data reviews that we have heard show this to be the case. We now need to move forward and act on this but we should not insist on some arbitrary level of quantitative perfection. We must recognize the strength of the data that we do have. We must take full advantage of the rich and reproducible support that we have for the effect of antibiotics, based both on our preclinical ability to demonstrate effect and the clinical observations available to us.

Sound, well-supported options to develop new agents do exist, but we must not replace the working, albeit imperfect process with an unproven approach that discourages further drug development.

Can we improve on this process? I'm sure that we can but we are going to have to do so incrementally and starting from existing paradigms. And clarity is needed urgently, as regulatory uncertainty discourages drug development.

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

Thanks again for the Committee to listen to our thoughts and we look forward to working with the FDA on an on-going basis in this area.

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

And that is it. Thank you very much. So we will take a break for lunch now. Please try -- whoops. One more statement to read.

Is Dr. Talbot here? Did you want to say something real briefly? Thank you, Dr. Talbot. You have three minutes.

DR. TALBOT: Okay, thank you. George Talbot. I gave my disclosures yesterday. So, Hal, if I could have that slide from Dr. Gitterman?

My comments yesterday were very broad and were, I think, echoed by a number of comments today. What I would like to do is be a little bit more focused here and hopefully make a suggestion that could help the

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

Committee in its deliberations this afternoon.

This slide, and I think Dr. Gitterman's approach are to be applauded because it is a very complex area and having a box, a series of boxes, is actually making it, I think, much easier to consider each point independently. What I would like to suggest, however, is that the distinction of oral or outpatient versus inpatient or IV does blur some important issues. Oral drugs will be used in some inpatients and some outpatients may require parenteral therapy.

Therefore, what I would like to suggest is that you replace the headers, oral studies and IV studies, with the measure of severity. So oral studies would be replaced by mild CAP and IV studies would be replaced by moderate to severe. And then that leaves aside the question of which route of administration or which location in which the therapy is provided. And then you can move down each of these boxes within that context

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

of the population that is being studied or treated.

The advantage of this is that it is consistent with the historical data. It is consistent with clinical practice, as reflected by the ATS guidelines, for example, as just mentioned. And it is also consistent with the label that FDA provides to users, which talks about CAP of mild severity or moderate to severe severity. So, hopefully, the Committee would consider that a useful suggestion in its deliberations.

Finally, two clarifications on the perspective of IDSA. In speaking about severity, we agree that PORT criteria are not, in and of themselves, sufficient. There could be other approaches. The one we have suggested in our position paper is to start with PORT but then to allow a shift from mild to moderate to severe, for example, based on other proven pathophysiologic criteria, such as the need for mechanical ventilation.

A second point is that I think we agree with all the points on the right-hand side for moderate to severe CAP, right down to the NI margin. And we also agree that clinical failure is an appropriate endpoint, including not only mortality but also other parameters that have been discussed.

On the left side from mild CAP, we would agree with everything except the following: superiority not feasible and PRO of interest but not yet proven, therefore, clinical failure, including even a small mortality affect, would be a useful outcome parameter, with PROs to be studied and validated and discussed at the next advisory committee meeting, perhaps in five years.

The point being, is that we need oral drugs now and we need a route to be able to study them. Thank you very much.

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

A statement to read and then we

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

will let you go.

The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience.

The Committee will now turn its attention to address the task at hand, the careful consideration of the data before Committee, as well as the public comments.

So, we will take a break for lunch. Try to be back here, we are going to try to get started at 1:00.

(Whereupon, at 12:17 p.m., a lunch recess was taken.)

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:05 p.m.)

ACTING CHAIR TOWNSEND: All right, why don't we go ahead and get started?

So, this will be the voting section of today's agenda. Before we actually get into the voting, Dr. Cox is going to review the questions for all the panel members so you know what to expect and give us an idea of what the FDA would like us to review as we consider the questions.

Thanks, Dr. Townsend. Just a couple of comments. First, I mean, first I want to start out by thanking all of the presenters, the committee, and for all of the information and discussion we have had today. I think, you know, the two day committee has been really a great opportunity to hear from a number of folks on a very important issue.

We have also heard, you know, clearly about the importance of the need for development of additional therapeutic agents

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

and the problem of antimicrobial resistance. And also a lot of the discussion here today has been about clinical trial designs will be informative so that we can understand and evaluate new drugs.

Clearly, there has been a tremendous amount of work done by a number of folks who are trying to look at the information that is out there and available to understand treatment effect and I think that is very valuable to our efforts here today. There are also differences in the data from many years ago compared to what is going on with the current day with regards to clinical trials and community-acquired pneumonia. But one of the key questions is, is how much can we learn from the data from the past and how can we use that data, given some of the uncertainties, to inform what it is that we are doing with clinical trial designs here in the current day.

So this is, I think, a very

valuable opportunity for us to hear from the Committee and to get your advice on to use the information we have available to us in the design of current day clinical trials.

And it is important, too, you will see as we go through the questions, that the issues here about trial design are very interrelated. You know, the types of patients you enroll, the type of endpoints you look at, they all kind of, are related to each other. And we have tried to structure the questions to keep that in mind.

As we work through them, I think it will be important, too, for folks to be sort of thinking about the whole package of informations or questions that we are asking about in question one and then separately for question two.

And now just to run through the questions. I will try and give you some idea of sort of the process we are envisioning for the questions, as far as approaching and

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

discussing the issues there.

So, for questions one and two, we provided an initial stem. And clearly there has been a lot of discussion about other things too, with regards to treatment effect, but I will just read the stem from our question.

"To rely on non-inferiority studies for new drugs to treat community-acquired pneumonia, 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 on the historical experience that 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 controlled studies. These data are derived from patients with pneumococcal/lobar pneumonia."

The first question deals primarily with well we either call it inpatients,

patients receiving IV drug, or patients with moderate to severe illness. So question one, and the first question we asked that folks vote yes or no. And we also would like to hear your rationale for either your yes or no vote.

So, number one is, "Can these data be utilized to select a non-inferiority margin for a contemporary CAP study for an IV drug in a hospitalized patients?"

And then as we move to the sub-questions, we would ask that people discuss and provide their advice on these issues.

The first one, "a) To what severity of pneumonia or types of patients would it apply and how should severity be defined?" So, a discussion question.

"b) Should a microbiological diagnosis be necessary for inclusion in the primary analysis population for the trial and if so, what organisms should be included?" Again, a discussion question.

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

"c) Should strategies be utilized to enrich the population for patients with a particular microbial etiology?" Again, advice for discussion.

"d) Please discuss whether the evidence which shows a treatment effect based on mortality can be linked to endpoints which are used in current non-inferiority CAP trials. For example, clinical success or failure. And if so, how?" And then we just provide a notation. The possible components of the clinical failure endpoint might include some of the following. Mortality, receiving rescue therapy, lack of resolution of clinical signs and symptoms such that additional antibacterial therapy is administered, a lack of resolution of signs and symptoms at the time the primary endpoint is assessed.

The E sub-question gets to the issue of appropriate comparators. Again, a discussion question. "The historical evidence for a treatment effect is based on studies

which evaluated penicillin, sulfonamides, and tetracyclines. Given the need to preserve the treatment effect, and that is the effect of the comparator agent over placebo or no treatment in the current day study, what are appropriate choices for comparator agents? Please explain the basis and information that supports the recommendation for comparator agents for a future study."

And then F gets to the issue of a non-inferiority margin. "What is your best estimate of the treatment effect size (M1) that the historical data support for treatment of hospitalized CAP (based on severity selected in part A of this question above) in a future CAP trial? And what is your recommendation for a non-inferiority margin that preserves a portion of the treatment effect, M2, for a CAP trial in this population with the endpoints discussed above?"

Question two moves more towards outpatient or oral therapies or also sort of

similarly defined mild to moderate community-acquired pneumonia. And the stem starts out, "Given the information presented mostly from historical data on the treatment effect of drugs for community-acquired pneumonia in patients with pneumococcal/lobar pneumonia, please address the following questions on trials of outpatient CAP (studies using an oral drug)."

Part A. "Can a treatment effect be reliably quantified for a non-inferiority study of outpatient CAP for an oral drug?" And we would ask that you vote yes or no on this question and provide the rationale that supports the yes or no vote.

And then the little i through triple i sub-bullets are discussion points.

"i. To which patient population would this information apply with regards to disease severity and microbiological etiology?

ii. What endpoint(s) should be

utilized?

iii. What is the proposed non-inferiority margin and what data support the proposed non-inferiority margin?"

The B question, we would also ask that folks vote on this question and provide a rationale for the yes or no vote. And this question asks about placebo-controlled trials. "Can placebo-controlled trials be carried out in less severely ill patients with community-acquired pneumonia? If yes, how can risk to patients be minimized? What patient population could be enrolled and what endpoints could be evaluated?"

And then the C question is a discussion question. "Can you suggest any alternative study designs that could be utilized which would allow for an informative trial of outpatient community-acquired pneumonia for an oral drug to be conducted? And if so, please describe."

Question number three moves to the

question of if you have data from severe illness and how that might inform the use of, for instance, an oral drug for less severe disease. And it reads, "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. 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 we would ask that folks vote yes or no on that question and provide their rationale.

And then question number four. "If the available evidence for settling a non-inferiority margin in current CAP trials is derived primarily from studies of patients with community-acquired pneumonia due to Streptococcus pneumoniae, should non-inferiority studies include patients with other etiologies of community-acquired pneumonia?" We ask that you vote yes or no on that question and provide your rationale.

And then, if the answer is no, the question goes on, "If not, what additional studies are needed to show that antibacterial drugs are effective for specific organisms? When addressing this question, please consider the following organisms." And we have listed some of the organisms that we typically see in community-acquired pneumonia.

And with that, I will turn it over to Dr. Townsend.

ACTING CHAIR TOWNSEND: Thank you very much. Before we actually get into the

questions, I have a request from Dr. Temple if he is up for it, if he would be willing to, again, for the benefit of those on the panel who are not quite up to the statistical stuff, like myself, go back over what you mean, what is meant by M1 and M2 and the preservation of the treatment effect.

DR. TEMPLE: Okay, remember, this is not statistical. Tom does statistics.

We call, this is just a nomenclature thing. We call M1 a non-inferiority margin that represents the entire effect of the active control. And what we are always testing in an non-inferiority study is whether you can exclude a difference between the treatments that is bigger than the non-inferiority margin. And the non-inferiority margin is usually the difference between the control drug and the test drug. That is, how much better is the control drug than the test drug. And if the difference, C minus T, is more than M1, then there is no evidence that

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

the test drug has any effect left at all. So that is what M1 is.

But as has been discussed before, the whole reason you can't use a placebo is that you value the effect of the test drug, you don't want to lose too much of that effect. So usually in an active control setting, you set something else called M2, which is a clinically judged difference that you are willing to be the difference that gets ruled out. And in a lot of cardiovascular trials, that will be half the effect and that is partly a practical matter because if you calculate sample sizes trying to preserve 75 percent of the effect, you get up to fifty, sixty thousand and nobody can do that.

In this case, and in antibiotics generally, where the effect is large, you can be more demanding. And so, people have thrown around the idea that ten percent, Don whatever your endpoint is, might be good enough, that is if you rule out a difference of ten percent

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

between the active control and the test drug, you will be happy.

And I want to add again that that is ruling out at the end of a 95 percent confidence interval, there is going to be, to succeed in that, the point estimates almost have to be on top of each other. Otherwise, you are not going to be able to show it. So it is not as loose as it first seems to be. Okay? How is that?

ACTING CHAIR TOWNSEND: To further clarify, to go back to, I think, your last point there, so about how much difference would you need in endpoints to be able to say that we have ruled out an M2 of ten percent or more?

DR. TEMPLE: Well, in this case you are going to look at, let's say the endpoint is some success criterion. Okay? So you are going to see what the difference between the control drug and the test drug is. And if, let's say it's zero, let's say the point

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

estimates are identical, you then figure out what the confidence interval for that difference is, which Tom will tell you how to do, but it depends on the number of patients in the trial. If it is a very small trial, the confidence interval is going to be large and the upper bound of it won't rule out a difference of ten. But if the study is good sized, then you will be able to say, I am 95 percent sure the difference between them is not as large as ten and then you are happy.

So that is really determined by sample size and whether there is a trend. I mean, as everybody knows, the best way to prevail in a non-inferiority study is to be slightly better. So if the test drug is actually somewhat better at this endpoint than the control drug, then it is going to be easy to show that the upper bound of the 95 percent confidence interval for the difference rules out this difference. And if you are almost significantly better, then it is a walk. It

is a piece of cake. Okay?

DR. FLEMING: Just maybe to add with just a very simple answer to your last question, you were saying, if you have a margin in place, what estimate of effect actually is a success?

So if you had a ten percent margin in place and let's say that was based on a control standard antibiotic that had a 15 percent mortality and you had a ten percent margin, you are ruling out that that 15 percent mortality could be more than 25 percent on this new therapy. And you successfully do that when your estimate is about three percent difference. So you would still win when your therapy has an 18 percent mortality and the standard has a 15 percent mortality.

Now, if you were using the relative risk scale that we talked about where, instead of calling it an absolute difference of ten percent, you were using a relative risk, we

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

want to rule out that you have what we were talking about yesterday, a 67 percent relative increase, you would win when you had no more than about a 30 percent relative increase but you would win then, if you had a 90 percent power trial.

So essentially, your estimate for a win has to be approximately, let me just give you an approximate sense, only a third of the way up to that margin from no difference. But it is allowing you to win not only when you are estimating that you are the same, you can estimate that you are a little bit worse and still win. That is essentially how it would work.

DR. TEMPLE: The one thing I should add, the determination of M1 is supposed to be data-based. We recognize that when you are delving into the past things aren't going to be perfect and so on. But there needs to be a cogent database basis for saying what that margin is.

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

M2 is very much a clinical judgment. You get to decide. And that also, I must say to me, means it is very hard to be too flexible, once you have decided what M1 is on something that doesn't rule that out. Because now you are talking about possibly having no effect at all. Well, that is not going to come up here because the effect is large, but in other settings that is true.

On M2, you know, ten percent, if it was really 11 percent, would you panic? So there is some intellectual flexibility on that because it is a clinical judgment.

ACTING CHAIR TOWNSEND: Thanks very much. Any of the Committee members need any other questions clarified before we get into the questions? Dr. Dowell.

DR. DOWELL: I'm just looking at this first question. You said we were going to vote yes or no. And it is hard to vote yes or no on two questions at the same time. So you say an IV drug in hospitalized patients

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

but it was pointed out that an IV drug could be used in outpatients in some settings. Some hospitalized patients might have an oral drug. And then you said maybe we would be calling this moderate or severe.

So my request would be to clarify are we voting yes or no on an IV drug, or on hospitalized patients, or on moderate to severe?

DR. COX: Yes, I am, in essence, using those terms sort of as surrogates of one another, if you will. So I am thinking of these are the sicker patients. These are the more severely ill patients. And I think this is one of the points where, you know, Dr. Talbot asked for some clarification, but this is, I would describe this as patients who are moderately to severely ill. Sicker patients, maybe that is the key.

Does that help?

DR. DOWELL: No. You are still asking us to vote yes or no on more than one

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

question at the same time.

ACTING CHAIR TOWNSEND: I think if we use moderate to severe as sort of our guideline to answer this question. Is that what you are looking for, Dr. Cox?

DR. COX: So we are asking can a non-inferiority margin for a contemporary CAP trial be set? And that is for a patient population that has moderate to severe illness. We are asking -- so the question really focuses on whether a non-inferiority margin can be set.

ACTING CHAIR TOWNSEND: Dr. Rex?

DR. REX: What endpoint?

DR. COX: Well, I think when you answer the question, you have to have the subsequent sections already in mind because I think that is the key here. And I think that is one of the things that makes this difficult is that it relates to the endpoint, the patient population you are studying, what the margin might be. That all fits together.

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

So I think you have to sort of think through the sub-questions to be able to answer the first question because it is all interdependent.

ACTING CHAIR TOWNSEND: Dr. Fleming?

DR. COX: So you could -- right. If you can do it for any endpoint well then, that would be valuable. We would like to hear what that margin would be, what that endpoint would be, what that population would be.

So the answer to the first part of this, you know, part of the thinking has to be what is this entire package of pieces that would fit together that got you to your yes answer. So we are trying to understand your rationale and thinking in the subsequent questions. But all of that comes into the first part.

DR. FLEMING: So the logic to this, as I had understood it, correct me if I am not understanding this, is that you had a lead

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

paragraph that talked about the historical data. That paragraph was talking about historical data on mortality. Then you were asking us in the question, could you, could these data on mortality be used to select a non-inferiority margin? I thought it was implicit that you would mean mortality. Because then under Part D, you then ask could in fact this evidence be used to link to other endpoints.

So I thought the logic of this was you were reminding us of the historical mortality data. Then in question one, asking whether those data could be used to define a margin. Then under Part D, could in fact there be with those data, other endpoints that you would have a margin. Is that a correct understanding of your question?

DR. COX: I think, we provided the information in the stem because we thought it was valuable information to understanding treatment effect.

The question as I view it, for one, is more general. You know, can you do a non-inferiority study in this population of patients. So if there are, you know, a particular committee member's idea of what this study would be would include a different patient population, a different endpoint, I mean, I think, we are trying to figure out, you know, the first question, can you do a non-inferiority study, and if so, what is it that you envision being the components of that non-inferiority study. Is that fair?

DR. FLEMING: So then after we vote, yes, we would come back and answer that other.

ACTING CHAIR TOWNSEND: Dr. Rex.

DR. REX: To paraphrase then, you are really asking -- Steve Gitterman put up a slide where he had a series of questions. If you can envision being able to put something in each one of those boxes that makes sense to you, then the answer to this question is yes.

And then, the subsequent discussion is going to be what do you put in the boxes? And maybe there are several columns of boxes, but can you envision at least a yes answer?

DR. TEMPLE: Actually, the answer is yes if you can fill in any box.

DR. REX: But don't you have to be able to fill in the whole column?

DR. TEMPLE: We will get to that. That is what he is asking but if you thought there was some endpoint, some category of people, then the answer to that is yes. And then the other questions go on to ask who do you think this applies to, what endpoints, etcetera, etcetera.

ACTING CHAIR TOWNSEND: Okay, great. Thanks very much for clarifying. We'll get started.

So okay, most committee members, I think, probably know how this works but just a reminder. What I will do is I will read the question in for the record and then I will go

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

around the room and ask the committee members to vote yes or no and then to give some clarification on your vote. And then we will have some time for discussion.

Remember that we, for all intents and purposes, will be concluding about 4:30. Most people are getting taxis out of here around 4:30. So we have to keep that time constraint in mind. Okay?

First question. And Dr. Rex, you are not a voting member. Correct? Okay. So Dr. Wong-Beringer, I will be starting with you.

For questions one and two. "To rely on non-inferiority studies for new drugs to treat community-acquired pneumonia, 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 on the historical experience that suggests a reduction in mortality with point estimates ranging from 18

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

to 25 percent in the observational studies and from approximately 10 to 19 percent in controlled trials. These data are derived from patients with pneumococcal/lobar pneumonia."

Question number one. "Can these data be utilized to select a non-inferiority margin for a contemporary community-acquired pneumonia study for an IV drug in a hospitalized/moderate to severe patients?"

DR. WONG-BERINGER: My answer is yes for those with severe pneumonia. And that would be the type of patients where this can be applied to.

How it should be defined, I think I would agree that we start with the PORT, the severe index but that needs to be augmented with the additional physiologic parameters. I think for one ICU admission, mechanical ventilation, the need for that, those are criteria that I think would define that.

I do think that we need to dedicate

extra effort in enriching this patient population because looking at the studies that were very well summarized by Dr. Nambiar, we have very few patients with severe pneumonia in those trials for us to see a real clear difference in these drugs, particularly for this group of patients.

ACTING CHAIR TOWNSEND: Okay. Point of clarification and protocol. So I am going to ask everybody who wants to vote yes to raise your hand and then I will ask everybody who wants to vote no to raise your hand to question one. Just question one, then we will do the discussion.

Again. Can these data be utilized to select a non-inferiority margin for a contemporary CAP study for an IV drug in hospitalized patients or patients with moderate to severe pneumonia? So I will ask you to both raise your hand and also to state your name.

DR. WONG-BERINGER: Wong-Beringer,

yes.

MR. MAKOWKA: Ken Makowka, yes.

DR. DOWELL: Scott Dowell, yes.

DR. MUSHER: Daniel Musher, yes.

DR. PATTERSON: Jan Patterson, yes.

DR. VENITZ: Jurgen Venitz, yes.

DR. CALHOUN: Bill Calhoun, yes.

DR. KAUFFMAN: Carol Kauffman, yes.

ACTING CHAIR TOWNSEND: Greg Townsend, yes.

DR. FLEMING: Thomas Fleming, yes.

DR. WIEDERMANN: Bud Wiedermann, yes.

DR. FOLLMANN: Dean Follmann, yes.

DR. WHITNEY: Cindy Whitney, yes.

ACTING CHAIR TOWNSEND: Okay, that makes it unanimous. I am assuming nobody is voting no. So we are going to now give members opportunities to discuss their votes.

So Dr. Wong-Beringer, I'm sorry I cut you off. You were discussing your justifications for your answer.

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

DR. WONG-BERINGER: You want me to repeat it?

ACTING CHAIR TOWNSEND: No. You are good. Just start up from where you stopped.

DR. WONG-BERINGER: I would also add that for a particular microbial etiology, I think with the change in epidemiology we need to also consider the drug's effect for MRSA organism as well. And I will stop here.

ACTING CHAIR TOWNSEND: All right. Should we go on and ask all of the questions under this or do we go around and --

DR. COX: Yes, I think, I mean, as we are working through, I mean, maybe the most efficient way to do it would be, you know, we have answered question one and then if folks are ready, if they wanted to then run through A through F --

ACTING CHAIR TOWNSEND: Okay.

DR. COX: In their discussion portion is that --

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

DR. VENITZ: For each one of us to discuss the rationale for --

ACTING CHAIR TOWNSEND: Right.

DR. VENITZ: -- before we proceed.

DR. COX: Yes, you are right. I apologize. Yes, let's get the rationale for one and then we will go back and do the other ones. Thank you.

DR. VENITZ: Okay.

ACTING CHAIR TOWNSEND: All right. Dr. Makowka?

MR. MAKOWKA: Yes. I also agree that there is not enough information regarding the most severe patients. As a cancer survivor, knowing a lot of -- in running a support group, I see a lot of people who are on chemotherapy who are very susceptible to pneumonia. I have had a lot of friends die from the diagnosis of pneumonia when really it was chemo-induced.

ACTING CHAIR TOWNSEND: Thank you. Dr. Dowell?

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

DR. DOWELL: I don't have anything to add, other than what I said before about I think it is important to clarify whether we are voting yes on severe pneumonia or hospitalized patients or IV drugs. Less for this issue than when we get to the oral versus mild versus outpatient question. Because that will be really important what the thing is that we are voting then.

ACTING CHAIR TOWNSEND: Thank you. Dr. Musher?

DR. MUSHER: I would like to add to Dr. Dowell's point. I think that the wording in that question should be whether the data can be utilized to select a non-inferiority margin for mortality differences. Because it really is only for mortality, the historical data, in my opinion. And that is for mortality differences in moderately severe or severe community-acquired pneumonia. So if I had my choice, I would reword the question. And I think that that probably more accurately

reflects the view of the Committee.

DR. KAUFFMAN: Not necessarily. I don't think we all believe we should put the word mortality in there.

DR. MUSHER: Okay.

DR. KAUFFMAN: I think it's better the way it is.

DR. MUSHER: I'm sorry. The moderately severe or severe is what people do agree on. I think it should be mortality because I think that that is the only basis for anything historical. The other stuff is just not there and we just have to develop clinical criteria and study them.

ACTING CHAIR TOWNSEND: Thank you. Dr. Patterson?

DR. PATTERSON: I voted yes because it is the best data that we have, you know, to compare it to non-treatment. And we are not going to have an opportunity to study that again. But I think the key term here is utilized. I think it should be utilized but

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

not accepted totally as the non-inferiority margin itself.

And I don't think we should limit the responses to just mortality. We need to look at other things in clinical response. You know, that was a different population in a different time 50 years ago and so we can utilize it.

ACTING CHAIR TOWNSEND: Thank you. Dr. Venitz?

DR. VENITZ: After the past day and a half, I think it is reasonable to come up to a couple of conclusions that I would like to share with you that led me to my vote.

Number one, I think we are dealing with a class of drugs that has a low placebo effect and has a large treatment effect. Which to me also means that, by implication, the HESDE, I think is what you call it, the assay sensitivity is high, compared to some of the other diseases that you mentioned.

And this is, obviously, based

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

primarily on mortality data. But in my opinion, I think that can be translated reasonably into other outcomes data, such as resolution of symptoms. So to meet clinical cure would be comparable, even though the literature hasn't actually studied that, then I can substitute mortality for clinical cure.

Okay, so my answer was based partly, at least, on the fact that you are using clinical cure as an endpoint that you could use the literature from 50 plus years ago to select an inferiority margin based on the same difference in mortality and translate that difference then into clinical cure differences. So you have some idea what M2 should be.

ACTING CHAIR TOWNSEND: Thank you. Dr. Calhoun.

DR. CALHOUN: Thanks. So my vote was yes, based on the magnitude of the effect size that we saw in the early studies and the ongoing clinical validation of experience with

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

antibiotic use in patients with pneumonia. And that is really the basis.

ACTING CHAIR TOWNSEND: Thank you. Dr. Kauffman.

DR. KAUFFMAN: I voted yes also based on the descriptive studies from decades ago, which I think are helpful. I think that we should study patients categorized initially probably by PSI scoring. But I think modification of that is needed as an ATS representative suggested and also the IDSA representative suggested.

And I think using criteria such as were done in the recent daptomycin study where they made it clear that you exclude patients who are going to be dead within 48 hours. In other words, really severely ill patients who are already septic. I think you don't want those in a study but you want severe enough patients who have a modest chance of survival.

So I think that is clearly doable.

ACTING CHAIR TOWNSEND: Thank you.

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

I also voted yes and I think for about the reasons that the other members have already articulated. I will say that I am very convinced on the, you know, you are talking about non-inferiority studies. You are talking about really meeting two criteria. One of which is if the study meets the historical evidence of significant drug effect, which I am fairly convinced that we have for community-acquired pneumonia trials. The other bit of information that you need is the constancy assumption to make sure that that is valid.

I am a little bit more wary of that than I am of the HESDE. So there are certainly some data suggestive that would see similar results today, as we saw 50 to 60 years ago. And clearly, we are not going to get any other data.

So I am willing to accept that we have some information suggesting that treatment effect in 2008 would be comparable

to treatment effect in 1939.

DR. FLEMING: I would agree with what I think George Talbot had indicated, as well as a number of others, that I might have preferred the question to have been written in terms of level of risk or severity, rather than specifically hospitalization outpatient.

But specifically in the context of patients that have sufficiently severe risk of mortality in the range of 15 percent, the data, I think clearly establish the appropriateness of a non-inferiority trial with a margin probably in the range of ten percent. And I think it is rational to extrapolate that to a moderate to severe population in the relative risk context. Then we would essentially be ruling out an excess increase of 67 percent or a relative risk of 1.67.

And I would say this remains an extremely important issue, as we look at slide 22 from Wunderink. Mortality hasn't changed

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

since 1950. Mortality remains an important issue in CAP and we have been reminded it is also still the sixth most significant cause of mortality.

So it is still a highly clinically relevant endpoint, as well as one that historical data provide us the best sense as to what the effect of the active comparator is, giving us a basis to do a valid non-inferiority assessment.

DR. WIEDERMANN: Let me try to run through a few of these items without repeating too much. I would just remind people the PORT score was developed and validated for a reason other than what we proposed to use it for. So it is an un-validated tool for our purposes and therefore, I agree that we should modify it, as it would make more sense.

I do favor having microbiologic diagnoses for data analysis very strongly. Community-acquired pneumonia is a very heterogeneous group. If we come up with one

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

number to summarize outcomes regardless of etiology, that summary number may actually not be the true number for any one of those different groups. So I recognize, certainly, I see every day what we deal with in the real world. But I think for purposes of drug approval, we need microbiologic definitions of the case.

And certainly, the daptomycin article is a roadmap for enrichment. I would also, as I read it anyway, it is also a roadmap to beware about prior effective therapy because that obscured the inferiority results. So the patients who received prior effective therapy, it clouded that observation.

And certainly there are situations where I can think of where secondary endpoints are actually going to be more helpful than mortality because as we have all said, we are going to ideally declare a treatment failure and get the patient out of the study before

mortality happens. So some of these secondary endpoints are very important.

You know, I am happy with F and what has been said for M1 and M2 in the moderate to severe illness. And I would just say for a comparative drug, I haven't heard anybody mention whatever you call it, the creep effect with non-inferiority trials, but if the comparator agent is always an agent that has been approved in a non-inferiority trial, if you have guessed wrong on the M1 and M2, eventually you will creep to potentially approving a drug that is no better than placebo. So that is why a lot of the angst that comes from this is from that fear.

ACTING CHAIR TOWNSEND: Thank you. Dr. Follmann?

DR. FOLLMANN: So I will just add a little bit to what people are saying, which I mostly agree with. To answer part 1(a), to what type of severity, I think, you know, we are picking margins based on historical data

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

which looked at death rates. And so to make that extrapolation, I think we are most comfortable if we can have a study that had similar death rates to what we saw in the past. And so that is very, that requires enrolling patients who have pretty severe CAP so we could achieve a mortality rate of around 15 to 20 percent.

Having said that, I also agree with the point Tom Fleming made about the ten percent margin really should be viewed more in a relative risk setting. So I am concerned, for example, if we, with good intentions, trying to find inclusion criteria so we have a 20 percent death rate and choose a ten percent margin and then, for whatever reason, we end up with a much lower death rate and a ten percent margin, I think that would be a prescription for an uninterpretable study. And so, I think it is essential that we look at a relative risk view with a margin.

So if you want to say a 50 percent

or a 67 percent increase in the relative risk of death, that is something I would be comfortable with. This is amplifying on a comment that Tom made. And I think those are the main points I wanted to bring.

ACTING CHAIR TOWNSEND: Thank you. Dr. Whitney?

DR. WHITNEY: Just to clarify, are we going to go through the A, B, C next? Okay, so you just want a general comment.

ACTING CHAIR TOWNSEND: Right. You are welcome to go with anything --

DR. WHITNEY: I don't know that I really have that much to add to what has been said already. I liked especially some of the comments about how it is important to study this in moderately to severely ill patients. But I also think we need to go beyond this mortality endpoint and have other endpoints we can work with as well.

ACTING CHAIR TOWNSEND: All right, thank you. So if we could now begin to answer

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

the sub-questions.

We have already heard some comments on how to define the severity of pneumonia on the type of patients that a study like this would apply to. A couple of members have already indicated that they would favor using sort of a modified PORT system; using the PORT criteria but also adding on some physiologic markers of severity, such as admission to the intensive care unit, the need for mechanical ventilation.

There were other ideas about how to assess the severity or what scale to use to place patients into the moderate to severe category.

Dr. Rex?

DR. REX: Not a vote but I think the data we have seen suggests that if the patient has a syndrome that is strongly suggestive of bacteria etiology, even better if you have a bacterium, a pneumococcus or in some cases staph aureus or even Haemophilus,

8b70aab3-cc41-4ff9-90d5-6b61e280f91a

that actually puts you in a surprisingly high risk category even if at this moment, you look good.

And the ATS guidelines, I think Dr. Wunderink showed it yesterday, one of their concerns is that somebody who looks good this instant is set up to crash and burn that afternoon on an unmonitored bed on a ward. And that part of the reason they have defined their criteria the way they have for predicting level of care that is required, is this concern about the fact that severity at any given instant is just that. It is, you know, how you look right now but there are folks who are closer to the edge than you might think.

And so, I think that there is, when you think about severity, just be aware that PORT and CURB are kind of quirky things. And I read some stuff yesterday to remind us how that works. So don't push them too far. And sort of the quality of needing to be in a

8b70aab3-cc41-4ff9-90d5-6b61e280f91a