FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ANTIMICROBIAL DRUGS ADVISORY COMMITTEE (AMDAC)

Thursday, April 13, 2017

8:30 a.m. to 4:36 p.m.

Tommy Douglas Conference Center

10000 New Hampshire Avenue

Second Floor

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. BADEN: Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. I would also like to identify the FDA press contact, Theresa Eisenman in the back on the left. If you are present, thank you for standing.

My name is Dr. Lindsey Baden. I'm chairperson of the Antimicrobial Drugs Advisory Committee. I would now like to call this meeting to order. We'll start by going around the table and introducing ourselves. Let's start on the far right.

DR. MARKS: I'm Lynn Marks. I'm an infectious disease physician and a senior vice president at GlaxoSmithKline. I'm in the research and development group, focusing on antimicrobial resistance in the challenges of drug development.

DR. HILTON: I'm Joan Hilton, professor of biostatistics at UCSF.

DR. WEINSTEIN: I'm Mel Weinstein, professor of medicine and pathology at Rutgers Robert Wood Johnson Medical school and chief of ID at the med school.

DR. MOORE: I'm Tom Moore. I'm at the University of Kansas in Wichita, Kansas.

DR. SHYR: Yu Shyr, biostatistician from Vanderbilt University.

MS. MCCALL: Debra McCall, patient representative.

DR. ANDREWS: Ellen Andrews from the Connecticut Health Policy project, and I'm a consumer representative.

DR. CLARK: Nina Clark. I'm in infectious diseases at Loyola University in Maywood, Illinois.

DR. OFOTOKUN: Ighov Ofotokun, professor of medicine at Emory University, infectious diseases physician.

DR. DASKALAKIS: Demetre Daskalakis, acting deputy commissioner of disease control, New York

City Department of Health and Mental Hygiene.

DR. CORBETT: I'm Amanda Corbett, clinical associate professor at the University of North Carolina Eshelman School of Pharmacy.

DR. WEINA: Peter Weina, infectious disease, Walter Reed National Military Medical Center.

DR. BADEN: Lindsey Baden. I'm in infectious diseases at Brigham and Women's Dana-Farber and Harvard Medical School and an ID practitioner and researcher.

DR. TESH: Lauren Tesh, designated federal officer for AMDAC.

DR. GREEN: Michael Green, pediatric infectious diseases at the Children's Hospital Pittsburgh and the University of Pittsburgh.

DR. GRIPSHOVER: Barbara Gripshover. I'm in infectious diseases at Case Western Reserve University in Cleveland.

DR. FOLLMAN: I'm Dean Follman, head of biostatistics at the National Institute of Allergy and Infectious Diseases.

DR. SCHAENMAN: Joanna Schaenman, infectious

diseases, David Geffen School of Medicine at UCLA.

DR. HONEGGER: Jonathan Honegger, pediatric infectious diseases, Nationwide Children's Hospital in the Ohio State University.

DR. LO RE: Vin Lo Re, Division of Infectious Diseases, Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania.

DR. GOETZ: Here I am, right by the -- Matthew Goetz, chief of infectious diseases, VA Greater Los Angeles, professor of medicine, David Geffen School of Medicine, UCLA.

DR. BENNETT: I'm John Bennett, infectious disease, part of the intramural program of NIAID at NIH.

DR. RUBIN: Dan Rubin, Office of Biostatistics, CDER, FDA.

DR. PRICE: Dionne Price, Office of Biostatistics, CDER, FDA.

DR. KIM: Peter Kim, medical officer, Division of Anti-Infective Products, FDA.

DR. YASINSKAYA: Yuliya Yasinskaya, medical

officer, CDER, FDA.

DR. NAMBIAR: Good morning, Sumathi Nambiar, director, Division of Anti-Infective Products, CDER, FDA.

DR. COX: Ed Cox, director of the Office of Anti-Microbial Products, CDER, FDA.

DR. BADEN: 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, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting, and I'm very appreciative of everyone making the time to join us for this meeting on such an important topic.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask the advisory committee members take

care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

I'll now pass it to Dr. Lauren Tesh, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. TESH: The Food and Drug Administration is convening today's meeting of the Anti-Microbial Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of the committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of

the committee have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 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 the discussion of the development of antibacterial drugs that treat a single species of bacteria when the target species infrequently causes infections. Examples of such drugs include those that are only active against Pseudomonas aeruginosa and Acinetobacter baumannii.

This is a particular matters meeting during which specific matters related to antimicrobial antibacterial drug development programs will be discussed. Based on today's agenda for the meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in

connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the meeting topic.

With respect to FDA's invited industry representative, we would like to disclose that Dr. G. Lynn Marks is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Marks' role at this meeting is to represent industry in general and not any particular company. Dr. Marks is employed by GlaxoSmithKline.

We would like to remind the members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, these 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 they may have with the meeting topic. Thank you.

DR. BADEN: We will now proceed with Dr. Cox's introductory remarks.

FDA Introductory Remarks

DR. COX: Good morning. I just want to start out and make a few intro comments. I just want to touch on some of the broad topics that we'll talk about today, and you'll hear more detail as we go through the series of presentations.

First, thank you all for joining us here today. And for folks that have been following this area, you're probably aware that there are investigational drugs that are being developed that target only a single species or that are active against only a single species of bacteria, and those bacteria occur relatively infrequently, which presents significant development challenges.

We've done a series of workshops over the last 10 months, as folks may also be aware. We started back in July of 2016 and started talking about this problem, about single-species active

drugs when the species that's the target of the agent is something that occurs fairly infrequently, and also had another workshop in March of this year. And you'll hear as we go through the presentation the summary of some of the key points from those discussions.

As folks are probably aware, there are already considerable challenges in developing a new antibacterial drug. And among the range of indications for which drugs are developed have that as a particularly challenging area of development, and the examples that we'll be talking about today target Pseudomonas aeruginosa and Acinetobacter baumannii, so agents that are found in HAPB/VAPB.

So you've taken sort of a challenging area of drug development already and then limited the proportion of patients in whom the particular causative agent is present, which makes development in clinical trials really quite challenging. You'll hear more about some of these challenges in Sumathi's presentation, which will follow me.

Just thinking in general about what we run

into when developing an antibacterial drug, oftentimes we're faced with diagnostic uncertainty. We don't actually know what the etiologic agent is that's causing the particular patient's infection at the time of presentation. It takes a little time to figure that out, then also, too, the issues of pre-study therapy, which may be important in treatment of the patient's condition, and concomitant therapy that may also cloud the assessment of the effect of an investigational drug.

So at least as we've thought through this, it seems like the component that somebody would put together when doing such a development program is really -- that's not the biggest challenge. The components are likely to be in vitro data, the best you can possibly do, animal models looking at the activity of the drug, PK/PD information to help select a dose, animal models that are more akin to disease to be able to understand how the drug works in a setting that's more akin to the human disease; clinical trial data to evaluate efficacy and also

to look at safety.

But I think the real issue here is that this is essentially new ground, studying an agent that is active only against a smaller proportion of the patients that would be in such a trial. And given the issues of pre-study therapy and concomitant therapy, how interpretable will the results be from the clinical trial I think is a question that we all struggle with.

One of the things we're hoping to hear from the committee today are ways to increase the likelihood that the clinical trial data will be interpretable or be able to evaluate the drug, given the likelihood that there will be pre-study therapy and also concomitant therapy, given the very narrow spectrum of the investigational agent.

I think as we talk about this, rapid diagnostics could certainly help. We have to deal with the situation as it currently exists. And we also have to keep in mind, too, that rapid diagnostics don't create patients, so diseases that are uncommon remain uncommon. You can just

diagnose them a little bit sooner. That helps, but the situation still remains challenging.

So we have to have a robust discussion and get your advice on what can be done to make the clinical trials more feasible, more likely to be interpretable. And then if such a trial is attempted and, despite everyone's best efforts, if the trial is one that's very difficult to interpret because of pre-study, and concomitant therapy, and small numbers of patients, what the role might be for animal models of disease to evaluate the efficacy of a particular drug.

We're also very interested, too, on thoughts that you may have about how such a drug might end up being used in the real world. Given the challenges of conducting a clinical trial, some of those spill over into the challenges of how a drug might be used in the real world.

So with that, I'll stop and thank you for your attention. And back to you, Dr. Baden.

DR. BADEN: Thank you, Dr. Cox.

We'll now proceed with Dr. Nambiar's

regulatory background information.

FDA Presentation - Sumathi Nambiar

DR. NAMBIAR: Thank you, Dr. Baden.

Good morning, everybody, and I welcome you to today's meeting of the Antimicrobial Drugs Advisory Committee. I thought I would start out with a little bit of background on antibacterial drug development and talk about unmet need programs before we move into discussion around species-specific drug development.

In general, antibacterial drug development can be considered in two prongs, standard programs and unmet need development programs. For standard development programs, we generally get non-inferiority trials at specific body sites of infection. With such programs, there's less uncertainty with regard to efficacy and safety.

Now, over the last few years, there's been considerable focus on unmet need development programs because we are in a situation where we had very few therapeutic options and increasing antimicrobial resistance.

We issued a draft guidance on this topic in 2013. And based on the approaches that were outlined in this guidance, clinical trials have been completed successfully, and there are other trials that are ongoing.

There is now increasing interest in developing drugs that only treat a single bacterial species, such as Pseudomonas aeruginosa, Acinetobacter baumannii. And designing scientifically sound and feasible trials for such drugs has been the focus of our more recent efforts and the topic for today's meeting.

With unmet need programs, there is greater uncertainty and risk because these programs are smaller than traditional development programs, and such development programs are acceptable and consistent with our regulations in subpart E.

It's important to note that clinical trials for unmet need should still meet the statutory standards for effectiveness, as described in the Food, Drug, and Cosmetic Act. Typically, we require a safety database of about 300 patients at

the proposed dose and duration. However, if safety concerns arise, we will certainly require additional data.

It's very important in these programs that there's a thorough evaluation of in vitro activity and also activity in relevant and animal models of infection, and risks and benefits from such programs would be communicated in labeling.

I won't go through each of these trial design options, but these are the trial design considerations that we have looked into for such programs. We're willing to accept a single non-inferiority trial at the body site of infection. A single superiority trial is also acceptable, and this could be considered either at enrolled patients with infections at one body site or we're willing to consider infections across multiple body sites.

We're also willing to consider a single nested NI superiority trial. And if one is developing a new beta lactamase inhibitor that is being paired with an approved beta lactam drug,

then one can rely in part on previous findings of safety and effectiveness of the beta lactam drug.

Lastly, if an adjunctive therapy is being developed, superiority of the adjunctive therapy in combination with standard of care should be demonstrated versus standard of care.

So moving on to single-species-specific drugs, as Ed has already mentioned, we acknowledge that there are many challenges in conducting clinical trials for such therapies that target a single species that occur infrequently at any body site of infection.

These patients are sick, and there's an urgent need to start effective therapy. Often, there is a need for empiric therapy because there is diagnostic uncertainty at the time these patients present. Often, there is need to use pre-study therapy and concomitant effective therapy, which can further confound assessment of the treatment effect. And unlike many of the other rare diseases, it's very difficult to identify these patients who might develop such infections

ahead of time or maintain a registry.

We also recognize that there is potential clinical utility for such drugs, and we've been working to find feasible solutions to develop such products.

As Ed mentioned, we've had two recent public workshops. Summer of last year, we had a two-day workshop on facilitating antibacterial drug development for patients with unmet need, and on the second day, we discussed developing antibacterial drugs that target a single species.

On March 1st of this year, we had a workshop to discuss the current state and further development of animal models of serious infections caused by Acinetobacter baumannii and Pseudomonas aeruginosa.

So as I said, on the first day of the workshop, we had a gentle discussion about facilitating antibacterial drugs for patients with unmet need, and the second day was really focused on species-specific drugs.

So the highlights of the first day were

discussions around potential clinical trial designs. There was a discussion around the significant challenges in conducting a trial, which is designed to demonstrate superiority. Achaogen presented the challenges that they encountered in studying plazomicin for patients with carbapenem-resistant Enterobacteriaceae in their trial.

It was also very clear that it is important to understand the pharmacokinetics of the drug in the target population and that the drugs behave very differently between indications and certainly between healthy volunteers and patients.

The second day of the workshop really focused on how one might develop a drug that just treats Pseudomonas aeruginosa. We presented a hypothetical case of a drug that had activity limited to Pseudomonas aeruginosa, potential clinical trial designs were discussed, and importantly, all of the trial designs considered had challenges and limitations.

These were some of the trial designs we discussed, and I'll go through them in the next few

slides: non-inferiority trials, superiority trials, studies in specific patient populations such as those with cystic fibrosis, and the role of animal models of infection.

So the first option considered and I think a fair amount of time at the workshop was spent on discussing non-inferiority trials. It was generally thought that a non-inferiority trial is potentially feasible, even for species-specific drugs, and this NI trial could be done at a single body site, as in HAPB/VAPB, UTI, or intraabdominal, or one could potentially include patients with HAPB/VAPB and/or bacteremia.

Such trials might be feasible if greater uncertainty is acceptable, which translates to allowing for wider non-inferiority margins. Such a trial will not need to limit enrollment to patients with Pseudomonas of specific resistance phenotypes. It would be enrolling patients -- it would be an all-comer trial.

Again, as Ed had mentioned in his introductory comments, availability of rapid

diagnostic would certainly help identify patients, but will not change the frequency with which they cause in any one of these infections.

We had a lot of discussion around potential for confounding both by prior effective therapies and concomitant therapies.

So if one were to undertake a superiority trial, then the efficacy of the test drug would be compared to best-available therapy. Such a trial will enroll patients with Pseudomonas aeruginosa resistant to available therapy, so one can demonstrate superiority. But there was, again, a lot of discussion around the difficulty in identifying and enrolling enough patients in such a clinical trial.

In this trial, one could enroll patients with Pseudomonas identified at one or more body sites of infection, but again, the difficulty in demonstrating superiority over existing therapies was discussed a fair bit. And the point was also made that the opportunity to show superiority is usually time limited and dependent on available

therapy becoming suboptimal because once new therapies become available, then the ability to demonstrate superiority becomes more difficult.

A third option presented, which really was not discussed in any great detail, was whether a study can be conducted in patients who have a higher likelihood of having infections due to Pseudomonas aeruginosa, such as patients with cystic fibrosis.

The last option was the potential for approval under the Animal Rule, where efficacy data is obtained from animal models of infection. And this might be an option if an informative efficacy trial is not feasible. If the Animal Rule approval was pursued, animal efficacy data would be supplemented with available clinical data from patients with a variety of infections.

So these are the four options that were discussed during the workshop last year.

On March 1st of 2017, we had a public workshop to discuss animal models of serious infections caused by Acinetobacter baumannii and

Pseudomonas aeruginosa. Dr. Yasinskaya will present in further detail some of the key points that were discussed during this workshop.

The workshop was well attended, and we had participation from all the key stakeholders, including academia, industry, and other government agencies. There was discussion around two species-specific products that are currently in development. And again, you'll hear more about them in presentations today.

The key topics that were discussed at the workshop are how the Animal Rule was used to support the approval of products for the treatment of plague and anthrax. There was discussion about the role of animal models in antibacterial drug development and what some of the key attributes and shortcomings were of the currently used animal models.

Given the urgent need to develop species-specific therapies, there was discussion around the role of animal models that could support the very limited clinical data that might be feasible to

obtain.

So we had mentioned this at the workshop. We do have a broad agency announcement for research proposals focused on advancing the development of animal models of serious infections caused by these two pathogens, and proposals that have been received for the FY17 funding are currently under review.

So we've been thinking hard about what these development programs might look like and what is practically achievable with programs that are really targeted single-species-specific drugs.

We think some clinical data can be obtained, but it certainly will be limited, and certainly much smaller than what we're used to seeing with the standard development programs, and even smaller than what we've seen for the unmet need programs.

There will be evidence of activity and efficacy in relevant animal models of infection. We will have a robust PK/PD data package, and we will have limited human safety information. And, again, non-clinical safety data that might give us

some suggestion of what safety signals to be aware of.

So the two options for the clinical data package is one that would be in the setting of a non-inferiority trial, and the second would be a superiority trial.

A non-inferiority trial, again, I think, though these trials with single-species-specific drugs are difficult to conduct, we think it might be a feasible option. But if one is to allow the use of a wider non-inferiority margin, smaller sample size, there is going to be much greater uncertainty in the treatment effect with these programs.

If there is a lot of use of prior and concomitant effective therapies in a reasonable fraction of the patient population, it would be very difficult to discern the treatment effect of the investigational drug.

We are willing to consider a single non-inferiority trial with a wider non-inferiority margin than we would typically use for a standard

development program. So for example, for HAPB/VAPB, we'd recommend an NI margin of 10 percent for a standard development program. And we've allowed for use of a 12.5 percent margin for therapies that address an unmet need.

For single-species-specific drug, we're willing to go one step further and willing to consider the use of an NI margin, which is equal to or close to that treatment effect, so really preserving only a small fraction of the treatment effect.

The superiority trial could be conducted. I think life would be a lot easier if it provides a clear finding of efficacy. We think it might be feasible to conduct superiority trials for maybe the first couple of drugs that are being developed, as it might be possible to demonstrate superiority over currently available standard of care. However, as the standard of care changes and new therapies become available, the trial may become infeasible or unethical because, at that point, the new standard of care will replace the less-than-

adequate comparator treatment that the trial had started out with.

So given these challenges, based on our discussions we've had with various sponsors, there is an unwillingness to take on a superiority trial as the first option.

Now, in these development programs, given that the clinical data package is going to be very limited, the animal models of infection play a very important role. In these animal models, it's important that the effect be demonstrated in more than one species, which is expected to react with a response predictive for humans.

The animal models of infection studied should be relevant to the clinical condition being studied in humans and that the study endpoint that's used in these animal models is similar to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity. So we're looking for something beyond just a log reduction in a microbial count.

We've also been thinking what might be the

outcomes of these programs. Again, we're thinking ahead, so we don't have a lot of experience. We have actually no experience with any of these products having gone through a development program. And one can certainly think of many potential scenarios, but we came up with maybe four likely scenarios, and I'm sure you can think of others as well.

The first and the best one would be where you have a successful clinical trial and either superiority or non-inferiority was demonstrated, depending on what the trial was designed to do, and there are no major safety signals of concern. So it's very easy, then, to make an assessment of risk-benefit in such a program.

The second possibility is that the clinical trial results showed us that there is a lack of beneficial effect with the test drug, and that again is easy to interpret.

The third possibility, which is certainly a likely possibility in this with these drugs and one that's really the focus of today's discussion, is

that a clinical trial was attempted. It was either not feasible; very small numbers of patients were enrolled; or the trial is just not interpretable because there are so many confounders. In such an instance, there will be a greater reliance on the evidence of efficacy coming from animal models of infection.

Another scenario -- and we haven't really touched much on safety yet -- is that although efficacy is demonstrated, there are safety concerns with the product that do not allow us to make a favorable benefit-risk assessment.

Now, most of our discussions so far have really focused on the efficacy, but I think it's important to keep in mind that safety is just as an important part or component of this discussion as efficacy is.

So as in any other development programs, we will assess the safety of the product in non-clinical studies, and based on the signal, if any, we will ensure that there's appropriate monitoring in clinical trials.

The database in these programs at the proposed dose and duration may be very limited. We would at least like to get about 300 patients, and if there is any safety signal, we would require additional data be collected.

For such products, there might be a need for additional safety data to be collected either in the form of postmarketing requirements or through enhanced pharmacovigilance. And it's also important that if such a product is approved, that it be used very judiciously and safety be closely monitored because there is very limited safety information available pre-marketing.

So before I close, I'll just start showing the 21st Century Cures Act because it's relevant to our discussion today, signed into law on December 13th of 2016. And the two sections that primarily impact anti-infective products are Section 304.2 about limited population pathway, otherwise known as LPAD, and Section 304.4 that deals with susceptibility test interpretive criteria and AST devices.

For LPAD, this pathway is for drugs intended to treat a serious or life-threatening infection in a limited population of patients with unmet need. Labeling for such products will include limited population in a prominent manner and a statement that the drug is indicated for use in a limited and specific population of patients. There's also a requirement for pre-submission of promotional materials.

The two key topics we would like to discuss at today's meeting are as follows, the development programs for species-specific antibacterial drugs, where the bacterial species is not commonly identified in any one type of infection.

Secondly, should such a clinical development program not be feasible or the clinical data not be interpretable, what the role of the animal models of infection would be.

We have two questions for the committee to consider. Both of them are discussion questions. We have no voting questions today. The first question is to discuss the unmet medical need for

single-species-specific products and the risks and benefits of the development proposals that we present today. We request that you please provide any additional recommendations you might have for developing such products.

The second question, I do apologize; the stem is fairly long. But essentially it is, if every effort is made to perform human clinical trials -- these trials are going to be challenging, and the data collected may not be interpretable or be very limited -- and should the circumstance arise, it may be useful to consider whether animal models of serious bacterial infections can provide useful information to assess the activity and efficacy of the drug.

In such a situation, please discuss the following: the types of animal models and appropriate endpoints that you think might be useful to assess the efficacy of an investigational agent; and secondly, if there is a situation where efficacy is principally demonstrated in animal models of infection and only limited clinical trial

data available in humans, how might such a product be used clinically?

So for today, following my presentation, we have a presentation by Dr. Yuliya Yasinskaya, who is a medical team leader in the Division of Anti-Infective Products. She will summarize proceedings of the March 1st animal model workshop.

We have two case presentations today. The first is an example of a drug with activity against Acinetobacter baumannii only. Dr. Robin Isaacs from Entasis Therapeutics will be presenting that example. And the second is an example of a drug with activity against Pseudomonas aeruginosa only. Dr. Kim, a medical officer in the Division of Anti-Infective Products, will be presenting this case.

This will be followed by a presentation by Dr. Perl from the IDSA. We have time for clarifying questions. And after lunch, we will hear from speakers at the open public hearing, and this will be followed by a discussion of the committee. So thank you all for coming and I look forward to the discussions today.

DR. BADEN: Thank you, Dr. Nambiar.

We'll now proceed with a summary of the March 1, 2017 current state and further development of animal models of serious infection caused by Acinetobacter baumannii and Pseudomonas aeruginosa public workshop from Dr. Yasinskaya.

Thank you, Dr. Yasinskaya.

FDA Presentation - Yuliya Yasinskaya

DR. YASINSKAYA: Good morning. My name is Yuliya Yasinskaya. I am a medical team leader for the Division of Anti-Infective Products, CDER, FDA, and I will present to you the summary of the March 1st FDA public workshop.

This workshop had taken the discussion that had occurred on the second day of the July 2016 workshop further and specifically focused on the status of animal model development and the role of animal models in the development of antibacterial products that target single species, Pseudomonas aeruginosa and Acinetobacter baumannii.

The morning session of the workshop delineated clinical and scientific challenges in

developing antibacterial drugs for such indications, provided clinical perspective and challenges in clinical trial design, as well as highlighted the lessons learned from the animal models for biothreat agents.

It was followed by the pathogenesis and pathogenic determinants for Pseudomonas and Acinetobacter infections, and in the afternoon, pharmacokinetic and pharmacodynamic considerations had been discussed followed by the animal model for Acinetobacter and Pseudomonas, their current status, and future directions. Both morning and afternoon sessions concluded with panel discussions.

The stage for the workshop had been set by the presentation of clinical scenarios of unmet medical need for the development of products for Acinetobacter and Pseudomonas followed by the discussion of the challenges in clinical trial design that had been already mentioned today by Dr. Cox and Dr. Nambiar, focusing on the narrow spectrum of activity of such products and the need

for concomitant therapies.

These type of infections are relatively infrequent and do span different organs. Thus, the typical clinical trial paradigm of focusing on a single organ of infection will not be readily applicable in these circumstances.

The infections are immediately life threatening and generally happen to have a pre-study antibacterial use. The use of antibacterials here is empiric due to delay in microbiologic confirmation.

Superiority trial designs are problematic for this type of infection, as it requires randomization to likely ineffective therapy and becomes totally infeasible once the new treatment has come to market. It was highlighted that PK/PD targets should be established prior to embarking on the clinical trial.

Animal models in antibacterial drug development had been used consistently, and generally those had been models of activity where the candidate products are screened generally in

small animal models to see the reduction in bacterial burden. This small animal model could also be used to establish and characterize PK/PD targets.

For the programs where the limited clinical trial data is available, a combination of animal models that are susceptible to clinically relevant bacterial strains with use of positive and negative bacterial controls could supplement the limited clinical trial data.

In the scenarios where the clinical trials are not feasible and animal models with sufficient closeness to the human disease exist, such models could be used for efficacy trials to support approval under the Animal Rule.

During workshops, there were two examples of clinical trial development programs targeting single pathogens that had been presented. Entasis Therapeutics had presented their program for non-beta lactam beta-lactamase inhibitor in combination with sulbactam to target Acinetobacter baumannii, and they will have an opportunity to

present their development program here today.

Polyphor had presented their program for murepavadin that targets outer membrane of Pseudomonas aeruginosa, including multi-drug-resistant strains. Their workshop presentation will be summarized today by Dr. Peter Kim, my colleague from the Division of Anti-Infectives.

The investigators for the infections of biothreat indications had shared their experience with developing models for pneumonic plague, pneumonic tularemia, and inhalational anthrax. Two of these models, African Green monkey and New Zealand White rabbit, had been used for the approval of products under the Animal Rule.

This is a model that represents a best-case scenario because the strains that cause human disease are fairly limited as compared to the infections we're discussing today at the advisory committee. The pathogenesis of the disease in humans and animals had been well characterized. The pathology in animals and humans is critical in establishing the animal model, and the clinical

course of this disease had been described via observation and telemetry in the animals.

The investigators delineated appropriate challenge doses with the clinically relevant isolates and the specific and non-specific indicators of the established disease had been established and characterized in order to identify clinically acceptable trigger and timing for intervention.

All the speakers have highlighted that development of these models have been lengthy, and it was an iterative process that allowed them to arrive at a final therapeutic model. The quality management systems and operating procedures have to be established from the outset, and close interaction with the FDA were critical to the success of these development programs.

The pathogens that we're going to be discussing today are very different from those of the biothreat agents. Pseudomonas aeruginosa, for example, is an opportunistic pathogen. It's highly adaptable and exhibits distinct virulent factors

depending on the site and the source of the infection, allowing for both acute and chronic infections to set in.

For Acinetobacter baumannii, although it is not opportunistic in men, it is in animals, and therefore requiring immunosuppression models in a majority of the models and therefore raising some question of how applicable these models might be for human condition. In vitro assays in general do not predict performance in vivo, however, there are some room for non-mammalian hosts used to characterize the novel virulence factors and resistance mechanisms.

The understanding of PK/PD for various models of infections is crucial for any product, antibacterial product development, and murine models of infection that assess bacterial burden have been used successfully in the past and will be likely in the future.

The PK/PD parameters have been established for sepsis, skin, and lung infections, and this model allows for testing of different clinical

isolates with variable MICs. Models showed good correlation to clinical outcome once PK/PD targets are established. However, there are no models without limitation, and for a lung infection model in the mice, this specific limitation here highlighted, there are some differences in lung anatomy and physiology in the pattern recognition receptors between mice and humans.

There are also antibacterial secretions present but lack neutrophils and defensins. There are also some differences in the drug penetration into alveolar macrophages and pulmonary epithelial lining fluid.

The rest of the workshop was dedicated to the presentations on the specific animal models of Pseudomonas and Acinetobacter infections. I will give you some examples that had been brought up during workshop.

On this slide, you can see the description of neutropenic murine model of Pseudomonas aeruginosa pneumonia. In this model, clinical relevant strains and inocula could be used and the

strains with variable susceptibility profiles have been proven successful.

The clinical signs could be monitored, and it has been shown that hypothermia, bradycardia, hypoxemia, and disorientation were predictive of imminent mortality. This model is a survival model. In addition to survival, target and bacterial burden and dissemination rate could be assessed. This model is also suitable for testing drugs and biologics alone and in combination.

As an antibacterial, baumannii infections had been presented using murine and porcine models of infections. These models also require immunosuppression, so both models are neutropenic.

In a pulmonary murine model, it allows for the testing of multiple strains and clinical relevant isolates. Specifically it highlighted the AB5075 strain of infection that is clinically relevant and disseminates in this model. This model is also a survival model, but organ bacterial burden had also been assessed. It had been shown to have reduction in bacterial burden and

improvement of survival with use of rifampin as a positive control.

Wound infections in pig and mice had been presented as well. A punch biopsy was used to standardize the wound. Use of positive controls had been performed, and outcomes assessed were wound area size as well as timing of closure, in addition to tissue bacterial burden per gram of tissue. Gross and histopathology in this model seems to replicate the human condition, and this model also allows for biofilm, cytokine, and chemokine evaluation.

The last two models that had been presented were models of Pseudomonas aeruginosa pneumonia that attempt to replicate ventilated-associated pneumonia in humans. This rabbit model closely resembles human disease in the inoculum pathogenesis and symptomatology. It allows for continuous ventilation and monitoring of vital signs, laboratory parameters, including blood gas, blood culture, and EKG. This model is also a survival model, and mortality in this model had

been deemed due to shock or multi-organ failure.

Ventilated pig model of Pseudomonas aeruginosa pneumonia even closer approximates human condition due to similarity in anatomy and physiology, as well as ventilated-associated pneumonia disease pathogenesis could be replicated, allowing for oral secretions aspiration, and gravity dissemination that had been confirmed by x-ray and lung pathology where right upper lobe had been spared.

This model is characterized by lack of significant hemodynamic instability, which is similar to that of humans, and intensive care-like settings are employed in this animal model. The animals are sedated, paralyzed, and ventilated.

As I had mentioned before, both morning and afternoon session had concluded with a panel discussion, and the key discussion points are presented here. It had been brought up that models similar to African Green monkey for plague will be difficult to develop for Pseudomonas and Acinetobacter baumannii infections due to variable

degrees of intrinsic virulence and differences in susceptibility of animal hosts.

It would be helpful to have consistent results across various animal models with the clinically relevant strains and mammal and non-mammal models could be used, immune suppressed, immune-competent model, and small, and large.

Sensitivity of the animal models could be assessed using positive and negative antibacterial controls from what we know in clinic, and monitoring of disease biomarkers and assessing histopathology in these models are critical. It's important also to test diverse, clinically relevant isolates with a well-described pedigree in the animal models.

The workshop had concluded to state that there is really, at the moment, no single animal model that might be best suited to study infections caused by Pseudomonas aeruginosa and Acinetobacter baumannii. However, there is utility to each of the models presented. And now with some short-term refinements and continued developmental work,

animal models can provide useful information to support the development of therapeutic agents for this critical unmet medical need conditions. Thank you.

DR. BADEN: Thank you.

We will now proceed with a presentation from Dr. Isaacs on the challenges with clinical design for a drug targeting a single species of bacteria, Acinetobacter. Thank you for sharing your thoughts with us.

Industry Presentation - Robin Isaacs

DR. ISAACS: Thank you. I'm grateful to be able to be here today to present on Entasis Therapeutics. My name is Robin Isaacs. I'm the chief medical officer of Entasis Therapeutics.

Entasis Therapeutics is a biotechnology company based in Waltham, Massachusetts. Our focus is on the development of antimicrobials to treat multi-drug-resistant gram-negative infections. The views expressed today are those of Entasis. The issues that are under discussion today are not theoretical to us, And we look forward to the

committee's deliberations.

As an ID physician, I'm fully aware that there's a very strong desire for people to get broad-spectrum antimicrobial therapy, but this isn't always possible, and this is particularly true of Acinetobacter baumannii and Pseudomonas aeruginosa infections.

Drug development is a complex and difficult challenge, and this is particularly true for antimicrobial agents. Pathogen-specific agents represent one potential path for the treatment of the difficult pathogens under discussion, and so too Acinetobacter baumannii.

Acinetobacter baumannii is a significant unmet medical need in the United States and in the world. It is one of the so-called six escape pathogens. The pathogens are listed at the bottom of the slide. In the U.S., there are somewhere between 60,000 to 100,000 infections a year, and in the big five EU, there is approximately 130,000 infections per year. Common infection sites include the bloodstream, lung, urinary tract, and

skin.

Acinetobacter baumannii causes infections among critically ill patients. The mortality rate can approach 40 percent or more with current therapies. Of potentially even greater significance, 60 percent or more of Acinetobacter baumannii isolates on a worldwide basis, including the United States, are multi-drug resistant.

In the data you can see in this table, this represents carbapenem-resistant Acinetobacter baumannii on a global basis, with the overall weighted average of 64 percent resistant to carbapenem. This is truly a major unmet medical need and a significant problem.

Entasis Therapeutics is developing a beta lactamase, beta lactam combination therapy, a beta lactamase inhibitor, beta lactam combination therapy, ETX2514SUL, to treat Acinetobacter baumannii infections. This is a pathogen-specific drug.

Interestingly, sulbactam, which many of you know in unison as a beta lactam inhibitor, a beta

lactamase inhibitor, is actually a beta lactam antimicrobial that has high intrinsic activity against Acinetobacter baumannii.

Unfortunately, over the last 10 years or so, this activity has diminished due to primarily the development of beta lactamase-mediated antimicrobial resistance to the point that, in our studies, only about 30 percent of contemporary Acinetobacter isolates are susceptible to sulbactam.

ETX2514 is a novel, non-beta lactam, beta lactamase inhibitor, which has extraordinary broad activity, with broad potent activity inhibiting against classes A, C, and class D beta lactamases.

ETX2514 restores the in vitro and in vivo activity of sulbactam in animal models against contemporary multi-drug-resistant Acinetobacter isolates. So for example, in our large panels, which have in excess of 1,000 isolates now, sulbactam has an MIC90 of 64 milligrams per liter. With the addition of ETX2514, the MIC90 drops to 4 milligrams per liter. And in a large collection

of 2014 isolates, greater than 99 percent of them had MICs less than or equal to 4 milligrams per liter.

The development, however, as has been noted by previous speakers this morning, of drugs of a pathogen-specific drug against Acinetobacter baumannii is challenging. These are some of the challenges that we face as we move this program forward into patients.

Firstly, identification of patients with Acinetobacter baumannii infections. These represent only approximately 2 percent of hospitalized gram-negative infections, although this is somewhat variable depending on the site in the hospital. For example, in NHANES data, it's somewhere between 5 and 8 percent in the intensive care unit in patients with ventilator-acquired pneumonia. In other areas of the hospital, it's less than 5 percent, in the range of 1.5 to 2 percent.

The patients who get Acinetobacter baumannii infections are sick. They are usually

hospitalized. They're generally compromised in their health, not immunocompromised as such, but generally compromised. They're often found in intensive care units. They're generally receiving broad-spectrum coverage, and many of the patients have renal impairment because of significant illnesses that require treatment. About 40 to 50 percent of the patients have pulmonary infections.

So how do we translate this into a development program? I'm going to take this over the next two or three slides in sort of answering slightly different questions about how we moved this forward, and then finish up with a conclusion.

The question I think we have to ask for a new therapy targeting unmet medical need is what is the unmet medical need. And in the case of Acinetobacter baumannii infections and Pseudomonas, the two pathogens you're considering today, it's the multi-drug-resistant pathogens.

Although Acinetobacter baumannii infections are relatively uncommon, multi-drug resistance, as I noted earlier, is very common. If we can

identify Acinetobacter baumannii by routine microbiology within 48 hours of diagnosis of a potential infection, we can enrich for multi-drug-resistant infections by just enrolling patients with known Acinetobacter baumannii who have less than or equal to 48 hours of prior therapy.

Prior knowledge of Acinetobacter baumannii would therefore be critical for enrollment, but prior knowledge of the susceptibility is not because, to repeat again, approximately 60 percent will be multi-drug resistant.

To echo a comment that Dr. Cox made at the beginning, a rapid diagnostic test would be useful to enrich enrollment, but, as he pointed out, it doesn't alter the underlying incidence of disease. All it does is it helps you identify patients earlier, before they get other therapies.

So what it does is it minimizes prior antimicrobial therapy, which is useful, very useful, in helping in the efficacy assessment in the studies.

Where do you find patients with

Acinetobacter baumannii? You find them generally in intensive care units or certainly in hospitals, and hospital-acquired and ventilator-acquired bacterial pneumonia has the highest incidence in the order of 5 to 10 percent in the U.S.

There are also geographies in the world where Acinetobacter is much more common. And this figure, which is taken from a paper by Chung, et al., I just highlighted and read a couple of countries where there are extraordinary high rates of Acinetobacter relative to other countries in terms of the hospital-acquired and ventilator-acquired pneumonia rates.

So for example, if you look in Thailand, about almost 30 percent of hospital-acquired pneumonia and nearly 50 percent of ventilator-acquired pneumonia are associated with Acinetobacter infections.

There is no easy way to do simple studies in relatively healthy patients with Acinetobacter because the patients who are infected with Acinetobacter tend to be generally unwell. So

before one can go into those populations, one needs to demonstrate, A, that the drug gets to the site infection.

Given that 40 to 50 percent of patients have pneumonia, you need to demonstrate pulmonary trinitration. And given that they're generally unwell and may have renal insufficiency for renal-excreted drugs or for hepatically-excreted drugs, you need to test and to identify dose adjustment as required.

In the case of sulbactam and ETX2514, both of the drugs are renally excreted, so studies to understand renal dose adjustment are necessary before one can study in the population of interest.

There is a need for some standard pre-clinical efficacy data prior to the clinical studies so that one can establish the pharmacodynamic targets, the PK targets likely to be predictive of efficacy, and then using those pre-clinical targets to establish clinical dose using robust modeling of phase 1 PK and the pre-clinical PD targets.

While establishing phase 3 readiness, once you get a limited amount of safety data in relatively healthy patients, this provides a baseline to review safety data in much sicker populations.

So how do we establish efficacy? This is our thoughts on establishing efficacy for Acinetobacter baumannii, an event-driven study based on multiple drug-resistant pathogens. So what does that mean? It means you enroll people with Acinetobacter infections, but the primary analysis would be on those patients who have multi-drug-resistant pathogens.

Second, enroll patients with proven infection. Third, focus on the most common infections, so lung and/or bloodstream. Allow other patients with other infections into a parallel, non-comparative arm in the study to collect supportive data.

Do a non-inferiority study with a test for superiority if non-inferiority is met. That means identifying standard of care. Currently, standard

of care is colistin plus or minus a carbapenem. In some countries, tigecycline is used depending on resistance pins.

Utilize a hard endpoint, for example, 28-day mortality. So we know that, for colistin, based on a detailed review of the literature, the mortality associated with colistin therapy is around 40 percent. There are literature out there of essentially no treatment where it's about 80 percent mortality. So one could propose a non-inferiority margin of approximately 20 percent.

Under those criteria, one could set a phase 3 study, non-inferiority comparing ETX2514 sulbactam against standard comparator. We would need around 200 patients to provide 118 patients with multi-drug-resistant infections, and such a study would have 80 percent power with a two-sided 95 percent confidence interval if one assumed a 40 percent mortality in the comparator group and a slightly lower mortality of 35 percent in the experimental group; still a challenge, but a relatively smaller number of patients than people

tend to talk about in some of these studies.

So once you've collected that data, what might a package for a new drug application look like?

A strong microbiology package; strong evidence of in vivo efficacy in relevant animal models;

Robust demonstration of PK/PD parameters based on in vitro hollow fiber and in vivo animal models;

Establishing a dose for phase 2 and phase 3 based on high probability of target attainment using robust modeling of pre-clinical and clinical data;

A safety dataset of approximately 300 to 400 patients and/or subjects, this is consistent, as was noted earlier, with FDA guidance documents; and demonstration of efficacy compared to standard of care in a single phase 3 non-inferiority study with comprehensive justification of the non-inferiority margin from published literature.

This isn't easy, but it is potentially

achievable. I thank you for your time.

DR. BADEN: Dr. Isaacs, thank you.

I am sure members of the committee have many questions from the presentations we've heard thus far. We will have discussion and be able to ask our speakers questions at the question period around 11:00. So please save up your questions, and I appreciate the speakers being willing to clarify issues that the committee members may have.

Dr. Kim will now present on a pathway for Pseudomonas compound. Thank you.

FDA Presentation - Peter Kim

DR. KIM: Thank you, Dr. Baden.

My name is Peter Kim. I'm a medical officer in the Division of Anti-Infective Products, FDA, and I'll be presenting an example of a development program targeting Pseudomonas aeruginosa.

POL7080 is an antibacterial drug with activity limited to Pseudomonas aeruginosa. It has no activity against gram positives or other gram negatives, including Enterobacteriaceae. It targets an outer membrane protein of Pseudomonas

aeruginosa.

While the sponsor has elected not to present at today's meeting, FDA will present a summary of the development program based on information discussed at the FDA public workshop held on March 1, 2017, and there is the link to the meeting materials. We should note that FDA's presentation of this information should not be considered an endorsement of the development program for POL7080.

Now for some background information. The sponsor noted in a neutropenic mouse lung infection model that increasing total daily doses of POL7080 resulted in greater log reductions of Pseudomonas aeruginosa, including isolates resistant to polymyxin B. The sponsor used PK/PD modeling in an effort to determine the PD target and inform selection of a dose for clinical testing.

Regarding clinical studies, the sponsor has completed six phase 1 studies and two phase 2 studies. Phase 1 has included but is not limited to drug-drug interaction studies with colistin and amikacin as well as an assessment of PK and safety

in participants with renal impairment.

Phase 2 included two relatively small studies, one in patients with non-cystic fibrosis bronchiectasis and the other in patients with ventilator-associated bacterial pneumonia, and in that study, 12 patients had confirmed Pseudomonas aeruginosa.

At the March 1st workshop, the sponsor presented a proposal for a multi-center, randomized, parallel group non-inferiority trial to evaluate the efficacy, safety, and PK of POL7080 in patients with HAPB/VAPB due to suspected Pseudomonas aeruginosa.

Patients would be randomized 1 to 1 to the following treatment groups for single coverage against Pseudomonas aeruginosa. In the study arm, patients will be treated with POL7080 plus ertapenem, and in the control arm, patients will be treated with meropenem.

The sponsor noted that ertapenem at a dose of 1 gram IV daily was modeled and appears to achieve acceptable levels of exposure in VAPB

patients. We should note that, in the U.S., ertapenem is approved for community-acquired pneumonia and not HAPB/VAPB. Ertapenem does not have activity against Pseudomonas aeruginosa.

The sponsor also proposed that in the protocol, there would be allowance for concomitant use of amikacin for empiric dual anti-pseudomonal coverage in both arms at the discretion of investigators until culture and susceptibility results were made available for a maximum total duration of 72 hours. The investigators would decide whether to administer dual coverage prior to randomization.

The proposed primary endpoint would be 28-day all-cause mortality in the microbiologic intent-to-treat population, that is, those with confirmed Pseudomonas aeruginosa. A rapid diagnostic test would be used to aid in identifying these patients. Based on feedback from key opinion leaders, the sponsor considers the proposed trial design feasible at centers with less than 10 percent multi-drug-resistant Pseudomonas

aeruginosa.

At the March 1st workshop, the sponsor noted the following challenges with conducting a phase 3 HAPB/VAPB trial. At an incidence of 22 percent of Pseudomonas aeruginosa, the sponsor estimated that over 3,000 patients would need to be randomized if a 10 percent NI margin was specified.

They also noted that superiority would be difficult to demonstrate; there may be challenges in enrolling patients in a study treating Pseudomonas with monotherapy that may be difficult to discern the treatment effect of POL7080 in the context of concomitant antibacterial drugs that may also cover Pseudomonas; and there could be challenges with obtaining consent quickly in HAPB/VAPB patients. Thank you.

DR. BADEN: Thank you, Dr. Kim.

We are running a little bit ahead of schedule, and I want to acknowledge our Web audience, where we have more than 100 viewers, I've been informed. We will take a break now for 18 minutes and resume at 10:00, and this can allow

our web audience to calibrate as well. And we'll resume with Dr. Perl's comments.

Thank you to the speakers, and see you all in 18 minutes.

(Whereupon, at 9:42 a.m., a recess was taken.)

DR. BADEN: Thank you all for taking your seats. We shall resume the meeting. We'll now proceed with a presentation from Dr. Perl, sharing with us some thoughts from the Infectious Disease Society of America.

Thank you, Dr. Perl, for joining us.

Presentation - Trish Perl-DeLisle

DR. PERL: Thank you very much. I am honored to be here talking to you.

My name is Trish Perl, and I am the chief of infectious diseases at UT Southwestern. I see patients at Parkland Hospital, which is one of the largest safety-net hospitals in the country, also at a university hospital that does tertiary and quaternary care, and at the second-largest VA in the country.

So I'm in the trenches, and I'm here not only to present on behalf of the Infectious Disease Society of America, but also to represent the 11,000 infectious disease physicians and providers out there who are dealing with these problems day in and day out.

I will say that some of the slides that are here today have already been dealt with by some of the previous speakers, so I may go over them quickly. And I also want to say that I'm a member of the board of the Infectious Disease Society of America, so I am in the position also to help make sure that this discussion is front and forward with our leadership.

So Infectious Disease Society, as I said, has 11,000 physicians and providers that provide primary care. As you can see, most of them do patient care, but many of them are involved in clinical microbiology, healthcare epidemiology, and are dealing with the issues of resistance day in and day out. We see the ravages.

Right now, even though I have gray hair and

look old, this is not a time that many of us are used to in that we're returning to a pre-antibiotic area. And the emergence of the mcr-1 and 2, which are highly resistant organisms and resistant to most antibiotics that are known to our generation, are transmissible on plasmids, and hence can be shared by multiple bacteria, and are causing infections that are difficult for us to treat. And yes, I think we should be scared and concerned about the ramifications of the increasing resistance that we're seeing.

We currently use antimicrobial agents where we have extremely limited and negative data, and some of these agents are actually very toxic. We use inhaled and parenteral colistin, which is a drug that was pulled off the shelf having had been developed before I was born, I think. And we're using things like phosphomycin for ESBL infections, where there's extremely limited data. And as someone mentioned earlier, tigecycline is being used despite warnings and known toxicity.

So while we are very interested in

prevention of this, and being good stewards of antibiotics, and monitoring this, we also recognize that this needs some additional and new tools.

This is from the CDC and represents the current U.S. antimicrobial threats. And if you look now, what you can see is the list of threats that the WHO also recognizes as urgent or emergent problems. And the list unfortunately is growing, and some of these have moved from being serious threats to urgent threats.

So I'd like to take a minute to present a case. I will say this is 1 patient and a very unfortunate story of 1 patient. But like several of you in the room, I can tell you also that there are many, many stories like this, and there are unfortunately even outbreaks of organisms similar to the one I'm talking about.

This is a 71-year-old lady with laryngeal cancer who had a laryngectomy, chemotherapy, radiation, and she was cured. She was at home on oxygen, had been recently admitted for tracheobronchitis, and was transferred from her

rehabilitation hospital back to a hospital in Boston -- actually, this is a case from Helen Boucher -- with fever, flank pain, and respiratory failure.

Her history was also significant for cough and sputum production. She had no fever, chills, or other constitutional symptoms. She was evaluated for viruses although studies were non-contributory.

Her blood sputum cultures grew a gram-negative rod that was ultimately identified as a multi-drug-resistant Klebsiella pneumoniae that produced a carbapenemase. She did well. Her blood cultures were cleared. She did not need to be intubated. And she was actually treated with a cocktail that included tigecycline, colistin, and inhaled colistin, and then she was switched from that to IV minocycline.

She was then admitted again in January and May, and she presented with respiratory failure, tracheobronchitis, along with a urinary tract infection. She was discharged on levofloxacin, but

again the sputum and urine cultures grew a carbapenemase-producing Klebsiella pneumonia.

Four days later, she had increasing oxygen requirements, and per the emergency room felt very tired, had urgency and other urinary symptoms, flank pain, was febrile, and her culture again grew the Klebsiella that was carbapenemase producing.

Here's the antibiogram, just to give you a sense of the resistance, and you can see it's resistant to penicillins, cephalosporins, meropenem, and other carbapenems, many of the aminoglycosides, fluoroquinolones, trimethoprim sulfa, and some of the newer agents.

After discussion about the limited options, the predictable renal failure, and neurologic, and other toxicities, the patient and her family decided on hospice care. So here is an unfortunate lady who was dying of a multi-drug-resistant infection and had been cured of her cancer.

So what did we learn from this case? We learned that infections caused by resistant pathogens are serious, they can happen to us, to

our families. We also learned that our pharmaceutical armamentarium is limited and commonly associated with very toxic agents.

It also gives us a hint that maybe we need to rethink things and perhaps drugs that target single pathogens have a place that we can even think about personalizing our approach to infectious diseases.

The data we have often is less than what we would want. And data on patients with infections at standard body sites are a foundation from which we built, but clinically, we extrapolate all the time to treat infections. And while we would like to go by textbooks, we are in an era where there are no textbooks.

So what we are now doing is working from a variety of sources and our own observations. So our aim today from an infectious disease society perspective is to really make a case for approaching a problem with a creative solution and thinking about the registration of narrow-spectrum agents.

One of the things we really want to recognize is this group has made tremendous progress. There have been multiple workshops, as you have heard, and we have come a long way over the past couple of years, really, in having this discussion.

There are still gaps, so as we're talking about this, I think we should recognize this is a huge step forward. We do think there's a role for narrow-spectrum single-pathogen drugs. And as you've heard from the previous speakers, there have been workshops that have really set the background, if you will, for making this argument.

We think that we have to rethink how we do this and consider pooling not only information we get from multiple patients, but from multiple sites.

There are other important issues, and we don't want to lose sight of those. They may be separate or parallel discussions that need to be considered, but there are bloodstream infections or endocarditis, osteo, that also have some similar

challenges. There needs to be improved, and developed, and more futuristic approaches to susceptibility testing. And these pathogen-specific indications may require different avenues for us to think about as we move forward in this discussion.

So we have limited drugs. Many are toxic, and we have limited data for the desperation combinations that we are using. So let's talk a little bit about these narrow-spectrum agents and some of the thoughts that we have.

One of the things I neglected to say in my opening is that a paper that was written by Helen Boucher in a group at the IDSA has been accepted at JID, and a lot of the slides and the concept from the IDSA will be forthcoming in that.

This is a schema that is in that particular white paper, And what this shows along the Y-axis is the quantity of clinical efficacy data that we normally expect or can generate with clinical trials. And then along the X-axis are a cartoon, if you will, of potential scenarios.

So the column A represents the traditional FDA trajectory, which is three studies. Column B is the three studies plus some smaller studies. And then what we're now moving into is a new arena, where we may want to start thinking about smaller studies or the FDA rule.

This is the area where we can start discussing these pathogen-focused approaches for unmet needs. What this will require us to do as a scientific community is really to think about the acceptance of smaller clinical datasets that may be imperfect to meet this need.

Then along the top is the arrow that indicates that we're going to have to, if we're going to take this approach, really think about increasing our reliance on human PK data to enhance the information that we have as we're moving into the arena of caring for patients.

We do want to make sure that there is one disambiguation, if you will, if I said that correctly. And if you think about the phase 3, you can see that C area, those smaller studies. That

and the pathogen-focused pathways can be confused, and they shouldn't be.

Really, when we talk about pathogen-focused pathways, we're only talking about a narrow spectrum for a single agent. Tier C studies could involve broad-spectrum agents for very rare infections or any spectrum developed for a specific focus. But when we talk about these pathogen-focused pathways, we really are talking about a single pathogen.

So there's good and bad news in this. The tier A and B are well and truly launched, and they have been the standard approach that we use for development of infectious disease agents. There is well-developed guidance to support this, and a lot of programs are proceeding. The bad news is that this tier B that is a little less structured has been criticized. And I'm an epidemiologist. I'm part of that group, but I think we also have to recognize that we have a new reality and that we're going to have to balance some of these things.

The other piece of bad news is design

options for these rare pathogens and narrow-spectrum drugs are a little less obvious. So efforts to direct and pursue this, such as trying to show superiority, as was mentioned earlier by a couple of the speakers, have failed.

The classic example is the difficulty that Achaeogen had in terms of screening many, many, many patients to actually identify very few potential patients that could be enrolled in their study.

This is a summary slide, and people have talked to you about this workshop, so I'd just really like to focus in on one area if I could. This is from the July 19th workshop, where they really worked through some hypothetical areas to try and understand how to better approach this.

What you can see along the columns, the rows actually, are the different infections. So you have pneumonia, you have intraabdominal infection, you have UTI, and then you have skin and soft tissue. And then you have, along the columns, some estimates of the prevalence of these agents. And

if you look on the far right, what you'll see is the consensus.

So you can see that, for Pseudomonas aeruginosa, the consensus, if you take all of this body of literature, is that these are relatively rare. This is just the isolation of these pathogens. This isn't actually looking at whether or not these people could be potentially enrolled into a clinical study, so it's almost like the best-case scenario.

Now, if you translate that and start looking at what that would mean for a non-inferiority clinical trial and say you take your culture positivity rate -- and I just showed you that 15 percent was about the rate. If you go to the very, very bottom row, what you see is if we had 30 percent culture positivity -- and this assumes that we can get everyone in there -- you'll see the number of patients you would need in each arm, around 1900.

If you move over to your right and you look at a culture positivity of 15 to 6 percent, what

you can see is the total number of patients that would need to be enrolled can go from anywhere from 3800 up to 19,000. And we all know that's not going to be feasible for an agent like Pseudomonas or Acinetobacter.

Now, all of us love diagnostic tests, and we recognize the critical need for diagnostic tests, but this isn't going to solve our problem. This is not going to create patients that can be enrolled in clinical trials. This just tells us how many patients have it.

These tests help us better select patients that can be enrolled in studies, but they're not going to identify all of these infections that may or may not be there. And the sponsor still has to screen all of these patients to make sure that they can be enrolled in these studies. So we are not convinced that non-inferiority is an option.

An earlier speaker from the FDA talked a little bit about the superiority clinical trials and also mentioned that this may not be a reliable path, either. In fact, if you look at the example

of extremely resistant Pseudomonas aeruginosa, what you can see is that, first of all, it would require the emergence of extremely resistant strains, which none of us are convinced is a good thing. It's not predictable, and it potentially could, as I said, be very, very devastating for our public health.

If we compare a new drug with standard of care versus standard of care, standard of care is commonly not clear with these agents. We are individually making up cocktails. We call our friends to say, "What did you use in this?" But the standard of care is unclear in this particular setting.

So I'm not sure we could define for you what a standard of care should be. And there's a very low chance that new plus standard of care could beat standard of care, and we may not have even enough patients to actually really define that.

As Pranita Tamma very nicely said, "Meta-analyses that have been conducted, exclusively evaluating randomized clinical trials, demonstrate no difference. But there are well-

documented increases in toxicities with these combination therapies, which is the other risk."

So what do we do? There have been mention of a couple of potential pathways, and there are four things that we should consider. One is the consideration of using PK/PD-based dosing. So this is looking at pharmacokinetics and dynamics, and actually trying to enhance the doses that we give people.

The pharmacists have been talking about this for a long time, and I think we really are gaining increasing knowledge and understanding of how we can enhance the predictability, and effectiveness, and efficaciousness of these drugs in a variety of body sites and lung sites. And we can garner a lot of information from looking at this, and I'll show you in a minute, even to the point that we can use this information to predict clinical outcomes.

We can look at validated animal models and fashion this after the Animal Rule based on one of the previous FDA workshops.

Here is the PK/PD data, and this doesn't

really tell you about toxicity, but drugs with well-validated dosing regimens can very consistently succeed in P3 studies.

So what this graphic actually shows you is that the probability of the PK/PD target attainment actually being clinically efficacious is relatively well correlated. And out of the 20 pneumonia programs that were looked at with 17 antibiotics, 14 actually received regulatory approval based on clinical data but had already had appropriate PK/PD information.

In terms of the animal models, I'm not going to reiterate what was said by previous speakers, but just really to point out that you can use this information in ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or disabling biologic, which is what we're interested, agents. So there is a precedent for this.

The other thing that's important about the animal rules is the postmarketing studies. We would actually really like to highlight this as one

of the components we think is critical if we integrate this kind of information into moving forward. These field studies really help provide information about safety clinical benefit in circumstances that arise.

So the other things to consider when you're thinking about these kinds of things is having some kind of surveillance system that will keep track of and garner all the follow-up information that you would collect, and then also think about ways of labeling to patients that really explains some of the ethical and feasibility reasons behind a drug's approval.

The two other considerations that we think are important are validated external controls and then the use of very small clinical datasets, which would require a pooling of data from multiple body sites. And I think that last one, I have a couple of additional comments I'll make.

So in terms of validated external controls, we do need to assemble well-defined sets of controls. There need to be enough to permit

reasonable matching to patients that get a test agent. There are a lot of issues with controls. Are they people who have less resistant organisms or are they just people in the hospital? I mean, what is a good control? Then you have to have enough data on the controls to be able to control for or to analyze some factors that may actually confound or alter the outcomes.

The pros of doing this is it's feasible. It's a technique we've used for a long time in epidemiologic studies. It permits clinical studies to put all patients on a test, and you kind of maximize the experience of a test.

The con is that they're easy to criticize as a weak approach. That being said, there's certainly data out there that well-designed case control studies, which essentially is what we're talking about, can actually provide you at least some reflective data that can be useful and reflect the truth, if you will.

In terms of very small clinical datasets, there's a lot to say for this. They can help focus

analyses and at least give us some information that we can use. We can't expect the level of information that we would get from a non-inferiority kind of analysis, but it is at least something that could be feasible.

We could also pool data from multiple sites. We would think about how to do that, maybe permit up to 48 hours of prior therapies so that you could enroll people. This would certainly push microbiology labs a lot. And you could also consider some more sophisticated analyses to enhance the quality of information that you get from this.

Both routes I think will provide some quality information. I think we also need to all recognize that there will be complaints, and there's not going to be a perfect solution.

The other thing I will say about very small clinical datasets is it's going to require somewhat of a paradigm shift than what we've been using in medicine. We tend not to share these data, and they haven't been available in the public domain in

a way that this kind of approach is going to need. So that also will require your leadership moving forward, and also I would say, IDSA's.

So these are the four potential ideas that have emerged. Possible plans could be combining some of this. You could have something like Animal Rule animal models with zero clinical efficacy data. You could have good animal models with some clinical efficacy data. There could be variations on this theme, if you will.

We do need to pull out our steel backs. There will be criticism. And I think either action or inaction is going to have risks and will lead to criticism. Some stakeholders have shown unrealistic thinking, and there are some recent examples, including the recent approval of an agent for mucormycosis.

In that, what we saw was an editorial with three senior academics that said the FDA needs to facilitate simpler and less challenging pathways, and then we shouldn't have approved this drug.

So we're in a catch-22 in a way, and part of

this process is going to be educating all of the stakeholders on the risks and the benefits, but also putting it into context of a really critical unmet need.

Other things to think about and development options, I think all of us would love to see the FDA develop a briefing document and enhance the briefing document. But I guess what we would say is the non-inferiority trial, while it's great in many instances, may not be feasible in this particular instance. Superiority trials, we agree, registration can depend on rare and accidental events such as a window in time when standard therapies are inadequate.

We could consider approval on the Animal Rule. Approving based on clinical trials in animals doesn't always make sense, but when it's possible to move forward with some clinical data, this could be helpful. And then we can use some surrogate endpoints and maybe work towards an accelerated approval. And this is where we really think the role of the PK/PD makes good sense. And

again, we'd love to see it married with something such as an animal rule or some clinical data.

There are not any simple ideas, and there are really, at this point, as far as we can see, no tricks that we can pull out of our hat.

So in summary, what we'd say is that we are currently treating patients with drugs that are toxic, where we have limited or no data. We're using combinations that are based on our best guesses.

We are looking ahead towards maybe new pathways to start dealing with some of these critical agents that are not necessarily going to be very common. And we think a reliable path may be a new path where we take novel ideas or other techniques, if you will, and start integrating them into a process where we can move some drugs forward for meeting this unmet need.

Then we think, as had been mentioned, that there are other mechanisms out there that will really support this type of path, including the LPAD mechanism. I can certainly say personally as

an ID physician that I think that the IDSA is really committed to making sure that there are content experts out there that are going to support any kind of moves that are in the process of occurring, and certainly we will want to assure that we lead stewardship efforts and other efforts that are going to facilitate this moving forward.

Finally, just to reiterate, the future resistance is pretty grim, and the list at the bottom are the WHO pathogens that have moved to the critical priority area. And for those of you who do take care of these patients, you will agree that it's very, very frustrating to actually not be able to cure someone from an infection.

What are we going to do as a society? We are going to work on educating the public. We think that's going to be important in moving this type of process forward. We are certainly going to be -- we will take a lead in trying to enhance clinician education about treatment guidelines, about the new processes hopefully that will be developed to look at these kinds of drugs, and

about the importance of stewardship.

We will continue to advocate for groups like this that we think are pushing new ideas forward, and we're more than happy to provide the technical expertise to support this kind of process. We do, however, feel that we need to act now, that this is critical, and that we don't have a lot of time.

These are our faces of resistance and people who shared their stories, and many did not survive their infections. So I just want to thank the group that has really championed this effort at IDSA, and thank you for this time.

Clarifying Questions

DR. BADEN: Thank you, Dr. Perl.

We will now move to a clarifying question part of the agenda. I just want to frame a little bit what the agency has asked of us. We're to provide guidance for a very real threat to health, as we have heard, yet it is conceptual. And that creates a challenge when guidance is often grounded in the particulars of a circumstance.

They have provided us information on two

real examples, but these are examples, not specific products that we are here to debate. But I think we need to leverage them to help explore the issues, to provide guidance as to a pathway to advance new therapies, which I think we all would agree we need, but how to do that, balancing the competing interests that have been raised?

This is restricted to the serious uncommon infections. I don't think our discussion is to expand to all anti-infectives. It's a narrow area of an important unmet need, and that our discussion should take that into consideration and work under that assumption related to uncommon, serious, life-threatening, limited other treatment options as the framework that we've heard from this morning.

I would like to make sure that the agency and Dr. Cox, Dr. Nambiar don't disagree with any of my framing, as that will facilitate some of the discussion over the next few hours.

DR. COX: The framing sounds good. Thanks.

DR. BADEN: In our discussion, please get my attention or Lauren's attention, so we can keep

track of those with questions. As we get on certain themes, if we can build on those themes, please let Lauren or myself know if you have a follow-on question to the area of discussion that is being pursued.

Are there any clarifying questions for the presenters? Please remember to state your name for the record before you speak. If you can please direct questions to a specific presenter, that would facilitate the discussion.

Dr. Daskalakis?

DR. DASKALAKIS: Demetre Daskalakis, New York City Department of Health. I actually have a question for Dr. Nambiar, just a clarifying question, and maybe a little bit more depth on, I think, a really provocative bullet on slide 16, which talks about treatment effect and using treatment effect to decide on a potential margin for a non-inferiority study.

So I have three directly linked questions around that, which is, how is treatment effect estimated for a novel agent? Will that margin then

be dictated drug by drug in each study? And then, does that mean that there is no standard treatment effect in that framework for a non-inferiority?

DR. NAMBIAR: Yes, sure thing. So first, in terms of treatment effect, we are talking about treatment effect of an antibacterial drug over no available therapies for a specific indication.

So if you take the indication of HAPB/VAPB, just as an example, we've estimated the treatment effect, and we really didn't have a lot of data on untreated patients. So where we were able to derive the treatment effect was based on patients who got inappropriate therapy.

So we have a treatment effect for HAPB/VAPB as an indication, and we have guidances that we issued. And as an appendix to each of these guidances, we write the justification for the non-inferiority margin. So there, we go through the process of how we define the treatment effect.

So for HAPB/VAPB, if I remember, there were two or three studies where there was inappropriate treatment. And then we looked at -- we don't have

placebo-controlled trials for direct comparison, so we had to do a cross-study comparison. Then we looked at treatment effect of effect of drugs that had been used to treat HAPB/VAPB, and based on that, we were able to quantify what is a treatment effect.

We use a very conservative approach. We look at the highest cure rate that you could get with placebo and the lowest cure rate you could get with an active treatment, and then compare the two.

So we do all that math. And essentially for HAPB/VAPB, where we ended up is the treatment effect was around 29 percent for HAPB/VAPB. And then given all the uncertainties, this is historic data across study comparisons, et cetera, we have accepted that the M1 is at least 20 percent. Then we try to preserve a fraction of that treatment effect, and that's the M2 or the non-inferiority margin.

So for standard development programs, for an endpoint of all-cause mortality at 28 days, we have allowed for the use of a 10 percent non-inferiority

margin. Now, we've certainly allowed for a little bit of flexibility for unmet need programs, we are willing to take a little more uncertainty.

If you have a drug that covers the spectrum of pathogens that treats HAPB/VAPB and you want to develop it for unmet need, we have allowed for the use of 12.5 percent NI margin, whereas for this particular situation where you have a drug that just treats one organism, in an indication which is already very difficult to study, one possible option is that we use a wider non-inferiority margin.

So we should be closer to the M1 so that an M1 of 20 percent, the treatment effect is really 29 with us discounting some when we came to 20 percent, we are okay with the non-inferiority trial with an NI margin somewhere close to the 20 percent. So that's for the indication.

Now, for a particular comparator that you're using for your non-inferiority trial, you might have to do additional work. So across the board, you're thinking that for most standard comparators,

this might be okay. But if you're, say, using a colistin-based regimen, because that is the standard of care for some of these, then we have to do more work because there is the concern how effective is colistin really.

So we have gone through that exercise, and we can in fact quantify a reasonable treatment effect, even with colistin-based regimens. So the margin may not be exactly 20 percent, but it won't be very far off from that 20 percent.

Does that answer your question? Sorry for the long-winded response.

DR. DASKALAKIS: Yes. No, that was great. Thank you.

DR. SHYR: Yu Shyr from Vanderbilt. I would like to follow up on that, two questions. First off, what you say, for some of them, you're equal to estimated treatment effect. Right? You allow that.

Do you do any simulation study to support that? What is the characteristic if you really widened that to as low as that? Even 12.5 percent,

10, any simulation study to prove or to understand the characteristic, if you lowered that, the M1 is still 20 percent now instead of 10, 12.5.

How would that affect it if we changed our margin?

DR. NAMBIAR: I'm not sure about simulation studies, but certainly -- do you mean impact on sample sizes?

DR. SHYR: Yes, so based on the traditional sample size now, I lose that to 12.5, and then how would that --

DR. NAMBIAR: Yes. So it certainly has a big effect, but I think the numbers that Dr. Robin Isaacs presented, I think their assumptions were using a 20 percent margin. So if you do a study of about a couple hundred patients, you can roll out to 20 percent non-inferiority margin.

DR. BADEN: Dr. Honegger?

DR. HONEGGER: Jonathan Honegger, Ohio State. Just a follow-up question about the treatment effect, say, for hospital-acquired bacterial pneumonia, is the 20 percent estimate

reduced when you consider that some of these trials might allow participation after 48 hours of pre-treatment with an effective antibiotic, and what would that be? Are there estimates on I guess the treatment effect after someone has been pre-treated for one or two days?

DR. NAMBIAR: Maybe, Dan, you can help me, but I don't know if you have a specific margin. The effect of prior therapies, particularly in HAPB/VAPB, I don't think we have data to say how much of a treatment effect is confounded by these prior therapies. I think a lot of the data that we have really comes from the daptomycin community-acquired pneumonia study where there was a big impact of up to 24 hours of prior effective therapy.

So really, from a feasibility standpoint, we have allowed for use of up to 24 hours of prior therapy in HAPB/VAPB patients because if you totally eliminate any prior therapy, it would be impossible to enroll patients in a HAPB/VAPB trial.

But really, what is the magic number? Do

you lose a treatment effect with 36 hours or 48 hours? I think it's really an unknown. So 24 hours is sort of a practical decision, but maybe Dan could comment as well.

DR. RUBIN: Yes. This is Dan Rubin from FDA. I think you're right, Sumathi, that the data in the appendices to our guidances on NI margins are not pristine, and we don't have a great way to quantify how those treatment effects of an active control over placebo are impacted by the degree down to the hour of the amount of prior therapy or concomitant therapy.

Then on Dr. Shyr's question on looking at operating characteristics of the trial as a function of the margin, we can calculate without simulations, obviously, how changing the margin impacts sample size and how changing the margin impacts the type 1 error rate for different degrees of differences between a test drug and an active control.

I guess one conceptual question I had for the clinicians is, widening this margin out to a

very large value of the estimated treatment effect of the active control over placebo, how do you balance the need for future patients to have therapy with what you're doing within this trial of potentially allowing a win criteria based on a test drug that may have a fairly large decrement relative to an effective active control?

DR. BADEN: Dr. Follmann? Would anyone like to answer Dr. Rubin's question? Dr. Goetz?

DR. GOETZ: I'm not sure I'll answer it, but I have a follow-up question and then I'll muse on his question. It's different than answering.

DR. BADEN: Otherwise, I'll have to muse on it. I appreciate it.

DR. GOETZ: So what I hear you saying about large establishment of M1 and M2 is that we're likely to be left with a great deal of vulnerability and uncertainty based upon our certainty that M1 for HAPB/VAPB as a whole treatment effect translates to M1 for Acinetobacter, Pseudomonas, or any other single pathogen because we don't have a well-curated

dataset that drills down to a single pathogen. So there's vulnerability there. We have estimates. We're going to be left with that.

Then I also hear clearly, and I agree with it, that we have the vulnerability of knowing how effective the agent is when a person may have received 24 to 48 hours of concomitant therapy with amikacin or some other agent, which would also have some activity, perhaps not the activity we want, but some activity against one of those pathogens.

So I think that sort of adds to all the discussions that we've had, if I'm understanding you properly, and I see heads nodding in agreement, of the reliance upon clinical data only will leave us with some fragility in our confidence.

Then as a clinician, I'll muse now. I guess that was more of a comment on your comments rather than a question, per se, but I see agreement with what I'm saying.

DR. RUBIN: I think you're right. You used the term "vulnerability" or "fragility," which sort of already exists for these non-inferiority trials

and margins. And I think the point here is that when we're talking about larger margins to increase the feasibility of these trials for single pathogens, that that vulnerability or fragility may be amplified to some extent.

DR. GOETZ: It's amplified by the larger margins and also knowing that the set point we have for that margin is more uncertain itself.

So speaking as a clinician, we have the vulnerability, which has I think been spoken of by the IDSA and many others, that the agents that we're using now to treat patients are not to our liking. They're the best available, or we think, and they are used. And I would pose that we have a great reason to move forward to find a pathway to find better drugs. That's my musing.

DR. BADEN: Yes. I mean, I think what's implicit in that is the more serious and life-threatening the pathogen with no established treatment allows greater fragility to the data than pathogens that are not as life-threatening or for which there are other treatments that are

available. And I think that is part of the reason we're here, to help figure out how to think about the extreme of that margin, the limitations of the data, in the setting where it's life threatening with limited other treatment. And then we have to manage the uncertainty.

I think Dr. Follman has a question or clarifying comment.

DR. FOLLMAN: Yes. I wanted to talk a little bit about the margin, and then I have a question for Dr. Isaacs. I guess I heard today that the FDA is considering moving to a margin of 20 percent. There was some rationale for why that was appropriate. It gives you a smaller sample size, so the studies become more feasible. And we understand that a downside of that is that there's more uncertainty of it.

So I was thinking about that. And when you have a 20 percent margin, say, in a mortality endpoint, you're willing to accept a greater death rate on the new drug of some magnitude.

I did a calculation that said let's suppose

the new drug is really 10 percent worse in terms of mortality, so there's 10 percent greater death rate in the new drug group. With a 20 percent margin about one time out of four, you'll approve that worse drug that has a 10 percent greater mortality compared to the comparator.

There are different ways to frame the consequences of a 20 percent margin, and that's particularly one. You're okay one chance out of four with a new drug that's 10 percent worse on mortality.

The question I have for Dr. Isaacs has to do with slide number 8, and it's sort of related to the margin question about the small sample size, what can we really know about the treatment harms and benefits.

So one thing I saw in this slide, slide 8 -- so there's a point that allows patients with other infections into a parallel non-comparative arm. So I take that, you're going to bring in patients and study your new drug in a one-arm study, basically. Is that right?

DR. BADEN: Please activate the mic for Dr. Isaacs.

Dr. Isaacs, thank you for clarifying on these issues.

DR. ISAACS: So thank you for the question. The intent of the study is to have essentially two parallel components. One component would be the formal comparator controlled, where you would be comparing the active agent or the experimental agent, sulbactam ETX2514 versus the standard of care, colistin plus a carbapenem in patients with hospital-acquired or ventilator-acquired pneumonia and/or bloodstream infections.

There are still other patients who are going to identify with Acinetobacter infections that don't have pulmonary or bloodstream infections. And given the relatively limited dataset that we are talking about for the comparative arm, it would be a shame to lose the data that one might generate from those patients.

So our proposal is that there's a parallel open arm where patients with non-pulmonary, non-

bloodstream infections get enrolled, get treated with 2514 sulbactam, and generate data which is supportive of the primary analysis. That parallel arm would not be comparative and would only be supportive.

Did that answer your question?

DR. FOLLMAN: Yes. The question was prompted by some of the discussion earlier where they talk about how you need a safety database. Sometimes, that's established partly with healthy people, so that's maybe not so translatable to the people in these studies.

You do have a comparative study where you compare your new drug to a comparator, so you get safety data on that as well along with efficacy. But it seems like this could be an opportunity where you give some of the people your new drug and some of the people the standard of care and look at safety outcomes there, so an expanded safety database to help offset in some sense perhaps the large margin that you have.

So we can't really get at efficacy, but if

there's off-target effects of your new drug causing greater mortality, maybe we could see that in your comparator arm, the arm you just talked about, people who don't meet the inclusion criteria for the comparative study and would be enrolled with your new drug.

But if you could randomize to that, then you would have comparative safety data, which could help see if there are off-target effects.

DR. BADEN: Dr. Follman, this slide caught my interest quite a bit. Dr. Isaacs, please don't leave us yet, because I think this slide has many issues embedded in it that we are struggling with. And again, I stress this is not an evaluation of your compound. It really is leveraging the thought that you all have put into this to help air the implicit complexities.

In bullet 2, enrolling patients with proven A. baumannii, how do you actually do that since that is, in my mind, a key element of the study design, since I find it in my own practice extremely difficult to understand the organism

causing VABP, among other infections?

DR. ISAACS: I think we meant by the comment on that slide that they needed to have culture-proven evidence that Acinetobacter baumannii was involved in the patient. I acknowledge the concerns that in polymicrobial infections -- and Acinetobacter baumanniis are often part of a polymicrobial infection -- you can have difficulty in elucidating which element that you identify in the polymicrobial infection as the dominant pathogen.

Having said that, one of the issues that we face -- and I did not specifically allude to as a statement, but it pervades our entire presentation, the reason you are here today -- is there is a certain feasibility issue here that we have to deal with.

So for example, to identify approximately 200 patients to enable you to get around 120 patients with multi-drug-resistant infections, we would estimate that we're going to need a hundred sites for 18 months to do that. That's a non-

trivial exercise. Anything which increases the size of that study inherently increases the needs for the size of the program you're looking at.

The comment that I would make in regards to that is, it's important to be able to generate the data in a time frame where the world is not changing so rapidly around you, that by the time you get to the end of the study, the study doesn't give you the data you want, or by the time you're halfway through, you can't complete the other half of the study.

So we have tried in what we have put together today to put together something which we believe represents a feasible way to generate data, which provides tractable and useful information about the efficacy of the product.

DR. BADEN: Along those thoughts on your arrow, near the bottom, why dominance of multi-drug-resistant organism versus demonstrating activity for the organism in question in general?

DR. ISAACS: So I think that's actually, from my perspective, a relatively straightforward

question to answer. It's because we think it's completely unfeasible to enroll a study where patients have no prior therapy and nor do they have Acinetobacter to start, or for that matter have 24 hours of therapy or less and have proven Acinetobacter at the time.

The chances that they're being treated with something appropriate in that group with multi-drug-resistant infections or carbapenem could just as easily be stated as carbapenem-resistant infections is pretty small.

So that group on this slide of 118 patients with multi-drug-resistant infections in many regards represents a population who's been receiving inadequate therapy, and so represents a truer test of the power of the experimental agent relative to control.

DR. BADEN: Thank you.

Follow-on questions for Dr. Isaac?

DR. BENNETT: This has to do with the limitations of non-inferiority trials, which are vulnerable to errors in diagnosis. To the extent

that the study populations have a different diagnosis, both arms of the study will tend to show the same result.

The problem with these organisms is they not only turn up in respiratory samples like VAPB and HAPB, they also turn up in the urinary tract of patients, particularly patients who are catheterized. They turn up in existing abdominal drains and wounds. And we cannot tell the difference between colonization and infection. And to the extent that this population is not actually infected, the non-inferiority trial will tend to show the same thing.

This has to do with the second point that you already discussed, Dr. Baden, enrolling patients with proven baumannii. So the issue is the culture is not always the diagnosis.

DR. BADEN: Thank you.

If no other follow-on questions, a follow-on for Dr. Isaacs?

DR. HILTON: I like Dr. Isaacs' illustration of an example where the comparator regimen has

40 percent mortality, the placebo has 80 percent, and the experimental agent is sandwiched in between those at 60 percent mortality. Right?

So in a non-inferiority trial, we assume that the comparator regimen response rate remains constant over time. And in this setting, it potentially is waning in efficacy, so that 40 percent mortality is growing ever closer to 80 percent. And that makes it very hard to conduct a non-inferiority trial when your margin, your reference is shifting.

So an idea that I haven't heard proposed is that maybe we think about phase 2 designs, because we can't randomize to placebo, but the placebo response rate will be remaining stable presumably. And we can at least look for a mortality rate that is better than the placebo and as much better as possible. Thank you.

DR. MARKS: I think I'm just making sure I'm hearing exactly what we're saying. In terms of the definition of proven, am I hearing correctly that if you have a multi-pathogen culture, if

Acinetobacter is one of the pathogens that grows out, that is part of the definition of proven? That's my first question.

Then the other is the value of why you're focusing on just the MDR pathogens out of this rather than the entire 200, I assume; roughly 60 percent times 200 gives you roughly 120. So you have 200 subjects with that pathogen, why focus on -- especially in a non-inferiority design, why focus on -- especially since you have a nested superiority subset where you could look at the 120?

So I'm just trying to make sure I understand the conversation.

DR. ISAACS: Can I start with the second question first? The study design -- this is a pathogen-specific agent. I think one of the things that really hasn't been discussed today is that when you're studying a pathogen-specific in such an ill population with a propensity for polymicrobial infections, there's going to have to be background therapy there.

So the study design essentially is the

experimental agent plus background therapy versus the comparator plus the same background therapy. So in this case, it would be 2514 sulbactam, ETX2514 sulbactam, plus a carbapenem versus colistin plus the same carbapenem.

So the need to focus on the multi-drug-resistant infections represents not just the need to take into account this prior therapy issue, but also that the background therapy may be contributing to the response in the patients who don't have the multi-drug-resistant infections.

The first question really related, I believe, to the definition of what represents a case to enroll in the pneumonia study. And this is clearly something that we will need to discuss at the time when we finalize the phase 3 protocol.

But it's my belief that the patients meet the criteria for hospital-acquired or ventilator-acquired pneumonia, and there are defined ways of representing that diagnosis. And they culture from their sputum Acinetobacter plus potentially other pathogens, and the magnitude of the Acinetobacter

suggests it's not just hanging around as a contaminant. But I think that that definition is a very critical component of the study design moving forward.

DR. MARKS: Just to make sure I didn't confuse you, so you did say that if it grows out of the culture, then it would be part of your definition of proven in the background of that and that it wasn't just hanging around.

I think you're hitting on what I'm trying to help guide people in the industry with. I'm not sure what hanging around means. It'll either grow or it won't grow. Right? Your culture's going to come back positive.

DR. ISAACS: Right. But I mean, if it's just a very small amount -- sometimes you get a marked predominance of one pathogen coming out of the sputum.

DR. MARKS: So you would have some type of quantitative measure that would be associated with that.

DR. ISAACS: Or at least semi-qualitative.

DR. MARKS: Then the reason why I was focusing on the background rate is because, by definition, these 118 won't be obligatorily resistant to your background therapy. So you're not really excluding that impact of the drug separating.

DR. BADEN: I think that the issue more is the generic issue that's trying to be raised as to the phenotype of the infection, the site of infection, the certainty of infection, and then characteristics of the organism that may be impacted by the optimized background plus/minus whatever the intervention is, whether it's some approved intervention or versus the new agent.

That is what you're driving at, is my sense.

DR. MARKS: Yes. It is. And I'm also trying to take advantage of the fact that you have 200 patients with this unusual pathogen, trying to maximize what we learned from that, because they're not going to be, by default, resistant to the regimen, best available background therapy that you're going to have as we move with more and more

new agents.

DR. BADEN: And what's implicit in that is also the toxicity issue, which is if the comparator extra drug A happens to be a polymyxin or colistin that has its own intrinsic toxicity, that is in addition to the optimized background, that is being compared to the new agent, and getting to the issue of side effects, that may or may not be easy to tease out. But that comes with the complexity of these types of illness where this infection occurs.

I don't know, Dr. Isaacs if you had other comments to follow on.

DR. ISAACS: Great summary. Thank you.

DR. BADEN: I think next is Dr. Andrews.

DR. ANDREWS: I have a clarifying question. I guess it's to the FDA. Well, two, really. One is, I was taken by your comment that we want to think about how this is going to work in the real world. After the study's done, what's the end game?

Is this meant to be another tool that's added to that cocktail that we heard about for

people who have multiple pathogens, or could this be something that's used by itself and might be less toxic for people? Or is it about the public health issues of just knocking out one bug as opposed to -- and the issues of side effects for people, because I think that changes how I as a consumer representative think about the question.

DR. COX: Yes. I think it's really all those things. You've mentioned a few different things, which is narrow-spectrum drugs may have less impact upon people's resident flora. And if you have less of an effect on the GI flora, maybe we'll see lower instances of C. diff colitis, fungal infections, other problems. So that's one of the issues you mentioned.

You raised the issue of how will people use this drug. Will they use it as part of an empiric cocktail or will they use it only in the setting of, say, an outbreak, in an ICU where there's a particular problem, bacteria where you have limited treatment options?

That's actually, I think, our last part of

question 2 because we're hoping to understand that also to get a little more insight into how clinicians envision using such drugs because, as you mentioned, it impacts upon the benefit-risk.

You had a third part, but pardon me, it's escaping me.

DR. ANDREWS: Just the public health benefits of not using wide-spectrum medications if you can avoid it.

DR. COX: Right. So we talked some about less impact on flora. Oh, you asked about the empiric use and would people use this as a single agent. And I think, as you've heard from some of the folks that were talking about the study design, and one of the issues that we're trying to grapple with, is that if somebody has an infection, a serious infection in the ICU, we know how important those initial doses of effective therapy are.

It takes time to make a diagnosis. It takes time to enroll a patient in a clinical trial. So we're already seeing -- I think the clinical trials are giving us some insights into this problem that

in fact people will at the point of not having a diagnosis, you're usually going with an empiric regimen with broad-spectrum therapies.

Some of the patients, as we've heard -- and we've looked at some data. Patients who have Acinetobacter baumannii, some fraction of them, it's somewhere in the neighborhood of about 50 percent, will also have a second organism isolated.

So in the critically ill patient, given some of the issues around diagnostic uncertainty, it may be that, in fact, people do use other agents despite having a diagnosis or having a culture result that gives them two different organisms. But that's certainly something, too where we'd be interested in hearing the insights of folks on the panel.

In a critically ill patient, how would such a product be used if it were out there? But we welcome thoughts from others on that topic.

DR. ANDREWS: I didn't mean to embed three questions in my first one, but I do it a lot.

DR. BADEN: Well done

DR. ANDREWS: Thank you. The second one was that -- I'm out on a very thin limb here -- I know that in other drugs that we've looked at, there are often clues, given the structure of the molecule or how it's expected to work, to what the toxicities -- I mean, as a consumer advocate, we're always worried about safety, and these are very toxic medications.

Given the results that you might get or even just knowing what the candidate is, do we have to give you like 1 through 4, and you have to pick one, or can you be more flexible based on what's presented to you?

Like in this case, more animal studies might make sense, in another case the small sample set. Do you need a definitive answer from us, or can we leave it as a menu? And we're not voting, but I vote for the latter.

DR. COX: I think you've raised another important point, which is that some of the therapies that might be developed that target a

single species may be different than the classes of drugs that we've seen in the past.

Oftentimes, adverse effects that we see in a class -- there are some that are common across the class, so we have some insights into how a particular molecule might behave within a class. But as the compound, the molecule becomes more novel, something that we have not seen previously or from a different class, the pre-clinical studies, the animal studies may give us insights into what that molecule may do. We may not have the benefit of a whole lot of experience with molecules of this type.

I understand your comment, which is, don't limit it to any one particular menu-driven approach, but take into consideration the nature of the molecule you're dealing with, what you've learned from the pre-clinical studies, and what may be less familiarity with the particular type of molecule, given that it may be different than things that we've seen previously.

Is that fair?

DR. ANDREWS: Yes.

DR. BADEN: I can't help be keep reiterating, if there's an 80 percent mortality versus a 0.8 percent mortality, in my own view, I look at safety a little bit different, and we wouldn't have cancer centers if we didn't accept toxicity. So it's balance with the alternative, assuming it's well defined what that alternative is.

Yes, Dr. Green?

DR. GREEN: So I would also point out that the science is really looking at novel targets. And many of these targets may be more specific to prokaryotes than eukaryotes. So it's possible that we could be identifying novel drugs who have an excellent safety profile because they're more focused on a prokaryotic target.

In fact, I don't remember if this is one of the options that I saw, but we could see a drug that has less efficacy, but higher safety. And in the patient population that we're talking about, avoiding renal failure -- because we're looking at

all-cause 28-day mortality. So it may be that by using a less toxic but also a little bit less efficacious drug, that you can allow for a greater 28-day survival effect than you could be having a drug that kills the bug but also kills the kidney.

I think we have to kind of keep that in our mind as well because, again, we're looking at a patient population that's fragile, not only an NI index that creates fragility in our interpretation of the data.

DR. BADEN: Thank you, Dr. Green. Dr. Ighov? Thank you.

DR. OFOTOKUN: [Inaudible - off mic].

DR. BADEN: Thank you. Dr. Shyr?

DR. SHYR: Shyr. Let's follow Dr. Rubin's question, the answer about the simulation. So I think now we are facing, say, it's not very feasible to get that many patients. The original RN1 was very conservative. We used the upper and the lower, the worst.

My question is, to think about -- to think to look at the two distributions, and to look at

simulation, too, because that's the most conservative. That's how we generate our first margin.

If we use the simulation to see -- if we simulate enough to see what's the most likely, not most conservative, and then to get some sort of idea, and then they use the relative risk idea instead of fixed 10 percent or 20 percent, and use that to look at the characteristics of the entire field -- because now we know you've fixed it, changed the 20, 10 to 12.5 to 20. I know how exactly to calculate the sample size.

If I use two distributions to simulate the distribution of that difference, and then use the relative risk idea, and to estimate how will that affect the sample size -- I don't know. I'm just kind of curious did FDA ever think about using that idea instead of very conservative margin, and use more like the two distribution. That's my number one question.

Number two, I want to clarify, again, you talk about possible designs for non-inferiority,

superiority, all this, randomized phase 3. I want to echo Dr. Hilton's question. Have you ever discussed during the previous two meetings about the possibility of two independent phase 2 trials?

Then we have a more clear pure study population, and they get some kind of conditional proof and follow a randomized phase 4 or very rigorous head-to-head comparison later on.

Have any of this discussion happened during those two days? Those are two clarifying questions.

DR. RUBIN: Thank you. So on your first question about the margin, in some cases, we have looked at other effect metrics other than the risk difference, such as the odds ratio. And in fact, I think there have been public discussions about that.

But in terms of looking at simulations and distributions, I guess maybe I did more detail offline about what exactly you were proposing. One difficulty is that from some of the historical studies, literature-based studies, we may not

always have patient-level data.

I guess I might turn it over to my colleagues on any comments about phase 2 studies, with the caveat being that sometimes if you're dealing with a pathogen or disease, it's already very difficult to study due to the rarity, that it sometimes may make more sense to put eggs in the basket of phase 3 earlier, assuming that it's ethical and possible.

DR. NAMBIAR: So in terms of your question about phase 2 and phase 3, we really don't draw this hard line between what's a phase 2 trial and what's a phase 3 trial. If we have an adequate and well-controlled trial and like the programs presented, and that's the only trial, then that would be good enough if the trial was successful.

I think your point was more can a smaller phase 2 program be done to get some idea of what the treatment might be. Is that what you were trying to get to?

DR. SHYR: What I say to phase 2 means, I should clear [indiscernible], it's non-randomized,

single arm. Okay? Single-arm study with multiple single-arm study, with more pure study population, was this ever discussed instead of traditional?

You do some non-inferiority or superiority; those are all randomized. Right? Have you ever discussed non-randomized phase 2, but serve as kind of surrogate for the panel for the approval discussion, for the conditional approval, and things like that?

DR. NAMBIAR: So certainly, conditional approval is not particularly a mechanism that we have. I mean, it's a mechanism that's available outside the United States.

Maybe Ed can comment, but I don't think we've considered the use of non-comparative data as a surrogate. So are you referring to it as using an intermediate clinical endpoint? Because we haven't really considered that as a surrogate as a basis for approval.

DR. SHYR: I just want clear, no discussion about this non-randomized to prove the drug based on non-randomized studies.

DR. BADEN: But Dr. Shyr, are you thinking then of, let's say, historically controlled, where you know that 100 percent of individuals with this condition die?

DR. SHYR: Correct. Exactly.

DR. BADEN: Therefore, would a case series be meaningful enough clinical data?

DR. SHYR: Exactly.

DR. COX: So there are circumstances where you can use historically controlled data. And when you've got a universally bad outcome, and that doesn't change depending upon who gets in the trial, then you can make valid inferences.

One of the issues that we oftentimes face with serious acute bacterial diseases is that the patients that get into the trial do better, and sometimes that's for reasons that we can't measure.

We've looked at some of the community-acquired pneumonia studies that have occurred in the past, not the highest mortality condition among serious acute bacterial diseases, particularly what we see in clinical trials. But when we use the

PORT score, which is a validated measure of mortality or predictor of mortality, when we apply that to patients in CAP trials -- and we've seen this over and over -- the mortality rate is cut in half compared to what PORT would predict.

So there's something going on in the clinical trials, and who gets in and how they're treated, that makes their mortalities generally appear better than the overall populations.

So you can use historically controlled data, but it has to be in the right circumstance. And oftentimes it's challenging with serious acute bacterial diseases to get to a patient population where you can make those comparisons.

If you can scientifically support that, then it could be doable. But oftentimes, we're dealing with variability in patient mortality depending upon who gets in any particular trial, which makes it challenging. And that's why having some data from randomized comparator patients can be very helpful and very informative. And even if that randomization is disproportionate, to have some

patients in a randomized comparator arm can really be helpful in these types of diseases.

DR. BADEN: Dr. Goetz, do you have a follow-on question?

DR. GOETZ: Well, I just wanted to clarify as to whether historical data can be used as part of the package for approval. I think I heard you say yes in that statement, but I just wanted to be certain that I understood -- or maybe the better question is, in what context, if any, could historical data or data comparing outcomes in a single open-label study be used to comparison of outcomes, say, in a registry of some sort.

DR. COX: Right. I don't know that it's a precise yes or no, but I think it really is a question of are the conditions appropriate for the particular disease that you're studying as to whether the historically controlled data, the data from historical control, are in fact a comparable group to those that you have in the trial, so that you can make valid conclusions.

So really, I think it depends upon the

circumstances of the trial as to whether you can achieve that or not because with factors measured and unmeasured, impacting upon outcomes, the real question is true comparability.

If you have a disease process, and there are some infectious diseases where the outcomes are universally just terrible, and if you see a change from that, then you can conclude there's a drug effect. In other circumstances, the mortality rate that's observed in that particular patient population may be jumping up and down by somewhere between 20 and 30 percent, depending upon the particular patient population in the trial.

If the effect of the drug is about 20 to 30 percent, you can see that you're bouncing up and down about as much as the drug effect might be, which can then make it very hard to draw conclusions of drug efficacy.

So it's not a precise yes or no, but it really is based upon the conditions of the trial that I think you're actually performing and the disease condition you're studying as to what role

those data might play

DR. BADEN: Dr. Goetz, you are next on the list. No? Dr. Schaenman?

DR. SCHAENMAN: Dr. Schaenman. I'm from UCLA. I wanted to thank Dr. Nambiar for her very detailed presentation, and I have two questions for her on unrelated topics, but both trying to get to a quantification.

I think those of us here who are infectious disease clinicians were very comfortable at the individual patient level of dealing with uncertainty, balancing risks and benefits, and coming up with an admittedly often subjective answer for the patient at hand.

But I think it's harder for us to think about a clinical trial in a population. And I want to circle back to the kind of thought question that was raised by Dr. Follman from the NIH. I think that those kinds of models are extremely helpful for us here whose strength is more in clinical medicine, to get a sense of what these differences in the non-inferiority percentage changes would

have in terms of type 1 error as well as risk of death.

I guess I wanted to ask whether the FDA could perhaps help us reconcile the numbers. The difference between 10 and 12.5 percent doesn't seem that large to me, but perhaps I'm not thinking about it in an N of 200 patients, and a way for us to reconcile the numbers that are presented in your slide 16 with the numbers presented in Dr. Isaacs's slide 8, where he was suggesting 20 percent.

So I would really like to ask where the FDA could help us, perhaps with a graphic if possible, in being able to really wrap our minds around what is the impact of changing it from 10 to 12.5 to 15 to 20 percent, because I feel that I don't really have a very good understanding of what we gain and what we give up.

I guess a sidebar is, could those numbers perhaps be different, whether we're going for the limited population pathway versus a more general indication?

DR. RUBIN: This is Dan Rubin from FDA.

Unfortunately, I don't think we have a graphic readily available that would help with this. Unfortunately, the sample size of a non-inferiority trial is proportional to 1 over the square of the non-inferiority margin, so if you cut it in half, you could be multiplying the sample size by 4.

In several of our guidances, or in many of our guidances, we use a 10 percent margin. And if you assume a 20 percent failure rate or 80 percent success rate, that translates into a normal sample size of 337 patients per arm for 90 percent power.

If you go to 12.5 percent -- I don't know. Is Joe here with the sample size, 200 something per arm, 250 per arm approximately. And you've seen the sample sizes here for the 20 percent margin; it's considerably less than that.

I'm sorry. I don't have a graphic, but hopefully that frames the numbers to some extent.

DR. SCHAENMAN: That is helpful. But what about the risk of, if we're incorrect, like Dr. Follman was suggesting, it'd be help to pair those two numbers together.

DR. RUBIN: Right. So a hypothesis of a non-inferiority trial is set up so that if your margin is 10 percent and you're really 10 percent worse than the active control, then you're only going to make the mistake of declaring efficacy 2.5 percent of the time.

If you raise the margin, then obviously that percentage will increase, and you'll have a greater chance of declaring an inferior drug to be effective.

DR. SCHAENMAN: Thank you. That is helpful. So if I can ask my second unrelated question. We've been focusing a lot on option 1, which does seem to be the most promising option, but I also was interested in option 4, that Dr. Nambiar also presented, regarding the animal models.

Again, as a clinician and as an immunologist, I find it a little bit concerning to think about using animal models, no matter how excellent they are, in lieu of more attention to clinical trials, even if it's combining small clinical sets.

I think it's difficult for us outside the FDA process to have an idea how many drugs that tested well in animal models did not go on to do well in phase 2 or phase 3 trials, since we're only aware of the ones that were successful, for the most part.

So I was wondering whether FDA had any data about how often there is that slip where the animal trials look very promising. But when we're in human beings, as was pointed out by one of the earlier speakers, and have very different innate immunity and not even getting into their adaptive immune system, one can expect in anatomy that the differences are going to be large.

But again, I'm just wondering if you could help us quantitate what that difference might be.

DR. NAMBIAR: I don't know if I have exact numbers, but I think what our hope is, and what we're really trying to do is, we want to get interpretable clinical trial data. That is our preferred option. And the reason we're having this discussion is we know it's difficult to get the

kind of interpretable data we would like. And in that situation, is there a role for other pieces of information that could be used to support the efficacy of the product.

I think that's really the question. In an ideal world, we would only want the clinical trial data, but I think here is a situation where that might be difficult to obtain.

In terms of animal data not translating into data in humans, I think it does happen. I don't have numbers, but there are a lot of important lessons we have learned. Just over the last 8 or 10 years, there have been phase 3 trials for products that have failed, and they failed across an area of indications.

In many of them, or at least in most of them I think the hypothesis is that there was an issue with the dose selection. But again, that's all in retrospect. When these trials were designed and the trials were undertaken, the best science was used to come up with the dosing recommendations.

So I think there is going to be a difference

between what you see in animals and what ends up in humans. The human data will be the best, but there might be a situation where you wouldn't get what you need in humans, and that's why we're having this discussion.

So I hope that answers your question. Did you have more? Is there something more I can respond to? Dr. Schaenman, I cannot really see you, so I don't know.

(Laughter.)

DR. SCHAENMAN: A ballpark percentage of how often there's --

DR. NAMBIAR: I don't think I can give you a number, then I would be giving you wrong information.

DR. COX: Maybe just one other comment on that, too, is that the animal models are of various different types, if you will. Some are just looking at levels of activity, where you're reducing colony forming units per gram of tissue. And then others are meant to be more reflective of the human disease condition, where the route of

inoculation and other factors, the animal susceptibility to the particular bacteria may change, too.

So there's also even a spectrum of animal models and what you would expect to be able to learn from them. And that's part of the equation, too that also makes answering the question somewhat challenging.

DR. BADEN: Dr. Weina, a follow-on question?

DR. WEINA: I just wanted to comment from my own experience in doing a lot of animal model development for drugs, particularly parasitic drugs. And Dr. Cox is absolutely right. I mean, it depends upon what you're using the model for. I've always focused on the safety side of it.

There are all these often quoted numbers in pharmacology that 80 percent of the animal models predict what happens in humans, and 10 percent are wrong from the standpoint that they don't predict the toxicity that you'll see in humans. But then there are other ones that predict toxicity that don't happen in humans.

But I can tell you, in practical examples, we always hear about the ones in which the animal model does not predict toxicity that shows up in humans later. But there are also plenty of very good examples in which animal models have predicted horrendous toxicities, and then we find out there are no toxicities in humans. And this is particularly found in anti-malarial drugs in which horrendous toxicities have been predicted and never show up.

So the animal models have a lot of flaws in them. They're good most of the time, but it depends upon how much risk you're willing to accept. And that really becomes the crux of I think what we're discussing here, is how much risk are we willing to accept, and how much do we want to hide behind the shield of an FDA approval, saying these guys said it was okay, so you can't yell at me for using it.

DR. BADEN: Dr. Weina, just to follow on to your follow-on, is it fair to say that the animal model is dependent upon so many factors, the

species, the organism, the inoculum, the route of infection, endpoints that are chosen as being meaningful on the efficacy side, not the safety side?

DR. WEINA: The efficacy side is even broader as far as the variability that you'll see than even what you'll see in the safety side of it. And I think that, efficacy-wide, there are so many unknown unknowns that there's absolutely no way of giving it an actual number.

DR. BADEN: My favorite are the unknown unknowns.

Green, did you have a follow-on? Dr. Moore, a follow-on?

DR. MOORE: Yes. I was just going to say that there have been two excellent animal models for the approval of levofloxacin for children who have pneumonic plague and then also for the anti-toxin, the monoclonal antibody against the PA toxin for anthrax.

In both situations, this panel in previous sessions approved the recommended approval based on

the animal data. And so far, the drug has performed excellently because it's never been used.

(Laughter.)

DR. BADEN: Another follow-on or did you have a follow-on, Dr. Clark?

DR. CLARK: I was just wondering if there was a non-human primate model for either Pseudomonas or Acinetobacter, and if not, if it was just a cost issue, or if you would consider that as a possibility. Thank you.

DR. YASINSKAYA: This is Yuliya Yasinskaya. So at the workshop, they did not present any non-human primate data models for Acinetobacter and Pseudomonas. However, in the discussion, as you had pointed out, the cost of the model had been brought up.

Even with the rabbit model for Pseudomonas pneumonia and pig-model Pseudomonas pneumonia, where it seems like pathogenesis of the disease was similar to that of humans, the cost was a driving factor. And therefore these models will be reserved for the efficacy trials that possibly use

the Animal Rule. So yes, but the non-human primate data had not been presented.

DR. BADEN: Then moving down our list, Dr. Daskalakis?

DR. DASKALAKIS: I have two questions, one for Dr. Perl from the IDSA if she's available. The question really has to do about, I see there are a lot of clinicians who are a part of IDSA's --

DR. BADEN: You can, Dr. Perl, come to a mic and, if we can, activate the mic, please.

DR. DASKALAKIS: I think one of the questions that's coming up in the committee is how would people use these drugs, and would they be willing to use these drugs.

So a clarifying question really is, has the IDSA done any survey of their front-line clinicians about the potential use of agents like this or their interest in using agents, which may have a lower level of evidence as compared to other agents they may be used to utilizing.

DR. PERL: So let me take the second question first. I'm going to try to get help. Has

the IDSA done a survey? So no. There's not an official survey, but they've done anecdotal work. I actually have seen some surveys go through EIN. I think it's mostly EIN, I've seen. And I've seen things posted on the message boards.

Then your first question, if you could, repeat it.

DR. DASKALAKIS: I think that was it. Has there been a survey done about willingness to use such agents? I think you've answered both.

But my second question is not for IDSA. It's for, I think, the FDA, which is a completely remedial question, which is, could someone teach us what a hollow fiber cartridge does for PK/PD evaluations? If the answer is none of my business, I understand.

DR. BADEN: Dr. Isaacs or Dr. Cox?

DR. ISAACS: I can give you a layman's point of view on this. I mean, we spent a lot of time using in vivo particularly neutropenic mice models and in vitro hollow fiber models to look at PK/PD. And essentially what the in vitro hollow-fiber

system allows you to do is it allows you to control the concentration of the bacteria, the concentration of the bug in an extended circumstance that mimics the PK that one would expect to see in the clinical setting.

So you can modulate the PK, you can modulate the frequency of dosing, and you can modulate the dose interval in a setting of controlling the bacterial load, and by monitoring response and bacterial load to those changes, you can then identify the most appropriate pharmacodynamic parameters.

Then you end up with those tables, which are figures that everybody's seen of Cmax, time over AUC, AUC over Cmax, and your various things. And you get various data points when you draw the curves, and the one that looks best is where you're going. That's a layman's point of view of this.

DR. DASKALAKIS: A quick follow-up on that is, does the system then also account for volume? Is there a way to control for volume and distribution estimate or is it just a bloodstream-

esque? Does it look at different tissue environment, simulate different tissue environments?

DR. ISAACS: I'm not sure I can really answer that question. My expertise does not extend that far, though maybe somebody with more experience can do that.

DR. BADEN: Dr. Rex?

DR. REX: My name is John Rex. I'm a board certified internist, ID specialist, and do a variety of other things around the pond. Hollow fiber refers to an idea.

Imagine two chambers. Chamber A has some fluid and some bacteria in it, and chamber B wraps around it in some way, and they are separated by a semi-permeable membrane. So you could fiddle with what's in B and it will diffuse in and out of A. So there are no white cells. It's completely abnormal in terms of immune system.

Volume distribution doesn't really have meaning because that's the volume right there. So I could measure the volume distribution in a human

being that I'm going to get, and I could decide whether I believe I'm going to get amount X at some body site. But in the hollow fiber itself, it's raw drug, nutrients for the bacteria, and things are just swimming around, and it's a dialysis --

DR. BADEN: Dr. Rex, I was informed that, as a non-formally invited speaker, we must curtail your remarks.

DR. REX: That was it. That's just plain hollow fiber.

DR. BADEN: Thank you.

Are there any other members of the panel who would like to clarify that point about the hollow fiber? If not --

DR. MOORE: I would be happy to reiterate what Dr. Rex said.

(Laughter.)

DR. BADEN: We thank you for that clarification.

The next question, one question that I'll ask just to Dr. Nambiar is a clarifying question.

You mentioned in your presentation about 300

needed for safety as a ballpark. I was interested in understanding the genesis of that number and what aspects of it we need to reflect on because I think safety is part of the equation that has to be weighed as we think about the efficacy.

DR. NAMBIAR: Sure. So the number 300 comes from the rule of 3. So that is, if you don't find an adverse event in the 300, then I think there's a 95 percent probability that the frequency of occurrence of that AE is less than 1 percent.

Is that correct, Dan?

DR. BADEN: So for the 1 in 100. So it's looking for 1 in 100 event. You're using 300.

DR. NAMBIAR: So that's just a rough estimate. Again, we are not bound to it. So if we have signals in the non-clinical safety studies that suggest that 300 might be too little, we can certainly ask for more. Or if there is a drug that looks pretty bland in non-clinical studies, and we think that the product offers a meaningful benefit, and the number ends up being a little short of 300, I think that's another consideration that we will

have to make.

So it's essentially a guide, but it's not an absolute number. I just want to make sure that's clear.

DR. BADEN: I thought that was the genesis, but wanted to confirm. A follow-on question from Dr. Lo Re?

DR. LO RE: Yes. So most of what we have been talking about really has focused on efficacy so far. And many of the strategies have focused on efficacy. And I understand that we're talking 40 to 80 percent mortality here. But I am sensitive to the fact that there is the possibility certainly of toxicities, and we've certainly seen people be cured, and they're left with residual adverse effects.

So now we're talking about animal models, PK/PD studies, and I just want to try to get a sense to follow up on what Dr. Baden was saying.

So if we're going to use some menu approach of different strategies for determining efficacy, what is the agency's thinking in terms of the

number of patients who will be needed to determine some initial safety requirement? And what is the thinking in terms of going forward for postmarketing if most of the studies are done in animal models, just to give you some sense?

DR. NAMBIAR: So there are two things. So we talked about animal models for activity/efficacy, and then there's also non-clinical assessment of safety. So they are two different topics.

So if you're only relying at the end of the day on animal models for efficacy, we need safety data in humans. So safety data will not come from animals. So the 300-patient discussion that we're having is 300 patients exposed to the drug at the dose and duration that they propose to take forward.

So really, the safety information is not coming just from animals. So we will have a limited human clinical safety database. I think as I mentioned in one of my slides, these might be products where there might be a requirement for

additional safety data collection postmarketing.

So if there is a signal -- we saw a signal in non-clinical studies, but the safety database was so small that you really didn't see the signal in humans -- there might be postmarketing requirements, or there might be a requirement for enhanced pharmacovigilance. There might be registries.

So I think that is certainly part of the discussion. And I certainly don't want to minimize safety, even though the focus of a lot of our discussions have been around the efficacy, but I don't want us or anyone to lose sight of safety. It's certainly an important component of the overall discussion.

DR. LO RE: Just to follow up, so the thinking would be that if the majority of studies that were looking at efficacy were focus on animals, there would be some requirement for separate either concomitant observational studies or postmarketing studies after the fact?

DR. NAMBIAR: Right. So I think there would

be a requirement actually for pre-market safety. So we have to get safety information on patients before we approve the product. The size of that safety data as pre-market may be very small, and that's the 300 number we are talking about.

But again, given what we know about the drug either from non-clinical studies or if it's a member of a class we've seen before, then we make decisions about what more data might need to be collected postmarketing. If it's a brand new class and we really have no prior information, I think our safety knowledge will be very, very limited.

So I'm not going to go into the Animal Rule, per se, but even for products that were approved under the animal rules, so products that were approved for plague or anthrax that have been mentioned, there was safety data generated in humans.

For products like the quinolones, which were approved for plague, you already had a lot of safety information because it was used in humans, but for the monoclonal antibodies, there was

actually safety data in healthy volunteers. You don't get patients in that instance.

DR. BADEN: Dr. Weina, you have a follow-on question?

DR. WEINA: Just a real quick clarification on this entire discussion. And that is that you're parsing out what are we talking about for efficacy and what are we talking about for safety. But in reality, what we're talking about is the risk versus the benefit.

So you need both of them at the same time to really make a decision because every time we make a decision on whether we're going to use a drug in a patient or whether the FDA is going to approve a drug, it's the balance of risk versus benefit.

So it's the balance of the safety versus efficacy that's really critically important here. So we can't really parse them out and consider them separately. I just wanted to clarify that.

DR. NAMBIAR: I agree. And I don't think we are looking at vacuum in efficacy. It's vacuum in the context of the safety profile for that product

in the small dataset that we have.

DR. BADEN: Dr. Clark, did you have another follow-on question?

DR. CLARK: So could the safety data be predominantly in healthy volunteers or would it have to be in people who would be likely to get the drug?

DR. NAMBIAR: So it would be a bit of both. You will have safety data in healthy volunteers, but the healthy volunteer data often tends to be single dose. Sometimes you will have some multiple dose.

So that's one component of the overall safety database, but certainly we are looking for safety database in patients with the disease of interest at the dose and duration, because sometimes the healthy volunteer studies may not go out to the entire duration. And so it is at the dose and duration in the patient population with the disease of interest.

DR. COX: Maybe just one more comment on this, too. Within the limited clinical trial, we

should be able to gather safety data, and we should be able to understand what's going on with the safety data if the trial is appropriately designed.

There are still considerable challenges because of the use of pre-study therapy and concomitant therapy that may particularly cloud the evaluation of efficacy. But we should be able to gather interpretable safety data from a comparative trial that will allow us to understand the safety in patients who are sick who are getting the drug at dose and duration.

DR. BADEN: Dr. Cox, I agree, but to some degree, if there's a 40 percent or 50 percent mortality, of course safety signals will be able to be seen. Nuance safety signals will take much broader use.

DR. COX: Right. And it just brings us back to really that benefit and risk are the two things that we weigh because depending upon the safety profile, the drug will be weighing it against what we see with regards to efficacy and how these things all balance out.

DR. BADEN: Another follow-on?

DR. HILTON: I wonder if the use of all-cause mortality as the primary outcome is an attempt to get at safety and efficacy simultaneously.

DR. COX: Yes. There is a point where, if you're looking at all-cause mortality, and in essence, safety and efficacy start to emerge, in a serious disease condition where there is a significant mortality rate, that may be what you're trying to affect. That may be the efficacy goal, reduce mortality, have more patients survive the condition.

That is also one of the ultimate safety parameters to look at, too. So if you're showing a marked reduction in mortality in a patient population for a disease that has a high mortality rate, then you've shown a beneficial effect of the drug and, in essence, very well also addressed the safety question, which is you can prevent patients from dying, so they start to come together.

DR. HILTON: Yes. Earlier today, a panelist

talked about a patient who was cured, but then died of renal failure, so it made me think of it in this context.

DR. BADEN: Dr. Marks, you had a follow-on question?

DR. MARKS: Yes, maybe just a comment on linking the previous discussion. And from a sponsor point of view, oftentimes, we talked about earlier these open-label, early phase 2 designs. One of the downsides of that is the inability to have a balance in the safety control arm. So whatever adverse events happen in that uncontrolled setting are attributable to the compound. And when you're talking about very small numbers, that's oftentimes why sponsors are reluctant to want to embrace those approaches.

DR. COX: Yes. And that's a very important point. Having looked at data from patients who have HAPB/VAPB, there is a rate of background events that occurs. And without an appropriate comparator arm, it can be very difficult to try and sort out whether that's background or whether

that's related to the drug. Having the comparator arm can be exceedingly valuable for understanding the safety of a drug. Agreed.

DR. BADEN: Ighov?

DR. OFOTOKUN: In the previous discussions of the previous workshop, I was wondering, in terms of the effectiveness or efficacy of the drug, non-inferiority margin, if FDA have considered other surrogate endpoint besides the harder endpoint of all-cause mortality.

DR. NAMBIAR: I can start, and then maybe Ed will add to it. So in going back a few years, we've had a lot of discussions, so maybe starting in 2007, 2008 is when we started having discussions around non-inferiority trial designs for antibacterial drugs.

Prior to that, I think definitions for some of our clinical response endpoints were probably less than optimal, and the non-inferiority margins were not really scientifically justified.

So then we've gone back and we have to go through indication by indication to decide what is

the appropriate endpoint, which endpoint can we have an adequate justification for the non-inferiority margin.

So specifically for HAPB/VAPB, all-cause mortality is the endpoint if one is pursuing a non-inferiority trial. That is the endpoint for which we an adequate justification of the margin.

There has been interest in using an endpoint of clinical response, which is what used to be used traditionally, but we have not been able to find data to justify an NI margin for a clinical response endpoint. Superiority trials might be a little bit different. We have a little more flexibility.

At the end of the day, the endpoint has to be clinically meaningful. It has to be reliable. So our current recommendation for HAPB/VAPB trials is to use a 28-day all-cause mortality as an endpoint, and trials are underway that are in fact using this endpoint. There's at least one recently completed trial, which was conducted successfully and was able to demonstrate a treatment benefit for

a mortality endpoint.

DR. BADEN: Dr. Bennett, did you have a follow-on question?

DR. BENNETT: Yes. Dr. Bennett. I have a question for Dr. Cox. I wonder how effective postmarketing surveillance has been in removing drugs from the approved list because of toxicity found by FDA-required postmarketing surveillance.

I say that because I can think of a variety of drugs that industry has removed, but I don't know if the FDA's requirement has actually resulted in withdrawal of approval.

DR. COX: All right. So let me just try and talk through this. Yes. Reflecting on experiences in the antibacterial space, we have over the years had the occasional drug that has had toxicities that were detected postmarketing or the severity was better appreciated once the drug got out and used.

The types of toxicities that would be discernible in that setting are things that would happen that are things unexpected, liver failure

being a prime example. It's something that either based on histologic examination or in a setting where a patient has a fatal liver failure event, there may be evidence that says that the drug is likely the cause of the patient's liver failure.

So that has happened infrequently over the years, both from the standpoint of a drug being removed from the market or increased safety labeling happening in the case of a drug where there was increased appreciation of hepatic adverse effects once the drug was marketed.

I think, Dr. Bennett, the heart of your question is, when this happens, how does it actually work. And oftentimes, in essence the safety data are out there. In some instances, there's a public discussion. And usually the decision to withdraw the drug is after discussions with the FDA and the company withdraws the drug.

It's a less frequent occurrence that the FDA is actually the one that goes through the whole process of withdrawing a drug because, usually, once the data are out there, the company and the

FDA appreciate the nature of the problem, and it's usually more expeditious that the company would then take an action on the drug.

Did I get your question correct? Is that what you were getting at?

DR. BENNETT: Yes. If we were relying on postmarketing surveillance, I just wasn't sure the FDA had the facilities to follow these. Even though you require the postmarketing surveillance, I just wasn't sure how effective that surveillance was. So if it's not very effective, then we shouldn't rely on it.

DR. COX: But the postmarketing adverse events, for certain events it can help understand what's going on. There's underreporting in the setting of things that are occurring out there in the real world.

Just one other thing to think about, there are other ways. You can do registries and things that are a little more formal that may allow for a greater detection of things in the postmarketing setting, adverse events in the postmarketing

setting, or safety problems in the postmarketing setting than just spontaneous adverse event reports.

So there are some other ways, but it can be particularly challenging in a patient population if the adverse effect is one that's also an event that could be associated with an underlying serious disease.

A patient in the ICU with HAPB/VAPB, if the patient expires from some event, is that drug related? Is that part of the disease condition? A comparative trial can be tremendously powerful in helping to sort that out. Trying to figure that out in the setting of just what's going on out there in an ICU can be particularly challenging.

DR. BADEN: We have made it to the noon hour. I think Dr. Weina and Dr. Green had follow-on questions. I ask that they be short so we can stay on schedule.

DR. WEINA: Pete Weina. So the related question to what Dr. Bennett just asked about, I'd be interested in hearing the FDA's perspective on.

And that is that I guess I'm less concerned about the FDA necessarily pulling something out because what typically ends up happening is that a drug that has a very high liability is going to end up being used less and usually more critically needed. But because it's not making a profit anymore, the company stops making it. And now it's not available, even though it's more critically needed.

Drugs that have a very low liability and are used more broadly and possibly less critically needed actually are more profitable, so they keep staying on the market. And maybe that's a very cynical way of looking at things, but it's the reality of life.

So I'm just trying to apply that to the question we're asking here. If we have a drug that has a very, very narrow spectrum of use, either it's going to be incredibly expensive to be able to make a profit or they're just going to end up having it until it's no longer profitable and then stop making it, and now we really need the drug.

Is there a way that you can continue to make

this available if a drug is approved?

DR. COX: Drug availability is the decision of the drug maker and their decision to continue to market the product. Not a topic for today's discussion, but other groups and other organizations are having discussions about these issues. So not within our scope today, but there are discussions, Chatham House and other places, where people have talked about various different models for reimbursement and such, but not within the scope of what we're talking about today.

DR. BADEN: Dr. Green, your follow-on question?

(No response.)

DR. BADEN: We have now made it to noon. As you can see, it's a complex issue that impacts all of us, and there are many strong views and many angles. There are many more questions from committee members, which we will resume at 2:00.

Well, we're going to resume at 1:00 for the open public hearing. When the open public hearing has completed its phase, we will then resume the

questions or clarifying issues for the presenters. And it will just depend on how long those different segments take.

So we'll now break for lunch. We'll reconvene again in this room at 1:00 p.m. Please take any personal belongings you may want with you at this time. Committee members, please remember that there should be no discussion of the meeting during lunch amongst yourselves, with the press, or with any member of the audience. Thank you. See you all at 1:00 sharp.

(Whereupon, at 12:06 p.m., a lunch recess was taken.)

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

(1:04 p.m.)

Open Public Hearing

DR. BADEN: So we should resume the meeting. I would like to, just for the panel members, review the next three or four hours and the agenda.

have the open public hearing element, where there are four commenters. We have to continue the discussion that we stopped right before lunch, clarifying many of the issues raised. We have the charge to the committee with the questions, which we will then continue discussion on, and then we will formally discuss each question, where after the committee discussion -- normally, we have votes, but since we have no votes, we'll go around and have each person on the committee share their integrative thoughts as to how to advise the agency on the substance of the two questions, so that we can give them the best possible feedback.

That way, you all can think a little bit about how to integrate the issues you've heard and provide advice and guidance to the agency.

So we will move now to the open public hearing element.

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, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship you may have with the industry, its product, and if known, its direct competitors.

For example, this financial information may include the industry's payment of your travel, lodging, or other expenses in connection with your attendance of the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any 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 FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. FOX-RAWLINGS: Thank you for the opportunity to speak today. My name is

Dr. Stephanie Fox-Rawlings from the National Center for Health Research. Our research center analyzes scientific and medical data to provide objective health information to patients, providers, and policymakers. We do not accept funding from the drug or medical device agencies, so I have no conflicts of interest.

We appreciate the FDA and drug sponsors working to determine appropriate methods for testing new drugs for rare bacteria. Even though good quality superiority trials are challenging, we should not lower the standards for trials and data. Well-designed trials are needed to make sure a new drug actually helps patients.

Fortunately, when a drug is highly effective, the trial doesn't need to be large to show a significant improvement. For example, a company called Achaogen recently reported a statistically significant 28 percent reduction in death even though they enrolled only 17 patients in the test group and 20 in the control group.

The goal in developing new antibiotics is to

make sure they actually improve the health of patients for the targeted infections compared to drugs that are already available. It is dangerous to approve new drugs that are not as safe and effective as the antibiotics already on the market or drugs that are not studied on patients with the targeted bacteria.

Non-inferiority trials for antibiotics are resulting in the approval of numerous drugs that may be less effective than previously approved antibiotics. It is not ethical to give these drugs to patients that have more effective options.

After several rounds of comparing new drugs to somewhat older drugs that were slightly less effective than previously approved drugs, we can end up with new antibiotics that are much less effective than the best available. This is more likely when clinical trials use larger non-inferiority margins or margins equal to the estimated treatment effect. Wider non-inferiority margins increase the likelihood that the new drug is less effective than the approved drug.

The development of rapid diagnostics would help. In many cases, researchers lack the tools to quickly diagnose patients with target bacteria. This means that studies are conducted on many patients who do not have the targeted microbe.

In some cases, most patients don't have the targeted microbe. This increases the number of patients required in the trial and makes the trial outcome more difficult to interpret.

Healthcare practitioners run into similar problems when they decide which antibiotic to prescribe a patient. This trial and error exposes patients to increased risk of adverse events from multiple drugs while delaying appropriate treatment.

In contrast, the development of rapid diagnostics would help researchers study the appropriate population and healthcare practitioners just prescribe the drug that is most likely to help.

Unfortunately, the limited population pathway of the 21st Century Cures Act was written

in a way that could easily increase the number of antibiotics that do not benefit patients. This exasperates what is already a problem.

Of the 61 new antibiotics approved between 1980 and 2009, 43 percent were later withdrawn in due part to safety or for efficacy reasons. This rate was about three times as often as other drugs from the same period. Unfortunately, smaller clinical trials for limited populations could make this worse because it would increase the risk that results are due to chance rather than proven.

As you know, once approved, the new drugs are often promoted and prescribed for a much wider population than was targeted. This can expose patients to unnecessary risks, lower effectiveness, and generate resistant bacteria. Simply labeling a drug as limited population is unlikely to be sufficient to limit a drug's use to appropriate populations.

Developing antibiotics for single-bacteria species that infrequently cause infections is difficult. We as a society and as patients want

these treatments. However, having effective drugs marketed for these specific bacterial species does not help patients and may harm them in addition to contributing to healthcare costs, which are already higher in the U.S. than other countries where people live years longer.

If the FDA wants to be more patient centered, it needs to ensure the new antibiotics actually work for the intended populations before they are approved. New drugs should be scientifically tested on patients who know that they are participating in a well-designed clinical trial that contributes to knowledge, not by patients who think they are receiving a proven treatment.

Thank you for your time and consideration of our views.

DR. BADEN: Thank you. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MR. BRODINE: Good afternoon. My name is

Joe Brodine, and I'm a graduating medical student at Georgetown University School of Medicine. I'm here representing the National Physicians Alliance FDA Task Force, and I have no conflicts of interest to report.

NPA is a nationwide multi-specialty group of doctors with principles of integrity, service, and advocacy that put our patients first. We are non-profit and take no funds from pharmaceutical or medical device companies.

Within NPA, the FDA task force supports a strong FDA dedicated --

DR. BADEN: You have the slide advancer.

MR. BRODINE: How convenient. Thank you.

Within the NPA, the FDA task force supports a strong FDA dedicated to valid science and keeping drugs and devices safe and effective for our patients. We believe FDA approval should be based on adequate and well-controlled clinical trials with solid scientific evidence as required by law and regulation.

As practicing clinicians, we recognize that

we urgently need rapid diagnostics so that we can appropriately prescribe all antibiotics, including those for patients with resistant pathogens. We also need improved diagnostics in order to enroll patients in trials who might benefit from the new treatments for infectious diseases.

Non-inferiority trials are actually a disincentive to developing these diagnostics. Doctors and patients are interested in drugs that have added benefits, especially for patients with unmet needs. In the setting of antibiotic resistance, added benefits means drugs that are more effective than current options when used in the patients who actually need them.

My practicing colleagues and I are not interested in prescribing drugs that are only non-inferiority to existing options. Drugs that are as much as 20 percent worse than what we already have are not clinically acceptable. They're actually clinically inferior. This means that superiority trials are a requirement for showing us when a new drug works and in whom it works.

Superiority trials in patients with no options are more feasible than non-inferiority trials since they do not require exclusions for prior or concomitant ineffective medications. In fact, trials with highly effective drugs require fewer enrolled patients.

Randomized superiority trials where the new drug works similar to penicillin would require only about 2 dozen patients. And the example of murepavadin in the FDA briefing materials is consistent with this effect, as were the claimed results from the CARE trial of plazomicin, where the trial enrolled only 37 patients and showed a 28 percent decrease in mortality.

There will always be continued unmet need and no single drug can treat all patients, so future superiority trials will remain an option. There is no need for a large safety database when the new drug decreases mortality, as adverse effects may be more acceptable to patients when the drug actually saves lives.

Non-inferiority trials are only considered

feasible because they enroll patients who are easier to find, but using patients who already have options to treat their life-threatening diseases merely for convenience raises serious ethical issues.

No amount of decreased effectiveness is acceptable in life-threatening disease where effective therapy already exists, and it is certainly not acceptable where no effective therapy exists. In fact, exposing patients to less effective drugs violates the basic principles of ethical research. We would not recommend or enroll our patients in such studies, since they will also put patients without unmet medical need in harm's way.

Outcomes in short-term acute diseases should directly measure whether patients live longer or live better. Surrogate endpoints are not needed with highly effective drugs when direct patient outcomes can be measured in a short period of time.

In conclusion, doctors and patients don't just need more drugs, we need better drugs for

infectious diseases, and we need rapid point-of-care diagnostics to be able to both study the drugs in trials and prescribe them properly in practice. Empiricism leads to increased harm, increased cost, and greater antibiotic resistance.

As in other therapeutic areas, FDA should insist on scientifically valid, ethical, adequate, and well-controlled superiority trials in patients without other effective options. Selection criteria for enrollment in such trials should be based on appropriate risk-benefit for patients. Trial designs should not deny a patient's existing drugs with known track records by enrolling them in a study that, if successful, would show the experimental therapy to be second best.

We should not subscribe to a belief that exposing today's patients to the potential harm of second-best treatments will somehow benefit future patients. As I anticipate my career as a physician, I join my practicing colleagues in NPA in calling for better diagnostics that allow for appropriate antibiotic selection and a more

effective approval process for superior new antibiotics.

I believe in strong FDA policies that assure me that FDA approved is still a meaningful label. Thank you.

DR. BADEN: Thank you. Will speaker number 3 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. DOSHI: Good afternoon, everyone. My name is Peter Doshi. As you can see from the title of my talk, I'll be providing what I hope is an easy-to-understand explanation of why non-inferiority trials in the context of serious and life-threatening illness are ethically very questionable.

I'm on the faculty at the University of Maryland School of Pharmacy and an associate editor at the BMJ, but my comments today are my own. These are my financial disclosures. I receive no industry funding.

I want to begin with a very high-level

overview of what non-inferiority trials are and their purpose. By understanding this, I think it is straightforward to understand where they can and cannot be used to address research questions.

Non-inferiority trials always involve two active drugs, an experimental drug that is compared with a standard, already-approved treatment that is known to be effective. The aim of these trials is not to demonstrate improved efficacy. That would be a superiority trial.

Rather, the aim of non-inferiority trials as described consistently in the literature -- you can see a quote I've put up on the screen from a major textbook -- is to investigate experimental drugs that may have no improved efficacy over standard therapies, but may still, quote, "be of interest because they are less toxic, less invasive, less costly, require fewer doses, improve quality of life, or have some other value to patients."

So the concept here is that patients are trading off some loss of efficacy versus standard therapies in exchange for some clinically

acceptable non-efficacy benefit such as fewer side effects.

One can imagine a patient with an uncomplicated urinary tract infection who might be interested in using an antibiotic known to take a bit longer than other antibiotics to clear the patient's infection, but was at the same time also known to have less side effects like nausea, diarrhea or rash compared with those other therapies. That's the trade-off that non-inferiority trials can hypothesize and then evaluate.

Within the context of unmet medical need, non-inferiority trials make no sense for the simple reason that non-inferiority trials require a control drug that is standard approved effective treatment. With unmet medical need, there is no such drug, and so one cannot use a non-inferiority trial. This is a showstopper issue for patients. The only way to address unmet medical need is with a superiority trial.

Now, I want to address trials in serious or

life-threatening conditions. I think we can all agree that an experimental drug aiming to treat a serious or life-threatening condition should demonstrate that it actually does save lives.

Are non-inferiority trials ethical in this context? One way to look at this is to ask, would informed patients agree to participate in such a trial? Because non-inferiority trials involve a trade-off of efficacy and non-efficacy benefits, one has to ask whether they think patients would be willing to accept the potential of increased risk of death versus a standard therapy in exchange for potential non-efficacy benefits like the experimental drug being less invasive or providing reduced side effects.

I would wager that it's the reverse that's true. If an effective drug exists, patients would want an experimental therapy to demonstrate improved chance of survival even if the drug had more side effects. Just think of oncology.

For this reason, it is a superiority trial that is required in the setting of serious and

life-threatening illness. Non-inferiority trials are the exact opposite of patient expectations. And European Medicines Agency -- you can see the bottom of my slide there, a quote -- agrees with me, that "it's very hard to justify non-inferiority studies in the context of serious disease."

Non-inferiority trial trials in serious and life-threatening conditions are also contrary to foundational ethical documents. The Belmont report requires three things, respect for persons, beneficence, and justice. And non-inferiority trials, as you can read on the slides, fail the test on all three accounts.

Likewise, the Declaration of Helsinki says that, "When one uses an intervention less effective than the best proven one," and that is what we are hypothesizing of the experimental therapy with a non-inferiority trial, "then trial participants should not be subjected to additional risks of serious or irreversible harm." But that again is actually what is happening in the context of serious or life-threatening illness with any drug

less effective than the standard therapy.

We have actually recently completed a study of informed consent forms in antibiotic trials. We wanted to know whether consent forms inform patients that the study purpose is to test a primary hypothesis that the experimental drug may be somewhat less effective than standard already-approved therapy.

We looked at 78 RCTs from 17 antibiotics. Around 90 percent of these trials were non-inferiority trials. And I should say, by the way, these are all pre-marketing, pre-licensure industry-funded studies. Ninety percent of the trials were non-inferiority trials, 10 percent were superiority trials.

Three-quarters of the trials were in serious or life-threatening disease as per FDA's definition. These trials happened over two decades and enrolled over 39,000 patients.

What did we find? We found that all informed consent forms included a section of the consent form talking about study purpose, as you

would expect, but that none, zero of 50, consistently explained the trial's primary hypothesis such that patients could tell whether they were enrolling in a superiority versus non-inferiority trial. I believe this raises serious questions of the ethics of these trials.

In addition, nearly all, 71 out of 72, of those trials provided no rationale for the selection of non-inferiority hypothesis or potential risk-benefits to potential participants.

We looked for those rationales in the protocols and statistical analysis plans, but none was to be found, nor did we find a single trial that offered a rationale of why a given amount of decreased efficacy, the non-inferiority margin, which generally was a 10 percent margin or median 10 percent -- we found no rationale for why that margin was deemed clinically acceptable.

Although feasibility is important, one cannot place it ahead of scientific validity and minimizing harm to current patients. Many features of non-inferiority trials make them less feasible,

including much larger sample size, between 600 and 1200 patients, compared to superiority trials, which can be performed with less than 50 patients with highly effective drugs as the first speaker pointed out.

Non-inferiority trials also require exclusions based on prior and concomitant administration of effective drugs in order to assure their scientific validity. Scientific validity, we must remember, is the basis for ethical research.

The hypothesis of the study, not the results, the hypothesis, is the basis for the ethical determination. Therefore, the hypothesis of non-inferiority trials is the new drug may be somewhat less effective than standard of care in life-threatening illnesses. Non-inferiority trials are too small to tell whether the new drug is substantially better or worse than an older agent. Therefore, they are too small to answer the primary research question, which impacts on trial ethics.

I should also mention here that it is in

phase 3 clinical trials where hypotheses of patient benefit are tested, not phase 1, not phase 2. And the FDA released a report in January of this year. Of 22 products that looked great based on phase 2 results: mechanism of action, modeling studies, phase 2 results using surrogate endpoints. But then those 22 products all failed to show efficacy or had adverse events in excess of the benefit, only discovered in the phase 3 trial.

Finally, some regulatory considerations. It's unclear whether non-inferiority trials can be used in this context, as the regulatory basis for approval based on a single study or with surrogate endpoints was for when a new intervention provides meaningful therapeutic benefit to patients over existing treatments; for example the ability to treat patients who are unresponsive to older agents.

By design, non-inferiority trials intentionally do not answer these questions about improved efficacy, so there is a lack of substantial evidence that the drugs are effective

in patients with unmet medical needs.

In conclusion, unmet medical need can be directly addressed through superiority trials. Non-inferiority trials in serious or life-threatening disease also raise substantial ethical issues as embodied in foundational ethical documents. At a minimum, non-inferiority trials should include accurate, informed consent, and recent evidence shows lack of informed consent to study purpose.

Just some acknowledgments. I don't obviously work in a vacuum. While my comments were my own, I would like to acknowledge my many collaborators for their help. Thank you very much.

DR. BADEN: Thank you. Will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

DR. REX: Thanks. Thanks to the committee for the chance to make a few comments. My name is John Rex. I am a board certified internist and ID specialist with 30 years of development experience,

equally split between academia and industry. I currently work as the CMO of a VC-backed anti-fungal company as the chief strategy officer for CARB-X, and as an advisor to Wellcome Trust on their investment strategies, but the comments today I make are my own.

Germane to today, I have direct development experience with both antibacterial and anti-fungal products targeting rare and resistant pathogens. From this integrated perspective, I see three themes at play today.

First is unmet need. We clearly lack adequate antibacterials in the global pipeline, and truly, XDR pathogens are emerging. The thin pipeline has many causes, but deep-down discovery is really hard. Sometimes, when you narrow your focus, however, to single pathogens, discovery gets a little bit easier. However, as we've learned today, developing those drugs is very hard.

It's this third point that brings us here today. FDA has led a good conversation on ways to approach this. The core conclusion should be

there's no easy way out. There's no brute-force approach, diagnostics won't fix this problem, and the clinical program you can do in non-geologic time is likely to be imperfect.

What do we do when non-inferiority or superiority data aren't possible? This is a tough, difficult problem, and you're not going to fix the problem with murky clinical data. Infections arise unpredictably and then progress over a period of hours. It's 2:00 a.m. on Tuesday and you either enroll the patient right now or you don't.

These infections occur in complex clinical settings that will often confound interpretation. And we try really hard to make these resistant infections and the difficult infections rare.

As an example, I once closed an ICU because of an outbreak of an Acinetobacter infection. I closed the services feeding that ICU. I eliminated the infection. Now, I would have loved to have had some new drugs at that time, but think about me as a clinical study site. If I had been clairvoyant, I might have been useful for about a week, but then

after that, I would have been useless as a study site. Nobody wants to be a study site where you can do these studies. Just keep that in mind.

So what shall we do going forward? I would like to argue that we need to use some combination of the tools of accelerated approval in an LPAD-like language to register such drugs based on four mutually supportive lines of evidence.

First, exhaustive, varied, and well-benchmarked animal models; second, a demonstration of PK in man that is predicted adequate from the above-mentioned animal models; third, an adequate definition of the safety profile, that's very important; and fourth, at least consistent clinical data. In effect, it reduces to the question of whether the clinical data or the pre-clinical data is sort of the thing that's 60 percent versus 40 percent in terms of your approval.

If appropriately labeled, I think having such agents in the pharmacy would be valuable. They would not and should not often be used. And I think the global focus on stewardship -- and you

heard about this from IDSA -- would be very helpful here. Nations around the world are having national action plans. Those get translated into plans at local facilities. People will not overuse these drugs in the future as we envision it in terms of good stewardship.

You've heard from the clinicians that we are comfortable with extrapolating likely antimicrobial to utility based on the best clinical data. We've been doing that for years in other settings, and this is just part of what you have to do in infectious diseases. You never have all the data for all the infections you want to treat.

So in closing, if we don't make a path available, we're going to continue to lurch from crisis to crisis. The path we're talking about should only be used when there is no other choice whatsoever, and that's an important caveat as well. If you can do anything better, you really should do that.

The problem we're talking about today is not theoretical. We are living it right now. We lack

adequate drugs for some bugs, and there are places in the world where there are bacteria that are resistant to everything.

The narrow-spectrum drugs that are emerging could be relevant here, but I want to emphasize a contradistinction to the prior speakers that the superiority trials, you might think it would be easy to go do these superiority trials. I'm telling you, it's really, really hard because people work so hard to eliminate the infections when they're occurring at their site, so it's very tough.

So our choice is really kind of between a sin of omission and a sin of commission. If the agent doesn't exist in the pharmacy, there's no way to do anything with it. If it is in the pharmacy, even with limited clinical support data, we can cautiously begin to develop our understanding. Thank you very much.

Clarifying Questions (continued)

DR. BADEN: Thank you. The open public hearing portion of this meeting has now concluded

and we will no longer take comments from the audience.

We will now resume with the discussion that we broke from for lunch. And I think, Dr. Green, you have a line of questioning that you wanted to start.

DR. GREEN: Thanks very much, and I think my questions may be even more relevant after the comments that we just heard.

I wanted to go back to the notion of surveillance or phase 4 studies should one of these agents be approved on a pathway that we are potentially talking about.

Earlier, this morning, the conversations were really all about identifying a safety signal that had been missed. And it seems to me that perhaps the concern is the opposite direction of our cost-benefit analysis.

That is, if we're choosing to approve drugs either based on non-inferiority studies, where we've expanded the range of potential error or that in combination with or using, instead of that, the

animal models, the PK/PD, et cetera, I'm wondering what FDA would say or think if additional use of the drug identified in fact that the error bars in the small or small-ish studies in fact had gotten it wrong, and so in fact they were inferior with ongoing exploration.

I think that Dr. Nambiar, I believe, said earlier this morning that we don't do provisional approval in the United States. I'm not necessarily saying that we should, although perhaps if we're being really open-thinking and we're coming to these drugs that we don't see another way to evaluate them, and perhaps the best evaluation is post-approval, whether or not we would be able to use those data. And if in fact we saw non-inferiority after the fact, there might be a way to revisit the approval.

DR. COX: So there's probably a few different things to touch on in relation to your question. So as you noted, we do need the data to assess whether the drug is safe and effective prior to the point of approval. As you've heard from the

discussions, these are with drugs that are active only against a single pathogen. The complicated patients in whom these types of infections occur can be very challenging to study, even in a prospective comparative trial.

So the pre-market studies, their design is very important to be able to understand what's going on with the drug and being able to discern both efficacy and safety in a patient population that's going to have a range of events, some of which may be difficult to distinguish between drug-related adverse effects, complications of the disease, other bad outcomes that could happen in this patient population just given the nature of their co-morbid conditions and their clinical state.

So you're bringing up the point of in the postmarketing setting, continuing to follow on to see if there's issues with efficacy. So we'd need to have enough to be able to evaluate safety and efficacy in making an approval decision.

Then I think as you think about what you

might do in the postmarketing setting, if it's going to be interpretable -- I mean, you're going to run into the same issues that you ran into in the pre-market setting with regards to interpretability, so it'd probably need to be a study of sufficient design to be able to understand efficacy.

So it feels a little bit like -- if there really are those sorts of questions, you'd hope to deal with that in the pre-market setting. There are things that we learn about drugs after they're marketed. They're used in a broader, more heterogeneous patient population or used in a larger number of patients. We start to learn things and see things. But oftentimes it's not from a prospective, comparative, randomized trial.

So there are real challenges I think in studying these sorts of drugs. We need to get enough information in the pre-market setting to make the approval decision. We can continue to monitor. If there are particular safety issues, we can have requirements to study those safety issues.

I guess what I'm coming to is to think about what is it that you could do in the postmarket setting, which is oftentimes less formally controlled compared to what you could do in the pre-market setting. So I think there are some real challenges and things to think about here.

DR. GREEN: Suggested follow-on, I guess I'm not talking about simply surveillance, but thinking phase 4. Again, I get the issue, and perhaps one incentive to the sponsors is that if they're mandated to do phase 4, which sometimes might be included, but they also get to start to sell the product, it's just a little bit of some incentive.

As I think about this, it's all about trying to encourage somebody to develop these new drugs that we absolutely need and to be willing to invest, knowing that they may not get any dollars back on their investment. And yet, if we approve a drug based on animal data with a relatively small clinical trial that has error bars that we've intentionally enlarged, I'm just thinking about -- instead of going with the classic

95 percentile, if you go P 0.05, the likelihood that you're going to make a false conclusion is 5 out of 100. But if we make the error bars bigger, it's going to be larger, and the statisticians were giving us those numbers a little bit earlier in the morning.

I struggle to hold on to those. And yet, as we struggle to give guidance to you all, it's just trying to think about creative ways to find the compromises that say the process ends up getting us new drugs, but also assuring.

Maybe it's that then we just end up going with what our speakers just said and say, well, you've got to do superiority or multiple non-inferiority studies. But I think I got your answer, so thank you.

DR. COX: Let me just add, too, phase 4 studies can be done to further define how the drug is performing, both with regards to safety and efficacy. I guess what I'm saying is that we need to have enough at the point of the approval decision. There could be commitments to do studies

in the postmarketing setting to help further define things.

DR. BADEN: I think Dr. Weina has a follow-on question.

DR. WEINA: So we're being asked to think creatively here, so why don't we really think creatively and say something like, well, you were asked earlier about provisional approvals and that we don't do that here. Well, maybe that's what we should be doing, is thinking about that type of approach rather than doing phase 4s in which the follow-on data is not so critically evaluated.

So maybe a new category could be created of a provisional approval in which more study is done, and then it's actually set up so that later on, you look at it the same way that you do a standard approval and do that type of approach rather than just accepting a lower standard.

DR. COX: We do have to work within our laws and regulations, and such, but something that would be quite helpful to us is just to think about -- you're thinking about a quantum of

evidence, what level of evidence would you want to have in essence before the products were out there and available for patients.

So maybe thinking about your point and trying to frame it, in essence, and that is really the heart of the questions. What is that quantum of evidence that would take into consideration the seriousness of the disease condition, the lack of available therapies for patients with multiply-resistant Pseudomonas aeruginosa or Acinetobacter baumannii?

What is that quantum of evidence that would get you to that step of having enough to understand the safety and efficacy of the product and use it in patients?

DR. WEINA: I mean, that's a good point, but again, thinking creatively, you said you have to work within the laws. Okay. And I realize getting anything through Congress today might be really difficult to do, but not all of this requires absolute congressional.

This could be an additional approach that

could be used because the problem is that while today we're only looking at two particular species, 5 years from now or 10 years from now, we may be looking at 30 species that don't respond to anything, and we really have to think creatively. So why don't we get started on changing some of the rules that you operate under now?

DR. COX: So I'm almost saying that's an interesting topic and an interesting point of discussion. But maybe we can get through what we think the science would be, and what the science would be that would be needed to be able to get us to understand the safety and efficacy, such that it could be used in patients.

We do have flexibility in the way that we look at and apply the laws and regulations, taking into consideration benefit-risk and unmet need. So if we can work out the scientific question, I think that will help us to understand whether anything's needed or not. Okay?

DR. BADEN: Dr. Goetz has a follow-up question.

DR. GOETZ: Yes. I just wanted to get to the topic of what can and cannot be required in phase 4 studies. And I don't know whether my memory or whether the example is right. But for drotrecogin, there were requirements for phase 4 studies that led to a reconsideration of the efficacy of that agent and ultimately from the withdrawal of that. And I believe that those studies were required by the FDA, and they were well-calibrated, well-performed studies.

At least conceptually, could something like that be done, assuming you have the quantum of evidence to approve, which I know we need to address? But I think it might help the committee in its considerations if it had confidence in what could or could not be done.

DR. COX: Right. For required studies, if there are safety issues, we can do postmarketing requirements for safety issues. This gets fairly complicated fairly quickly when we think about accelerated approval or animal rule. The accelerated approval, there's a confirmatory trial

that's generally required. The Animal Rule talks about doing field studies should there be an event or an exigency that would allow for study.

Then there's also postmarketing commitments. So we can enter into a postmarketing commitment with the company to do additional study based upon their agreement to do so. And both the postmarketing requirements to further evaluate potential safety issues and postmarketing commitments are described in the approval letter. So they're all listed there with time frames for various different milestones along the way.

DR. BADEN: Dr. Schaenman has a follow-on.

DR. SCHAENMAN: I appreciate Dr. Weina bringing up the question of thinking out of the box and trying to be creative with this difficult topic. And it made me think about another way to kind of maybe do a de facto provisional approval or just make it easier to start building up clinical data more quickly because I think the point that was made before that time is often of the essence, is a good one would be if there's some way that FDA

could help us with emergency IND applications.

I'm thinking about some of my most tragic and challenging patients. Some of them were saved and some not saved through that process. But it's time consuming. It's frustrating. There are a lot of regulatory barriers. And that might be one way where we could achieve two goals, where it's not approved, the physician and the patient know that they're doing something experimental, but it allows us to accrue clinical data more quickly and get patient access to some of these drugs that look promising.

DR. COX: There are mechanisms for access to investigational products, and there are instances where we've actually gone back and tried to look at some of the data that have been accrued from products that have been used under emergency INDs, in some cases in a fair number of patients.

We have found that data in the instances where we've looked back very difficult to interpret. Absent a controlled trial with a randomized comparator arm, given the condition of

some of the patients, it can be very difficult to understand whether you're looking at a lack of drug efficacy, a drug adverse effect, or a complication of the disease.

So there are access mechanisms that are used in circumstances when appropriate to do so. But I don't know -- our experience has been that access mechanisms, even when you're trying to gather data, are often not an opportunity for a serious acute bacterial disease where you'd be able to really expect to make appraisals of safety and efficacy of a drug. They're sort of a separate and parallel track, if you will.

DR. BADEN: Dr. Gripshover has a follow-on.

DR. GRIPSHOVER: So actually, I had been thinking about that when I was preparing for the meeting, and I noticed in one of your prior workshops, when I reviewed, there had been some discussion about making a standardized control protocol. And it hasn't come up today, but I was thinking, if we have like an ongoing cohort that we're collecting of HAPB/VAPB patients, and then

when you get the multi-drug-resistant bug, you can click right in for maybe to the trial, but as a way to link them together.

DR. COX: Just thinking about your and Dr. Schaenman's comment, one way to think about this might be if there could be a trial of very simple design, and in fact that the access was also done in a way where patients got best-available therapy, but then also could also be randomized to the test drug. It may be the way to actually learn because you'll have a control arm and also provide access.

In that setting, where patients are getting the best available standard of care, it would seem that that would be an okay design. It would provide access to some in a setting where, at this point, there would be equipoise about the use of the drug in comparison to best-available therapy.

So it may be a way of a hybrid approach to what you're describing that might help direct it to something that you could actually learn about the drug and whether it's helping or not.

DR. BADEN: Follow-on, if you have a follow-on, Dr. Shyr?

DR. SHYR: We talk about out-of-box things here. Just use the word he just mentioned, the "hybrid." Have you ever thought about a hybrid design? Because you mentioned that we do need active control in some way, the patient there. But can we borrow some of the information if it's available and to design a way -- a hybrid means that you do have it randomized here, but you have a certain portion of the data that's borrowed from somewhere else.

Have you ever thought about this kind of out-of-comfort-box?

DR. COX: We have, and probably the area where this comes up the most is in emerging infectious diseases because something pops up, you didn't expect it to start affecting the population, and there may be some agents that have some activity in cell culture or something like this.

So there's tremendous pressure to make drugs available for patients who are affected with this

new disease. You're not sure what works. Time is of the essence. And this is not easy, but the question is can you put together a fairly simple clinical trial so the design isn't something so cumbersome that it impedes the ability to be able to put something in place quickly.

It is still a clinical trial. You still need informed consent. You'd still need IRB approval. But can something be done with relative facility in order to be able to do something where you are providing both access and learning about the drug.

So emerging infectious diseases is where that has popped up and may serve as an idea. This is a little bit different because these things are occurring on an ongoing basis. They're not popping up unexpectedly. But perhaps a simpler trial design with randomization and a control arm might be able to get there.

DR. BADEN: Dr. Marks has a follow-on.

DR. MARKS: Just following on, there have been lots of discussions, as Dr. Cox and Nambiar

know, in terms of these clinical trial networks, platform trials of trying to put these infrastructure in place so that we can capture the patients when they appear.

One of the challenges is the outbreaks are sporadic, they're short lived, and then you have a site there that's sitting idle, waiting for another patient to come along. So can we put together these studies?

The other thing is that, as sponsors, we worry about GCP, so being able to conduct these studies to good clinical practice that can go back, and be audited, and withstand the test of time.

When you start taking shortcuts in terms of is it an investigator IND, and you take that information and put it together with others, it begins to break down in terms of that durability and that quality aspect. So if we can get the networks together, train the investigators, and capture that, I think there's a lot of interest in that on a global basis, actually.

DR. BADEN: Do you have a follow-on?

Please?

DR. ANDREWS: Going back to your idea of provisional, I like it. I mean, yes, nothing passes in Congress, so if you can't do it, you can't do it. But I think about, if I was thinking about a medication or if I was a clinician thinking about giving that to someone and I saw provisional, it would be a red flag for me.

Another way that the FDA can give a red flag is through the label. We've talked about strong language in the black boxes, right, isn't it? There are other ways to at least flag to consumers and to clinicians that -- you could even say, this was done as a study with a very small sample size. We have concerns about this, this, or this.

You could give an A to F in terms of how strong you feel about the evidence that led to getting that. And it doesn't require the drug companies to come back with it, but I bet they'd want to get an F off their label and to come back with more studies.

DR. BADEN: Back to the future.

I think that we've exhausted that line of questioning. We can move to Dr. Follman, to a new line of inquiry.

DR. FOLLMAN: My line of questioning, I guess, is similar to what was brought up. I was thinking about postmarketing studies basically, accepting the landscape that the FDA has given us to contemplate, which is a very wide non-inferiority margin or approval using the Animal Rule with these animal models, which from the conversations don't seem to be very reliable.

So I was wondering, the logical way, if you're going to approve something that has a large cloud of uncertainty over it, what is the hope that you can try and understand it more in postmarketing studies? And I think what Dr. Cox and others have said is, there's really not much hope for it at all, that really what you need is enough evidence at the time of licensure that you're comfortable with it.

If the post-licensure studies are non-comparative, which I think they most likely will be

non-comparative, it will just be single arm, I don't see how you remove that cloud of uncertainty. So if you approve something that's got a 20 percent margin, it might increase the death rate by 10 percent, and you'll just never know.

So that was part of my thinking. And I have more of a pointed question, I guess, for Dr. Cox. We were talking about the Animal Rule, maybe approving some of these on the Animal Rule. That's been done for other compounds where there's been a strong body of evidence, a good surrogate variable, and so on. And at the end of the approval, there's been, I guess, a charge for postmarketing studies in the event of an outbreak.

So that's a little different than surveillance, and I wondered if you'd comment on the kinds of studies or the designs that have been done under the Animal Rule and whether there's much hope that they'll actually be executed.

So I think sometimes there will be these studies on papers that might be good if they could be done, but in fact there's not much of an

incentive for those studies to be done.

So just to comment on the studies that are required, postmarketing studies required for the Animal Rule and what's been the experience for those.

DR. COX: So I'm most familiar with the five drugs that have come through our shop for animal rule approvals. And fortunately, there hasn't been an event, so there hasn't been an opportunity to study the particular biothreat agents that they were approved for.

The studies that you might do in follow-up to an approval for a drug for plague or anthrax bring with them additional challenges, if you will, if there were to be an event, to actually conduct a study.

It's sort of what we were talking about with the emerging infectious disease. If something happens, fortunately, there's pre-preparation, but still it's very challenging to do a trial. In addition, the drug is approved under the Animal Rule, so those drugs have been found to be

effective. So that impacts on what the design can be of the trial that's out there, too, in patients.

Here, if we're talking about serious acute bacterial diseases, I do think it is possible to do a trial even after a drug is approved of an appropriate design where you could conclude something. I should just qualify my comment there.

I think many of the same challenges that you have prior to approval will exist post-approval. And Dean, as you said, I do agree that if the trial isn't designed appropriately, it could be extremely difficult to interpret because of the variability in outcomes that you'd see with a disease like HAPB/VAPB.

So a postmarketing study to provide interpretable information, you'll have many of the same challenges that you have in the pre-market setting, but you would, I would think, need to have an appropriate design in order to be able to draw conclusions about efficacy in the postmarketing setting, say a phase 4 commitment to do an additional trial.

DR. FOLLMAN: What incentives are there for the manufacturer to actually do this study?

DR. COX: So at the time of approval, they make a commitment. It's in the approval letter, so it is public information. There are goal dates along the way for the protocol submission, and time to get the study reported, and time to get the study reported, and such.

If somebody doesn't meet their timelines, it's posted on an FDA webpage so that folks are aware, there's a public awareness of it.

DR. FOLLMAN: So that's a rather small stick in a way.

DR. COX: Yes. And that's just a postmarketing commitment for a phase 4 trial. If it's accelerated approval, there's a little more we can do there. An animal rule is written more in terms of should an exigency occur. But generally there is a commitment to do this and information is out there and available to the public if folks are not completing a trial in a timely fashion.

DR. FOLLMAN: Just to finish up and to try

and think creatively, you don't have a provisional approval, but you have I guess a patent for a certain period of time. You could incentivize that by maybe shortening the period of time that the patent runs if they don't do this study, or for a carrot -- I think you have the scheme where you will allow a company to go to the head of the line for approval or for evaluation. And maybe you could use that as kind of a carrot for a person to do a phase 4 study.

So even if you don't have partial approval, there might be other incentives you could do to improve the possibility of getting these studies done.

DR. BADEN: I have a follow-up, a point of clarification, Dr. Cox. With the Animal Rule, is there a different legislative mandate for follow-on study, or is it sort of built in, we think you should do this?

DR. COX: It is a requirement to do the study, but it's written more in terms of should something occur, should an event occur that would

allow you to do the study.

DR. BADEN: The reason I ask is can that language -- if one thinks of the tier A, B, C, D or tier 1, 2, 3, 4 of evidence that people have been bandying about, if one has the most limited nugget of clinical efficacy, could one adopt some of the Animal Rule requirement as a way to generate the data while still allowing access to the unmet medical need?

DR. COX: Right. So if you get to the point of having enough information in the pre-market setting to be able to conclude safety and efficacy, then you could put in place a postmarketing requirement for a study either responsive to what's in the Animal Rule or the accelerated approval regulations to be able to further evaluate the clinical efficacy that you'd seen that was sufficient to lead to approval earlier on.

DR. BADEN: Follow-on, Dr. Lo Re?

DR. LO RE: Yes. So could you just clarify, Dr. Cox? As I understand it, the Animal Rule has really only been invoked for the bioterrorist

agents. Is that correct?

DR. COX: People are going to help me here a little bit, but I'll try and do some of the indications. So it's been used for indications of treatment in prophylaxis or plague. We have three fluoroquinolones that have that in their label.

It's also been used for monoclonal antibodies that bind the toxins of anthrax, so if a treatment is an adjunct to antibiotic therapy for treatment of anthrax disease. And then it's also been used for cyanide toxicity and myelosuppression from radiation. So that's what it's been used for to date.

DR. BADEN: Thank you. If no other follow-on, then -- no, I'm up next. Nice try.

Is Dr. Perl still here? No. Okay. Then I will pass my question to Dr. Corbett.

DR. CORBETT: I have two two-part questions. One, I think is really easy to answer, likely for the FDA. Just to be very clear, to make sure I'm understanding this, so these agents are clearly identified in vitro to only have activity against a

very specified bug. Correct? So Acinetobacter and Pseudomonas in these individual cases.

DR. NAMBIAR: Yes, that's correct.

DR. CORBETT: They could have activity of those that are susceptible to other antimicrobials in addition to being multi drug resistant. Correct?

DR. NAMBIAR: Really, the organism is susceptible to the particular drug, irrespective of what its susceptibility profile might be to other drugs. It might cover certain resistance mechanisms, it might not.

DR. CORBETT: It might not. Okay. So I just wanted to make sure I was clear on that.

The second of the two part, just brainstorming -- and I'm sure you all have thought of these other scenarios, and perhaps borrowing from other specialties, and I think we've already mentioned some of these already, both of which I realize are not exactly like the situation that we're talking about, but just to help me think about how to adapt from other disciplines to think

about the situation.

One would be for HIV, which I know is very different. We have a clear biological marker. I know there's been studies with newer agents that have been mostly non-inferiority-based studies, but from my recollection and talking to others, I believe those are based on the 10 percent non-inferiority most of the time. Would that be true?

DR. COX: Yes. With HIV, you're correct. You have a surrogate that really has been shown multiple different drugs correlates with reduction in opportunistic infections and reductions in mortality.

It's a chronic condition, so fortunately, with the advances in therapy, we don't see the opportunistic infections, we don't see the mortality within the time frame of a trial that's usually 24 or 48 weeks.

As you go from single-agent therapy to two-agent therapy to three-agent therapy, the jumps are really quite large. So it allows you to pick a non-inferiority margin, even if you're just adding

a third drug to an existing two-drug regimen because that incremental increase in treatment effect is quite large.

To your last question, I can't remember what the exact margins are, but it's something in the neighborhood of 10 percent or thereabouts sounds reasonable for what I would expect.

DR. CORBETT: That's my recollection. Yes.

DR. COX: Some of it is based on the size of the trials and practical issues in addition to what degree of loss would be acceptable. There's the sample size calculation using that margin, and then there's actually the result of the trial. There's a bell-shaped curve where less is out in the tails than is at the point estimate.

DR. CORBETT: I would assume that's true. I was not back when single-agent anti-retrovirals were developed. I know lots of things have changed since then. So I would assume, AZT, DDI, even aquinavir, when those were available, I would assume we can't really borrow from that information, either.

DR. COX: So we did use that information about what were the outcomes when you had just single-agent therapy versus when you had two agents, versus when you had three agents. And the jumps were so large across those additions that it did allow -- the margin that I recall being set was you went from a second to a third agent, where the incremental gain was still very large. But there were large jumps all along the way.

DR. CORBETT: I didn't think that was terrible helpful, but I just thought -- the other scenario, which I'm sure you all have talked about, is cancer to chemotherapy for oncology patients. And that's just my ignorance of not knowing how traditionally those are developed and approved.

So perhaps you could maybe summarize a little bit about how that process works, especially those that are later-stage cancers.

DR. COX: So I don't claim to be expert in this, but I'll give you some information as I've tried to explore this a little bit.

One of the things that makes these studies

so challenging in the serious acute bacterial disease is the diagnostic uncertainty and the urgency with which therapy needs to be initiated. And that really makes these trials tough because oftentimes you're treating empirically. You're treating with other drugs that may cloud the effect of your investigational drug. So that's the serious acute bacterial disease issue.

With oncology, typically, they're making a tissue diagnosis. There's often times for receptor studies and further characterization of the tumor. So the diagnosis is known quite well at the time that the investigational therapy is either the drug that's used or it's added on to existing therapies.

Some of their studies will look at its tumor progression or progression-free survival. And they are able to do a study. And if there is progression, then they can take the patient and give them rescue therapy. And you can see how, with a serious acute bacterial disease, the issue may be that if the patient doesn't get effective therapy within that very early time period, the

outcome may be determined, and the patient may expire if they've got a condition with a serious mortality. And there may not be a second opportunity to intervene or rescue in all cases.

In some cases, there would be. If the patient stopped responding, you could still jump in with another therapy. But it's more challenging in the serious acute bacterial disease space because of the nature of the disease and the opportunities to rescue or not, to be able to effectively rescue.

So I hope that helps a little bit with your questions.

DR. CORBETT: You were very helpful, yes. But I guess to continue on that and just to be complete, or maybe you don't know or someone else knows, most of the approval on that is still based on small clinical data, so mostly phase 2-like-ish?

DR. COX: Maybe not so much concern about whether it's labeled phase 2 or phase 3, but from what I've understood, many of their conditions don't get better. So the tumor doesn't shrink on its own, so if you start to see a tumor shrinking,

you've shown something that would never happen on its own spontaneously. So they have that very stable baseline that helps them in discerning efficacy.

In the serious acute bacterial disease, depending upon who gets in the trial, if we're jumping up and down by 20 percent on the outcome, if it's mortality in a trial, it can be difficult to discern that.

Also, there have been some really remarkable advances in the area of cancer chemotherapy, where even in a not-so-large trial, they've been able to show mortality advantages. So the numbers of the trials are not huge, but given some of the therapeutic advances that have happened, even within a trial of relatively limited size, they've been able to show mortality differences because of the advances in therapy.

DR. CORBETT: Right, which we don't necessarily have.

DR. BADEN: So a follow-on, because I've thought about what can be learned or inferred from

the oncologic model. And I think there are substantive differences, some of which have already been mentioned. But I think there are some aspects that, at least for me, resonate a bit. And that has to do with the precision phenotyping.

If someone has a swollen node, is that adequate where you know they have lymphoma? Or if they have lymphoma, does it matter if it's Hodgkin's or non-Hodgkin's? Or does it matter if it's mantle-cell or marginal-cell? And you can go on and on, and then that changes the treatment.

Here, we have someone with pneumonia. We don't even know they have pneumonia. They're on a ventilator, and we think they have pneumonia. And then we treat them, and hope they get better, and try to infer. And maybe there's a culture that's positive. Maybe it's a non-sterile site culture that's polymicrobial.

So at least in my own mind, the issue of precision phenotyping, and could one learn more? You can learn a lot in an oncologic study, in my view, of a small number of cases that actually have

the disease that is relevant to the intervention versus they have swollen glands.

So I guess I'm not satisfied, at least in the practice in my part of the country that we have precision phenotyping for what infection is causing what syndrome. And as long as we're syndrome based, it creates so much more noise.

Then it gets to Dr. Bennett's comment about if there's more noise than case, how can you ever tell a difference because everything will be the same? So I do wonder about the issue of precision phenotyping, and I could imagine with an Acinetobacter or Pseudomonas study, where 10 bacteremias treated may be more informative than 250 pneumonias that may or may not be Acinetobacter.

How one would think about that, I welcome Dr. Isaac's comments if they've thought about this or the agency's comments about how one would weigh the precision of a sterile-site culture with the organism of interest versus the imprecision of a syndromic/non-sterile-site culture.

DR. COX: Yes. Diagnostic certainty and identifying a patient population where the outcome is expected, where there's an evidence base to expect that the outcome would be worse, could help in essence being able to show a larger treatment effect in that patient population and help to alleviate some of the uncertainty. If such a sub-population of patients can be pre-defined and identified, it could be quite helpful.

We have done this to some extent. Just thinking about it, it's typically been, we always do look at the bacteremia cases in a variety of infectious diseases. So whether it's community-acquired pneumonia, whether it's a complicated urinary tract infection study, the bacteremic subset within an overall trial that's successful is something that we look at because we think it helps us to look at a sub-population where there is diagnostic uncertainty, it's a sterile site, that bacteria should not be there.

Usually, too, with bacteremia, there's also an associated degree of severity of disease that

helps us to understand how the drug works.

DR. BADEN: I think Dr. Shyr [Shire] has a follow-up.

DR. SHYR: Shyr [Sheer]. So I think that's a great question to follow up. Do we have the characteristics of the patients who failed for the current active control drug? Do we have that dataset?

DR. COX: So help me a little bit more, Dr. Shyr. I'm just trying to understand your question.

DR. SHYR: I mean do we know their phenotype. Two ways. Right? We know the clinical characteristics of dose subgroup patients, they're most likely to fail Or second, from molecular, do we have the detail, even sequencing data, of the bacteria to know they may have different -- so those two angles, do you have that data?

DR. COX: I'm not sure that we do. And I'll just make a couple of points. I'm not sure I fully understand your question, but we do see patients who come in to the hospital, and depending upon the

stage of their disease -- are they far along or are they earlier in the disease -- even those that have exquisitely sensitive bacteria to the drug they're being treated with, they will die, or expire, or have a bad outcome, whatever that outcome may be.

When we see failures in a clinical trial, we'll oftentimes try and understand why those patients failed. Is it a situation where the patient's been underdosed? Is there something else going on? Do we not understand susceptibility testing in the way that we should or something like that?

But I'm not sure I've answered your question, but those are a few things that come to mind that I think may be related to what you're asking.

DR. SHYR: So my question is rephrased this way. If we know the particularly subtype of the patient, we know they're likely to fail. Do we have that data? That's my question. If we don't -- for the cancer, they have cancer registry data. We don't have a registry. Do you have any

plan for those multi-resistant or for a particular subgroup where we should have registry data to study them?

DR. COX: I think I'm understanding now, and you'll correct me if I'm wrong. But you're talking understanding characteristics that would lead to worse outcomes, so a patient population based upon an understanding of the natural history of disease and the factors that impact upon outcomes. Because if you could identify a patient population that was likely to have a very bad outcome, even given standard of care, could you then study that particular population of patients? And if you had an agent, it might be able to show a large treatment effect.

(Dr. Shyr nods in affirmation.)

DR. COX: I see you nodding, so yes. Okay. Good.

DR. SHYR: Exactly.

DR. BADEN: Dr. Weina, do you have a follow-on?

DR. WEINA: Dr. Corbett's question actually

touched on something that I had thought about as I was reading through the briefing packet ahead of time. And that is, one of the questions she asked is, the drug or drugs that we're talking about are truly for a single species, usually for a multi-drug, one, and do they also have effect on the non-multi-drug species.

But I guess my question is even broader. And that is that one of the strategies that we used to think about when I was doing a lot of drug development was what's the easiest path to licensure. And let's take that path first. Then the drug is out there, and it can be used off label by just about anybody for almost anything. And tat's just the reality of it. And it was also brought up, once a drug is on a shelf, it's on the shelf.

So the question becomes, as we think about changing the standards for this, are we going to have to start thinking, too, about what's the burden of proof? It's really this niche-type drug that only treats this one single species and

doesn't have a potential for other indications, so that once it gets approved and it's on the shelf, it can be used for other things.

Is that something to think about as well?

DR. COX: Right. We are trying to work within the existing standards and recognize that we can take into consideration benefits and risks. And taking benefits and risks into consideration, unmet need, patients who have serious disease and don't have treatment options, is an area where we do have flexibility.

I think we can work with benefit-risk and understanding unmet need for these disease conditions. We tried to outline some of the approaches that we hope would be doable, primarily focusing on what can be done clinically, and then if in fact that turns out to not be the case, some discussions around what role the animals might play.

So the ideas that we threw up were ideas that we would hope, if successful, would be able to provide us the type of information that we would

need in order to make an assessment. But I'll stop there, Pete, and then you'll help me understand if there's more to it that I didn't get to.

DR. BADEN: Dr. Moore?

DR. MOORE: I just have a follow-up, I guess, point about Dr. Shyr's. A point is the difficulty with studying these pathogens, and as with almost any infectious disease, really, the patients who come in who are the sickest are actually paradoxically less likely to be enrolled in a clinical trial when you approach the family and say, "Look, Mom's really sick, and we're not sure she's going to survive. How about this experimental medication?"

So the approval rates for informed consent in those situations are less. The other is that these patients, especially with the pathogens we're discussing today, these patients almost informally have a wide variety of complex and significant co-morbidities that play into outcomes.

So it's one thing where you have biopsy-proven malignancy, where you have proof that

the patient has the infection. It's another to be able to completely unable to -- or not completely, but reliably unable to distinguish between colonization and infection to even enroll the patient and follow those patients.

So Dr. Shyr's point is well taken in the sense that it would be great if we had those endpoints for patients who had a higher likelihood for high mortality, but in reality, those are difficult to come by.

DR. BADEN: Dr. Cox?

DR. COX: I'll just mention briefly that you're right. I mean, it really is challenging, and enrolling in a HAPB/VAPB trial is particularly challenging. And the folks from the Clinical Trials Transformation Initiative are working on a project to see if patients who are at risk for developing pneumonia, I should say HAPB/VAPB -- can patients who are at risk, can they identify patients who are at risk for developing HAPB/VAPB.

Can they in essence study a pre-consent process to make the likelihood that a patient who

is willing and interested to be in a clinical trial, the logistics of some of the consent process can be handled and managed in a more efficient way in order to be able to improve accrual in a clinical trial for patients who are willing and able to consent for getting in such a trial?

DR. MOORE: I'm sorry. Just one last point about that, that I failed to mention also is when you have greater emphasis on infection-control outcomes for hospital-acquired infections, you have every institution doing its best to try to eliminate, because it cuts into their bottom line, reduce the rates of VAPB, it becomes increasingly difficult to perform a clinical trial on VAPB in the United States. And this relates to the other question. We'd have to start taking or accepting studies where the majority of the patients are enrolled overseas, and that brings another problem.

DR. BADEN: Dr. Ofotokun?

DR. OFOTOKUN: I'm still trying to wrap my head around this issue of design, non-inferiority, superiority, study design. So assuming we are able

to, maybe by some strange reason, we have the technology to clearly define the phenotype or we have diagnostic certainty, that we know this is what we're dealing with, and we have these new agents that have a new mechanism of action and that are likely to be effective against the pathogen, wouldn't a superiority study design be a more effective approach, an easier approach than a non-inferiority study design, at least for the first two or three trials?

DR. COX: I'll try and walk through this, and I'll ask others to help me. So at least when I think about infection, I think about the bacteria, the host, the immune response, and the antibacterial drug. If we look over time, we've seen a number of antibacterial drugs studied, and we very occasionally show a finding of superiority. There are the occasional drugs that do better than some of the existing drugs.

In some instances, where we've seen that, it may be driven by the comparator agent, there being resistance to the comparator drug so it's less

effective there. But if you have a fully effective comparator drug, the question is, is it a new drug that's essentially doing about the same sort of thing, it's killing the bacteria, the likelihood of showing superiority on that alone may not be too terribly high.

So then you can ask the question of who needs it. Well, many people might need it because it may operate via a different mechanism of action. It may be tolerated because it has a different antigenicity. It may not provoke hypersensitivity reactions. It may have fewer drug interactions.

Those characteristics may not be fully brought out in a non-inferiority trial. The finding of superiority is either the drug is truly better, and that's wonderful, and we'd love to see that. But even an agent that's doing about the same as an existing drug that operates via a new mechanism of action may need a drug that is critically important to patients out there.

If you think about the setting that we're in now, where we rely upon drugs because of

susceptibility testing results that show that this drug is still active, when that drug was originally studied, that resistance mechanism that we're relying upon it is an alternative treatment or it is an option that still works, may not have even been around at that point in time. But we're very thankful that we have those drugs and we can use them to treat patients' infections that would otherwise not be there.

So superiority findings are very interpretable. It's wonderful when we have a new drug that's superior, but even options that are not necessarily superior but things that operate via different mechanisms of action that perform about the same with regards to efficacy or have different drug interaction profiles, different toxicity profiles, can be very beneficial to patients out there.

Does that help some?

DR. BADEN: Thank you. Dr. Hilton, you had a follow-on question?

DR. HILTON: Yes, thanks. I'd just like to

come back briefly to the phase 2/phase 3 question. I think I would be less concerned about this if I had seen phase 2 data, but I feel that getting that before going towards a phase 3 trial is pretty important. But I'd also like to lay out a big contrast that I see between these two designs.

They can both be randomized, and I would recommend a randomized phase 2 trial. So if the study designs are the same, the key difference then for me is the order in which the primary and secondary analyses are defined. So for phase 2, I would do within-arm analyses and sample size calculation, and for phase 3, I would do between-arm analysis and sample size calculation.

So the latter is going to be driven by this tiny difference that we're struggling with, whereas the former depends just on how wide a confidence interval, how much uncertainty we're willing to put up with.

So I feel like we're discussing animal models and stuff. This has got to be stronger than an animal model. It's in people. It's using the

relevant drugs. You can have as a baseline characteristic the participant's drug susceptibility and colonization level. Until I see phase 2 data, I'm not comfortable moving forward to phase 3.

I just would like to raise one more point and ask a question. I think that it would be useful in hospitals or any other relevant settings to begin surveillance for development or estimation of rates of development of drug resistance to these infectious drugs.

Because we've talked about different rates of response by body compartment, I wonder if a simple blood-sampling strategy would be able to answer that question or if it has to be more complicated sampling than that. Thank you.

DR. COX: Maybe just one comment on your last point. People do try and understand tissue levels, whether it be levels in the lung, levels in the urine, levels in the bloodstream. And it does help them to select indications to pursue or not pursue depending upon the levels attained, and it

can be very helpful in deciding not to do something.

There are instances, too, where even despite doing that sort of information, where it was in fact a clinical trial later on showed us a surprise that it didn't work at a site where we actually did attain a level.

But very good points as far as you certainly do everything you can do to understand the drug levels in the target organs that you're trying to treat the infection. And it can be very helpful in deciding where not to study the drug. But sometimes even when we think it will work, sometimes clinical trials teach us something we didn't expect.

DR. BADEN: Dr. Marks, you had a follow-on question?

DR. MARKS: I think it was back from earlier. I was trying to remember where -- we've progressed.

DR. BADEN: That's okay. Then we can move to another line of question. Dr. Lo Re? No.

Dr. Daskalakis?

DR. DASKALAKIS: I have more of a comment than a question, actually, which has to do with the conversation about postmarketing evaluation of these agents.

I was thinking about this from the real-world perspective of what would happen when these agents come out. And I think that a couple of things that would happen is that they would be priced very high because not very many people will use them.

Many hospital formularies would consider not including them on their formulary, which would potentially mean that postmarketing evaluation of the drug will be stymied by a very small number of folks who will actually be using the drug, and it will take a very long time to figure it out.

So I'm saying this in support of your comment, which is looking at the intro, the data-end approval is going to be really important because I don't think it's going to be an easy to drug to evaluate postmarketing.

I'm not sure if you have a comment about that as well.

DR. COX: No. It's a fair point. I think most people are looking at these drugs that would be used judiciously in the real world out there. Pricing, I won't comment on. And then yes, as we've mentioned, given the patient populations here, to really be able to understand efficacy, it would seem like you would need a randomized control group. And that will be tremendously helpful in trying to interpret any results, so fair points.

DR. BADEN: Dr. Marks, a follow-on question now?

DR. MARKS: No. I just remembered what I was going to say. Thank you. It had to do with the type of the host that the infection is in. In the current day, most of these antibacterials are targeted towards killing the bacteria, and that's what they do, and that's the limit of what their ability is. So depending on your phenotype and how many co-morbidities you have, that's probably not going to be affected by the antibiotic.

In the new generation, where we have host-modifying approaches, then maybe that will play through more and more in that situation. That's what I was trying to say.

DR. BADEN: Thank you.

Dr. Shyr, do you have another line of questions or have they all been asked?

(Dr. Shyr gestures no.)

DR. BADEN: So are there any other general questions? Yes, Dr. Honegger?

DR. HONEGGER: I guess this is somewhat specific, but for Dr. Isaacs, given the geographic differences in Acinetobacter prevalence, was the trial that's being proposed going to be enriched in Asia or other countries, or was that a U.S.-based trial that you proposed?

DR. ISAACS: So given the paucity of patients suitable for the clinical studies, the clinical studies will be run in those areas where we're most likely to get patients, so that would be a global program.

DR. BADEN: Dr. Bennett?

DR. BENNETT: I want to offer an anecdote, and it has to do with that I work in a hospital that made national headlines because we had more than 12 KPCs in the course of a year and a half. These isolates were resistant to everything except colistin, and at least in vitro, tigecycline.

At the end of this experience, I have no idea if colistin was effective. And I did learn that the NYCs could creep up week after week because of Pseudomonas aeruginosa or the KPCs, and that the nephrotoxicity of colistin was easy to see.

So why couldn't I tell if colistin did anything? And the answer is these patients receiving normal drugs, typically an anti-fungal, antiviral, as well as several antibacterials for empirical use for other conditions, although many of them died unfortunately, the cause of death was usually not clearly multi-factorial.

So we're talking about the populations. I think it's important we find populations in Dr. Cox's [indiscernible] way he's been saying

this, where we can actually evaluate the efficacy. For many of these patients, you cannot really evaluate the efficacy of a new drug. Thank you.

DR. BADEN: If no other comments, we'll let Dr. Bennett lead us to our break. We will take a 15-minute break, and then reconvene and discuss the specific questions before us.

I will re-advise the committee to not discuss the meeting topic during the break, and we will resume at 2:45.

(Whereupon, at 2:34, a recess was taken.)

DR. BADEN: We shall now resume. The committee will now turn its attention to address the task at hand, the careful consideration of the data and discussion before the committee as well as the public comments.

I will ask our colleagues from the antimicrobial office to give us our charge.

Charge to the Committee - Edward Cox

DR. COX: Great. Thank you, Dr. Baden. I'd like to thank all of today's presenters, and the speakers at the open public hearing, and committee

members for all of the presentations and discussions so far.

We brought this issue of single-species active drugs to the committee because this is both a particularly challenging and important issue. And as we've heard, there are patients out there with infections that are serious infections, where there's unmet need and have few or no available treatment options, Acinetobacter baumannii and Pseudomonas aeruginosa being two particular problematic pathogens in that they cause serious infections, and we don't have much in the way of treatment options for patients who have multi-drug-resistant isolates of these particular organisms.

We appreciate the committee's engagement on this difficult topic. And as Dr. Baden noted earlier, the discussion is largely conceptual, but based on some of the examples we've heard, and as you can see, there are sponsors who are developing such products and embarking on such programs. So that brings the importance of the conceptual discussion to help get advice on these sorts of

programs in general.

As you also noted, this is a challenging issue, so we did have some workshops previous to this to help develop some of the thoughts that we've presented to you here today. We think it's important to do what can be done to increase the likelihood of generating interpretable clinical trial data to evaluate the safety and efficacy of single-species active antibacterial therapy when that species occurs particularly infrequently, and we'd appreciate any advice the committee has on how to increase the likelihood of generating interpretable data from the clinical trials.

As you can see from the questions, we're also interested in advice from the committee on what role data from animal models of disease might play in evaluating a therapy if, despite all the best attempts possible, an interpretable clinical trial cannot be achieved.

As we've discussed, and really this has been at the heart of the discussions, there's a very complex weighing of risks, benefits, and certainty,

and the degree of unmet medical need that are faced in these particular therapeutic areas where Acinetobacter and Pseudomonas aeruginosa cause infections.

So we have two main questions for the committee, and they're not voting questions. So really important to us will be understanding your thoughts and advice on the particular questions that we have for you.

Should we project question 1 at this point? Question 1 is discuss the unmet medical need for single-species-specific products and the risks and benefits of the development proposals presented. And please provide any additional recommendations that you might have for developing such products.

So again, we're looking for any advice that you might have on the components of such a development program and any advice that you might have on ways that would make this more likely to be interpretable or achievable, any advice you have.

We've heard some of those points being made during the discussion so far, so we welcome the

opportunity to hear more about that and/or reiteration of some of the ideas and crystallization of some of the ideas that we've heard so far.

You want to do the second question now, too? I'll do the second question, just so folks know where we're going. So question 2 is, while every effort will be made to perform human clinical trials, performing clinical trials for antibacterial drugs that treat a single species of bacteria when the target species infrequently causes infections will be challenging, and data collected may not be interpretable or may be very limited.

Should this circumstance arise, it may be useful to consider whether animal models of serious bacterial infections can provide useful information to assess the activity and efficacy of the drug.

In such a situation, please discuss the following. We've got two component questions here, the types of animal models and appropriate endpoints that you think might be useful to assess

the efficacy of an investigational agent. Then the second component to the question, if there is a situation where efficacy is principally demonstrated in animal models of infection and only limited clinical trial data are available in humans, how might such a product be used clinically? Thank you.

Questions to the Committee and Discussion

DR. BADEN: So we will first address question 1, which we will open for group discussion. And after group discussion, then we will go around and each, under a minute, synthesize what we think are the key issues for the agency to consider.

I wish to do that in part because we are here to help give the agency advice, and all of us have heard lots of information. It is difficult to know how we each prioritize the complex information and to try and crystallize what we think is most relevant.

So we'll start with the first question on the right, the second question on the left, just so

my colleagues can prepare their thoughts. We will open with question 1 now for general discussion, for us to debate amongst ourselves as to any salient issues. Dr. Andrews?

DR. ANDREWS: I can't remember where this came from. I think it was in one of the presentations today, but it may have been what I read on the plane here. But there was a discussion that if animal models or early tests suggested that there was a need to be careful about how this rolled out, that you would choose centers to essentially pilot it through so that it could be better studied and then also better targeted to people who would benefit the most and people who would be the least likely to get the toxic effects.

Well, that's how I read it, and that sounded like a good idea to me.

DR. COX: Just thinking about a drug -- and we do learn a lot from the early pre-clinical studies, what the target organs of toxicity are, and things of that nature. So it does help us to provide information about the drug, and that could

help to identify a patient population.

For example, if a drug has renal toxicity as its target toxicity or there's drug interactions that enhanced renal toxicity, there may be particular patients to avoid. So a reasonable thought to try and figure out how we can use the information that we know already to try and reduce the risk in the patient population that would be in the study.

DR. ANDREWS: I understood it to be also post-approval, or can you not do that?

DR. COX: The same principles would apply. The information that we can provide about a drug, what we know about its toxicity, if there are particular patient populations where the efficacy is not borne out from the clinical studies, those same ideas and principles would apply. Providing that information could help to guide the appropriate use of the drug.

Does that help? Okay.

DR. ANDREWS: Yes.

DR. BADEN: Dr. Lo Re?

DR. LO RE: I actually really like that idea, and I think that if we consider the mini-sentinel model, which was the creation of a distributed database, collaborating with different health plans specifically for the purpose of safety, maybe the development of a single-species drug, clinical trials network, perhaps even internationally, given what Dr. Isaacs told us about the prevalence of the infections, might be something that the agency might want to certainly consider. I think that would give potentially a larger opportunity to get good evidence in terms of clinical trials data.

I guess one of the other thoughts that I had was I was very compelled by the concerns about the identification of appropriate phenotypes, particularly with regards to the challenges in identifying pneumonia, urinary tract infection.

I guess I wondered if the focus was made from the agency standpoint of looking at, for example, bloodstream infections, would there be a consideration that, potentially, given the narrow

number of patients with these diseases, with these infections, to consider potentially that if efficacy is shown with bloodstream infections, potentially that could be extrapolated to other sites, or something in terms of labeling the potential?

DR. COX: The labeling usually reflects the population studied. So if the study were one where it enrolled patients predominantly with, say, HAPB/VAPB and bloodstream infections, then that's probably what we would reflect in the label.

We haven't gone beyond the patient populations studied. If we look back over the last 10 years, there's been really a handful of occurrences where we've seen drugs, although we didn't expect it, that worked in one body site and not another.

So that's been one thing that's popped up. And oftentimes, those studies were undertaken in those other body sites, expecting that the drug would work. Obviously, you don't do a study if you don't think the drug would work. So there are

those issues with extrapolation.

Then beyond that, too, sometimes, depending upon from which sites you're extrapolating to, to another, there may be differences in dose and duration that would be appropriate for different body sites, so something to think about.

DR. BADEN: Dr. Weina?

DR. WEINA: Certainly, one of the things that we can learn from other drugs, for example snake venom -- I mean, these drugs are made available, anti-venom. They're not sitting on a shelf somewhere. Basically, what happens is that there's a distribution network set up, and principally, it's done that way because it's just not cost effective for places to buy it and have it on the shelf.

We do the same thing with intravenous artesunate for malaria for immediate use. And the turnaround time from requesting the drug to actually having it in the vein is typically under seven hours because it's prepositioned by the CDC all over the place.

Those are possible ways of doing it. And I'm kind of curious as to -- those are all done principally for economic reasons more so than anything else by the sponsors, and how much leverage could the FDA have on that as making that as a postmarketing requirement? That way, there's a little bit more control over the potential use of the drug and also gathering the data back afterwards for postmarketing surveillance reasons.

DR. COX: So it is possible under accelerated approval or an animal rule approval to have various restrictions in place to assure the safe use of a product. The thing that Dr. Weina is mentioning is the CDC's IND. And I'm talking about an IND because this was published in the Morbidity and Mortality Weekly Report several years back, where they have the availability of IV artesunate.

It is a model, and it probably merits some additional comment and discussion from others as to how that would meet clinical needs out there of patients, but it is a model.

DR. BADEN: And clofaz. I mean, they're

different agents prepositioned that way.

Dr. Daskalakis?

DR. DASKALAKIS: This may be in the same vein, which is beyond the snake-venom model, are there any other regulatory mechanisms that limit the use of a drug to salvage?

DR. COX: It's a tough definition. What we usually have written in indications when we've been in situations like this have been things like the bedaquiline label for treatment of tuberculosis, where there was a mortality imbalance in the study, the major study that supported approval.

We said use this drug for the treatment of tuberculosis when an effective regimen cannot otherwise be constructed. So because of the available data, what we had at that point in time, and also the consequences of inadequately treated tuberculosis, we thought there was an important role for the drug. But that role was when, in essence, you couldn't otherwise construct a drug regimen.

So we can describe that. And there's

probably an important role, too, for the greater healthcare community, and physicians, and hospitals, and such, formulary committees, but we can certainly provide the information about where we think the benefit-risk is appropriate. And if there are certain procedures that are necessary in order to assure the safe use of the product, we could do that. It is a complex scenario with the acutely ill patient.

DR. BADEN: Dr. Green?

DR. GREEN: I wanted to address the first part of your sentence for question 1, which is, discuss the unmet medical need for single-species-specific products.

So first off, I just thought we should comment on that. And actually, I don't know that there's any need for a single-species-specific product, but there is a need for our drugs that use novel targets. Right?

So if it turns out that because this species has a unique target, that that becomes attractive and also identifies a potentially efficacious route

towards antimicrobial therapy that's really only due to one organism because that's the only organism that has it, then I think, yes, it's fine to do single species.

But bacteria tend to be genetically related over time. So I don't know how many true targets are really only in one organism. So maybe this outer membrane target in Pseudomonas is really only in Pseudomonas, so it is sort of unique. But you wonder if it's really going to cross-react with other bacteria.

The beauty of a single-species drug, I guess, is that you could only select for resistance in one, and that potentially when you're using it to treat Pseudomonas, you're not impacting anything in the GI tract or the respiratory tree that wasn't your original focus of treatment.

So I really think it's really important to get that because even the concept, I think, is sort of novel, and it's really dependent upon new targets. We definitely need to have unique targets that aren't related at all to what we're using

because if you look, things like tigecycline, really are just tetracycline taken to the organic chemistry lab and manipulated.

So it's really fairly close, and then all the cephalosporins, and penicillins, and carbapenems, and monobactams are really one drug class even though they have different names. So they really are all at risk to expanding change.

Having said that, additional recommendations you might have for developing such products, just to kind of I think review what we've already said is, I would comment that the non-inferiority may be the way to go even though 3 out of the 4 public speakers really were suggesting that non-inferiority was really an inferiority study.

I don't know that that's true. Right? The error bar can go in either direction, so there shouldn't be necessarily, in my mind, a premise that if something goes by non-inferiority, you're planning to accept something that works less well because it could work better. I think it's just a statistical strategy to try to make studies

feasible in terms of accruing enough patients.

So I really wanted to at least express my thinking that differed from the comments that we heard from the first three speakers during the public comment expressed.

There's no guarantee that doing non-inferiority means that you're accepting inferior drugs. I think what you're really trying to do is, as you said earlier, to have more available weapons on the table because what we think is happening over time is our currently available weapons are becoming inactive. So you need to have unrelated medications that are readily available to go.

DR. BADEN: So Dr. Green, just to follow up on your initial comment, since you made many, the unmet need is to treat serious life-threatening infection that we currently can treat, which does not require it to be single-species targeted.

However, wouldn't we be better off if our antibiotics only targeted the bug of interest versus totally alters the microbiome indiscriminately?

DR. GREEN: We would if we only had single organisms to consider with our initial choice of treatment or in our infections. So in the spaces that we're thinking about, as has already been discussed, for pneumonia, particularly associated with the ventilator, I suspect that at least a reasonable amount of the time, it could be a truly polymicrobial infection.

That is to say if you actually took that patient's lungs out at the time of the infection, gave them a new lung transplant, and they got taken care of by Joanna, and you looked at their old lungs, you could find many different organisms living in the lung at the same time, so true polymicrobial infection; and then trying to be able to not use four or five different medications to cover all the possibilities.

So I think if you know that there's just a single organism growing in the blood, and you know that that organism's name is Pseudomonas, and you had a drug that only worked for Pseudomonas, that's great, but if the patient is sick up front, you

don't know, obviously.

DR. BADEN: I will ask that since the hour is late, that we keep our comments targeted as well. So your point is well taken. Your point is well taken.

Dr. Weina?

DR. WEINA: Just to follow on your point, you made the point yourself in which you said that it would be great, but we're trading syndromes here. When a patient comes in sick, it's not we throw on the biggest gorillacillin that we have until we know what we're dealing with, and then we narrow our focus. I mean, if we knew what it was, then a single-species-specific drug would be absolutely wonderful, but we don't have that capability.

DR. BADEN: Dr. Marks?

DR. MARKS: Yes, just two quick areas that we talked about. One was can sponsors preposition drugs and work with public health agencies to make sure that limited-use agents are available. And I think the answer to that is yes. The problem is

how long you want to wait? Is that seven hours for an anti-serum the same as it is for a documented bacterial infection in the hospital.

Then again, it's what risk you're in in terms of whether you're in a community hospital or whether you're in a major regional transplant center who might well see this from time to time. So I accept there's some trade-offs there.

The other pieces was to act on the superiority/non-inferiority. That tends to be bouncing around a lot. I think, for sponsors, we'd love to do superiority trials. That would be great. And if we had something that was going to be able to move above and beyond, certainly it would be in the best interests of science, et cetera, patient care to do that.

But Dr. Bennett hit the nail on the head in terms of how infrequent a truly pan-resistant organism is versus a multi-drug-resistant. So if you're going to construct a control arm, you're going to try to construct a control arm that is active. The ethics dictate that you try to give a

control arm that is active in comparison to your new agent. And the number and frequency of the truly pan-resistant organisms are so sporadic and infrequent that trying to run those trials makes them prohibitively long.

Then again, just to build on the non-inferiority concept, we are not going in trying to find inferior drugs. We would like for the observed estimate to be on the good side of the control arm. And even if you have something that the observed is slightly on the smaller end, it's only going to be a few percentage points because the non-inferiority margins are going to prevent you from falling below that. So the observes are going to be very close to each other, even if you move out to these 15 and 20 percents.

So we're not looking for agents that don't work. We're actually looking for agents that are improvements upon what we have. These are fail-safes to prevent us from putting out agents that truly look inferior to the others.

DR. BADEN: Dr. Honegger?

DR. HONEGGER: My comments were a lot of what Dr. Green had to say already. The one point I have is that we're thinking about these clinical trials in the context of a drug that's needed in a dire situation for a multiple-drug or MDR/XDR type scenario.

But what you brought out about the long-term benefit of a super narrow-spectrum agent is that preventing perturbing of the flora and selection of resistance has long-term benefits. And there may be a desire to use these drugs in organisms that are sensitive to other agents, in which case there could be a broad use of these agents.

So that should probably be considered as these are tested for approval.

DR. BADEN: Dr. Goetz?

DR. GOETZ: A brief comment. I'm wearing my antimicrobial stewardship hat. And I think that there's a very strong role and statement to be made in favor of the single-use agent generically, where available, in de-escalation for decrease perturbation of flora. I think the antimicrobials,

too, which are programs complete, will inevitably play a strong role in the use of any agents we are discussing for the foreseeable future, not only because of that, but because of the economic considerations regarding the use of these drugs.

DR. BADEN: Dr. Follman?

DR. FOLLMAN: This is in response to something Dr. Marks and also Dr. Green mentioned. They were making the point basically that the error bars will be larger with a larger non-inferiority margin. And some people were talking as if therefore all the drugs will be inferior that come through.

That's not necessarily the case. As they pointed out, they could be superior. They could have a modest benefit in terms of mortality. The point is, we won't really know. And I think the hope that we can get such knowledge through postmarketing surveillance and so on won't be realized, either. So you prove something, could be better, a bit better, could be a bit worse, you just won't know.

DR. BADEN: Ms. McCall?

MS. MCCALL: Now I know why I'm at this ADCOM. In 2010, I was diagnosed with atrial fibrillation after a year of misdiagnosis. I failed a couple of meds, and I went in for a catheter cardiac ablation.

I was discharged the very next day. It was my very first inpatient stay ever. I was discharged, and a had a low-grade fever that day, but they thought it was -- because literally my hospital room was a sauna. It was scary.

Three days later, I'm running 104 fever, sitting at the front door of my primary care's office going, "Please see me." I had a raging Klebsiella UTI.

Over the next three months, which is supposed to be my blanking period for my ablation, where I'm supposed to heal, I had not only that UTI, I had a sinus infection. I had pneumonia. I had a second UTI. My ejection fractions were dropping. My kidney functions were not very happy. And I was on subsequent antibiotics for three solid

months. You can imagine what my GI tract was like. It was not fun.

Eventually, I did get ahead of the circle of infections. My heart settled. In the middle of all of this, my poor heart went from proximal a-fib to persistent. I was in 24/7 and highly symptomatic. All of this happened while I was trying to maintain a therapeutic INR on warfarin. What part of fat chance is unclear?

Eventually, I did convert. I got off the antibiotics. I stopped the infections just before my EP wanted me to go through a second catheter ablation in six months.

That's why I'm here. This is difficult. Sure. You want a single species to hit the single critter, because that's what I had. They knew exactly what bug I had the first time. But as it got worse, and I kept having one infection after another, it was more and more bugs. So then what do you do? It was hard. And I have a lot of sympathy for my GP going through this.

Now, you jump forward -- and I've been on

multiple ADCOMs, and I want to address the non-inferiority portion. Quite a few of the medications in the cardiovascular space, where I normally sit, are non-inferior trials. We're comparing one drug to another, an old drug that's been around to a new one.

As a patient, I look at risk versus benefit. Is this at least equal to what we already have? Does it offer something the old drug doesn't? And that's what patients need. And I would think clinicians as well would want options. As these bugs get harder and harder to kill and the broad spectrums are getting more and more difficult, you need options. And I think we can find a happy medium with some of the options that have been presented today on how to do these clinical trials, and I think that's really important.

So I am not as sold on the non-inferior as bad. Sometimes that's the choice we have because these things are so very rare.

I do want to address one other comment that was made in the public portion, which is about the

informed consent. I've seen some of these. Sixteen pages is insane. I mean, come on, how many of you download software and actually read the user agreement before you click yes?

We're looking at those, and these are in words we don't even understand. If someone could please come up with one of these that's shorter and easier -- I know, they'd have to do something with lawyers. I get it. But we need that assistance because, in the long run, most patients want quality of life over quantity.

If we're sick, if we're suffering from horrible side effects, what's the point? We want a better quality of life. And I think we can find a happy medium with these single-species products.

DR. BADEN: Thank you. What I will propose is that we start with Dr. Marks. For 30 to 60 seconds, what do you think the most salient issues are for question 1 for the FDA to consider. As we move around the room, you don't necessarily need to reiterate what others have said; You can quickly acknowledge. And that way, we all can give

our thoughts to the agency.

DR. MARKS: So in terms of the unmet need, I think it's clear we need the single agents. And I appreciate the agency having a series of meetings trying to get us to this approach and find new ways forward.

HIV was mentioned earlier. It wasn't easy. But we worked together and we found solutions now that are durable for patients. I think the same thing can be true here.

Even our broad-spectrum gorillacillins, as it was put earlier, oftentimes have low percents when it comes to these two particular pathogens, so we need to be able to augment and supplement the armamentarium we have around this. And I hope we can find a pathway through this that will allow that to occur.

DR. HILTON: It was mentioned that these will be event-driven trials. And to that end, if we could come up with a composite endpoint, we might get more events and be able to complete the trials earlier.

I also feel that, prior to running an RCT, we should do a preliminary study to estimate the prevalence of patients who are susceptible to both of the study arms that would be studied so that we can guesstimate what the accrual period would be.

DR. WEINSTEIN: I think the agency, as mentioned by the IDSA representative, has done an excellent job of surveying the options. And I think that, based on the discussion that I've listened to day, there clearly are no easy answers. I thought that the fourth speaker in the public session, Dr. Rex, put the problem and the potential solutions in an excellent perspective.

With regard to clinical trials, at least for bloodstream infections, the rapid diagnostics revolution is really going to help us in this arena. There's already an FDA-cleared direct-from-blood test that will identify the organisms of interest within one to two hours. And there will be the ability to have phenotypic susceptibilities with that assay within six to seven hours.

There is another company that currently has

in clinical trials a direct-from-blood assay that will identify all of the ESKAPE -- if the clinical trial is successful, will detect all of the ESKAPE pathogens within seven to nine hours.

So this stuff is coming, and it's going to help us over the next two or three years.

DR. MOORE: Dr. Moore. I think Dr. Weinstein's statement is really the crux of the matter, and that is until there's a reliable and robust method for proving that organisms like Acinetobacter is the culprit of the patient's infection, then any clinical trial of any agent, whether it's done as a path to FDA approval or a post-approval field study, is somewhat doomed to failure.

Having said that, you're going to have to enroll an enormous number of patients to be able to find the patients that actually have that infection, and then those that have an infection where you can see the difference.

I've just been giving this a lot of thought, and I think the best option for the FDA that I

would recommend would be some version of the Emergency Use Authorization Act, which is used for public health emergencies for bioterrorism events.

There are four criteria that are required in order to meet that act. One is that the condition has to be a serious or a life-threatening disease or condition. The other is they have to have evidence of effectiveness of the agent either through animal model or what have you. Then you have to have obviously risk-benefit analysis and that there are no alternatives available.

I think a lot of those four criteria can be met with things like HAPB/VAPB due to Acinetobacter, where the mortality rate is significantly high and where colistin is used, that has in and of itself a high morbidity mortality rate, when the organism is susceptible to it.

I don't see any other way. I think in order to entice pharmaceutical companies to come to the table and develop drugs against these very difficult pathogens, rare and deadly pathogens, you're going to have to allow the acceptance of

less than optimal data or less than ideal clinical trials.

DR. SHYR: Yu Shyr from Vanderbilt University. My suggestion is, first of all, big picture, move toward precision medicine direction.

What precision medicine is, you change a bell-shaped distribution, correspond to response rate or mortality rate, move that to rectangle, called a uniform distribution. Your target for the patient most likely will be success, and then that is the one way.

How you do that, again, I already mentioned from my discussion, you may really need to have a registry. You may need to have a consortium network, and because your endpoint is 28 [ph] mortality, it's not that hard to collect that, to get a current trial approved to study, get the rarity of a large database to study who may or may not be likely to respond to active control.

Once you identify that subgroup, that may create a window from the sponsor side to design a superiority trial. At least we understand which

group of patients may not have a good outcome based on their patient characteristics. Therefore, we may use that patient as our study population.

Number two, rethinking about a fixed N1/N2 margin, 10 percent, 20 percent, use the relative risk concept. Not all active controls will always have that 20 percent margin compared to placebo effect.

Usually, the relative risk concept -- I know this may not be well taken in this community, but start to think of the research. Use the relative risk concept to do some simulation to see will that reduce the total sample size.

For instance, if your drugs or active drug really act very, very well, you reserve 85 percent of that active drug, the efficacy, you may end up having a smaller sample size. So think about don't fix that 10, 20 percent, but use relative risk just by the combination.

The third is please allow the flexible design into your entire design set-up. Flexible design including, as I said, is a hybrid design.

Do I really need to use all the trial, from my randomized trial? Is it possible to borrow the information from the existing information to strengthen my final interpretability?

The very last comment I have to mention is, again, non-inferiority trial design does not want to prove the drug is inferior. As all of you know, from your comment, we base it on the confidence interval. Most non-inferiority trials, the upper bound is across zero. That means it's not really inferior.

So I wanted to assure everybody in the audience a non-inferiority trial is not to design it as inferior. It is the worst-case scenario. We are not much worse than that amount. But in a lot of cases, it was a chance even better than that. I will stop there.

MS. MCCALL: Thank you, Dr. Shyr, for making one of my points about non-inferiority. I also agree with Dr. Rex's points. And I really like the idea of pulling in a mini-sentinel and using data partners for more data and hopefully getting more

robust numbers.

DR. ANDREWS: I think that we're all circling around how to make the best use of less than ideal evidence and when you can pull the trigger and say, yes, we approve it.

I'm not in a place where I can have an intelligent conversation about that, but in terms of when you do, I think there's a general consensus that that should not be the end of the research. And you need to find a way, get creative -- maybe you need to bring in some behavioral economists or something to talk about incentives to ensure that that happens in a way that you're going to feel comfortable with that's not just anecdotes.

There are lots of ideas. I think you need to get flexible about the design. You should use it as a menu and take a little from column A and a little from column B if you need to, to make a study that works for the drug that you're looking for. I don't think you're going to get a recipe from us. We don't do that.

On the non-inferiority, I was remembering

that one of the first drugs that I looked at, and that I was here in this committee looking at, was something for MRSA that was non-inferior. As a matter of fact, I remember it being kind of lackluster and I remember being surprised, why are we just talking about a drug that's no worse than what's there.

But it moved people out of the hospital. They didn't have to be there for 14 days getting an IV. They could get an injection on day 1 and on day 7, and they could go home. People with MRSA left the hospital. That's better for them. That's better for the person in the bed next to them. It's probably better for the bottom line.

So just because something is labeled non-inferior, it may be actually a real innovation.

DR. CLARK: The development proposals presented, I think non-inferiority studies are reasonable for the reasons that were already described. And I appreciated the public comments against these, although perhaps there wasn't as much of an appreciation of how marginal or toxic

the available therapies are for some of these infections.

I think having better-defined patient populations such as the bloodstream infections would be helpful and, again, building up clinical trials' networks, having centers that are able to do these trials, and perhaps notifying patients in advance, like my population, transplant patients, so we have them tuned into these kinds of studies when they're in need.

The other thing I would say is, coming into this, I thought perhaps postmarketing rules or requirements for studying drugs would be somewhat of an answer, but that seems less clear to me now. So that influences me a little bit more to have some clinical data before drug approval.

DR. OFOTOKUN: I also agree with all that has been discussed, and I think the issue of design seems to be well-ironed out. And I think, again, non-inferiority study design would be informative in this setting, like everybody else has said. We would need good pre-clinical data before we move

forward with approval.

The one main comment I wanted to make was about the quality of the animal data. I don't think we discussed this very extensively. My background is in HIV. We learned a lot from the non-human primate model. A lot of the data that were generated before drug went into clinical trials were generated from the non-human primate model.

I think somebody raised that issue the issue of both efficacy as well as safety and toxicity, we can be well informed by using a good non-human primate model, regardless of the cost, and I think especially in this situation where we know that it's going to be very difficult to recruit the number of patients to achieve the kind of quality clinical data that we need. We definitely need to be certain that all these studies that are done in animal models, we're using the best animal models that are out there.

DR. DASKALAKIS: Demetre Daskalakis, New York City Department of Health. So from the

perspective of unmet medical need, I think that there are not enough antimicrobials that treat highly resistant infections, so it's clear that we have to prioritize this. In many cases, single species are the problem in this setting, so I think it's reasonable to pursue a single-species product.

From the perspective of the development proposals, I want to agree about the idea of a menu. And I think that when a drug is being evaluated, just like we've heard about in these development proposals, that it should demonstrate some efficacy and safety in an animal model that approximates human disease, and that a small non-inferiority study should be adequate, then, to move the drug on with the agreement that there then will be some postmarketing evaluation.

So I think that in place of a large clinical study that may not be possible, several small components of study would be necessary with some very clear guideposts as to what is an adequate outcome. Thanks.

DR. CORBETT: Amanda Corbett, University of

North Carolina. So I agree with everyone. I think there's clearly a need, and I think that this is clearly a public health emergency. I mean, it has been.

I think there are at least two potential, likely more potential agents, that could be approved, and we've heard about both of those today. So I think no matter what it is, we need to find a way to get these if they truly are safe, number one.

So to me, I'd think of safety almost perhaps even a little bit higher in clinical data than efficacy at this point simply because I guess what we would not want to happen is -- yes, we know it's effective in vitro. There are reasonable animal models, which I understand are not necessarily well developed for every sort of disease state for these organisms. But if we can show that at least they're effective -- we need to ensure that we at least can predict some sort of level of safety, and know that if people need these, a lot of the distributed ways that people have described I think

are very reasonable -- we will get it to the patient.

I know, if it were me, I would say if that is my only option, I would surely like to have that medication available. But I would like to know that at least it's been evaluated fairly strenuously from a safety standpoint.

Also, I'm sure this has been discussed and thought of, but HIV is also my background, so I think we really did as a community come together with multiple governmental agencies as well as lots of individuals, academia, industry, networks, NIH, CDC. Everyone came together and realized that this was critical.

So I would just hope that our community with government, public sector, industry, would really support industry to help make these things happen because it is a huge situation, perhaps a huge financial burden and risk to them as well. And I just feel that's really important.

Then finally, I think Dr. Shyr sort of took this already, but precision medicine, I know that's

not going to get these drugs to market and show their safety and efficacy, but I think it's equally and parallel important. I know a lot of folks are thinking about that.

Our school of pharmacy is really, really thinking a lot about precision medicine. So finding a way to making sure these agents are used at the most appropriate doses in whatever population that they are studied is also equally important.

DR. WEINA: Pete Weina, Walter Reed. Today, we're asked to focus on a very limited set, and we're just being asked about two organisms right now. But in the not-too-distant future, and I'm talking the next couple of years, we're going to be asked to discuss this about a broader and broader set of organisms and more and more multi-drug-resistant problems.

So whatever we propose here, we have to be thinking about the second, third, and fourth order effects of anything we propose or anything that the agency decides to accept. And that comes down to

managing expectations.

So the first thing is we have to, first of all, redo our thinking. We have to think about what's the FDA's role and what's their liability. What role does the FDA actually have in approving these drugs? Is this a shield that people can continue to hold up and say, "Listen, the FDA approved this thing, so it's a good thing," or are we going to lower the standards to such a degree that more uncertainty for the approval means that more risk is going to be accepted by the user for these drugs, and is the labeling going to be enough?

We have things with black boxes and people still say, "Well, I didn't know about that black box," or, "I didn't read that black box," even though it was all over the place.

We're in a zero-defect society, and do we need a change? We're not necessarily going to change society's understanding of what zero defect is, so I feel a little queasy about lowering the standards, if you will, for approval of

medications.

In that light, I kind of thought about, first of all, when we design these things, how would a single-species drug be used in the real world? As has been said many times, let's look at an organism that's 2 percent of all the gram-negative infections that happened in this population X.

Well, if it's less than 2 percent of all the gram negatives, that means it's much less than 2 percent because it's not just the gram negatives; there's also gram positives, and there's viruses, and there's a variety of other things that are out there already.

So when a patient presents as being sick, the first thing we do is we throw the biggest, baddest, broad-spectrum agent that we can at them until we can get a diagnostic. And we sit around and we wait for that diagnostic, and then we have to sit, as has been pointed out by Dr. Bennett, and decide is this just hanging around, is this just basically there, or is it actually causing the

disease? Or even worse, when these cultures come back, they typically come back with multiple different organisms, and you sit there and you say, well, which one is actually doing the problem?

So you change the therapy, and the patient does well, and you narrow it down, or they do worse. And if they do worse, then you put a different antibiotic on. So you can see how this quickly spins out of control.

A single-species drug, when we design the trials, we have to think about how is it actually going to be used. It's not going to be, "Oh, my God, yes, it's Pseudomonas. Let's throw them on it first thing."

So I would encourage those two points. Think about the real-world application, and also if we're going to change the standards, think about what the second-, third-, and fourth-order effects are going to be on the credibility of the agency.

DR. BADEN: We're dealing with evolution. We need to be adaptable as well. That's a challenge, given the structure of regulation.

There is a significant unmet need. It's small, but it is quite serious, quite severe.

I think, in reflection to Dr. Weina's comments, we have to balance global public health emergency versus a very targeted but very severe set of problems in certain circumstances, and how do we deal with moving a medication forward that is designed for targeted use versus broad use, and how do we develop a dataset to enable us to convince ourselves that there's actual efficacy?

I think that the issue of precision phenotyping is critical. I worry when we do studies of syndromes that it's very difficult to discern efficacy because the syndrome is noisier than the event rate. And that requires greater thought on our side as to how we design the studies and the diagnostics, or the other advancing technologies that we need to better understand to sort out how to deploy. But I am dubious of inferring efficacy when the syndrome has more noise than the margin of efficacy we're looking for.

The issue of incentives I think is something

else we have to think seriously about. We need developers to be willing to take the risk to develop compounds, otherwise, we shouldn't be surprised if we have no compounds.

So there has to be a path that developers can move through that can enable us understanding efficacy. And I accept other comments that we have to be careful that it will be misused. On the other hand, we must develop compounds that provide new options, or else we'll be caught short with the next emergency that's highly transmissible.

One of the challenges that is implicit is the definition of the limited dataset that will establish the efficacy and whether we use different statistical techniques versus a much smaller end but much more carefully defined, that there are different ways to deal with defining a limited dataset.

But in the setting of a true unmet medical need with a high mortality that's carefully defined, one can have a carefully defined study with evidence of efficacy and not have to manage

the expectations of the company, the scientists, and the community when the product does emerge, and as it reflects on the agency, not being perceived as lowering standards as much as responding to unmet need.

Different ways to deal with this has already been mentioned from prepositioning to e-INDs, to different ways. And I think that there are a variety of potential ways to make it easier to the studies, but I think that's a smaller set of comments.

DR. GREEN: Thank you. Mike Green. So I want to just begin by agreeing in general with the comments that have been made by my fellow members of the committee. Your thoughts, and comments, and questions have really helped me to understand better and have taught me much.

I want to applaud the FDA for their longitudinal effort to really address this concern. Obviously, the sequential way that you've approached it in coming to us after you have done your previous meetings have really given us a head

start.

I'm going to begin by agreeing with the current approach of a menu, but I think it's clear that we have to have human trials, and it looks like it's likely these are going to be non-inferiority trials, and I'm fine with that; the larger, the better, but recognizing the potential limitations.

I do want to raise a caveat about the role of animal models for Acinetobacter because it doesn't have much good models unless you manipulate the host or the inoculum. If you manipulate the host, it may not be applicable to the human situation, which might mean that we turn down drugs that are beneficial.

If you manipulate the inoculum, life is confusing because many antibiotics have an inoculum effect. So we again may not be able to judge truly how well it would work in a human if you had to give a log or 5-log extra inoculum to create the model effect in the animal.

Also with the current approach in the menu

again, we've talked about it, whatever strategies we can to get additional data after a drug could be approved, not only to get, as I said earlier, the safety signal that might be missed in small studies, but also if there's a change in efficacy.

I want to reiterate and support the comment that was made previously about composite endpoints. This is particularly true when you're going to be comparing to colistin. So you could be a bit inferior in microbiologic efficacy to colistin, but if you weren't nephrotoxic, you could really have a winner drug.

So that's been done, I know, from at least clinical studies of anti-fungals where drugs of choice that have come out by guidelines have been based really on composite endpoints, so I really endorse the person who said that.

Then just a strategy that may be of value for centers that might be participating in studies, sadly, many of the patients who get infected with these organisms have been infected in the past, and so there are the opportunities for centers who

might participate in these studies to identify literally dozens of patients who have had these organisms previously.

It's clearly a clinical strategy we all use at the bedside. When we have a sick patient, we see what we've had before. And more times than not, if we cover those bugs, we're going to identify the pathogen that they have. Thank you very much.

DR. GRIPSHOVER: Hi. Barbara Gripshover. I agree with most of what the panel said, too, and I feel also that I've learned a lot from all of you, and also reviewing the prior workshops. Like everyone said, there's clearly a need for these new drugs, especially drug-resistant pathogens.

Just one thing for me that I would really like to emphasize is I think that maybe we could -- I also came from the HIV world, where a lot of our drugs were approved by optimized background regimen plus the drug. And good drugs do show a big difference. And if we're talking about, really, high mortality infections, I would

think if we really got people with resistant bacteria and you had a drug that worked, we should actually be able to see a difference.

So if maybe we could establish some kind of a control again, whether that's a cohort of HAPB/VAPB patients going forward, and maybe different agents could be tested depending on what pathogen it was in real time, you'd have those controls.

So I appreciate what the agency says about how these are sick patients that have a lot of other co-morbidities. It's hard to sort out what's the drug, what's the disease. So if we had a good control group to go with them, and then we added in the drugs in the drug-resistant group, we might really be able to see through superiority, too, just as another way to go forward.

DR. FOLLMAN: Thanks. Dean Follman, NIH. I thought the discussion today was very good, and I think we all learned a lot. I wanted to make a couple comments.

I think for these drugs, there is an unmet

need, but we need to do human studies. I'm not very optimistic or think the animal studies will be reliable. Maybe we'll talk a little more about that later. I think everyone would prefer superiority studies, so I'll take that as a given and talk a little bit more about the non-inferiority trials.

I think the 20 percent margin is kind of large, larger than I would like, and I've done a calculation that says if it's 10 percent worse, there's 1 chance in 4 you'll approve such a drug.

Such a drug, I know some of the drugs will be better than that. Some of the drugs will be worse than that. But basically, with a margin like that, you'll be approving stuff, and you just won't know what you have.

I don't believe that there will be the ability, really, in the postmarketing studies to discern that. So we all want more drugs, but we all want drugs that work, and I think this is a way to just get more drugs without ever being able to know whether they'll work or not.

Two more comments. One, if we do non-inferiority studies, it'll be a limited number. We'd like to expand the safety database in patients who aren't healthy that have similar diseases. So if we could enroll patients who have, say, non-bloodstream and non-lung infections to the new drug versus a comparator just to see not so much efficacy, but to look for safety signals in that, that could augment the safety database relative to just looking at safety of the drug in healthy people, which I think is not very informative and not comparative.

Then the final point I'd like to make is related to something Yu Shyr brought up, to where we should try and look for a benefit of the drug. So in these studies, we can figure out the MIC, and with pharmacokinetic modeling, we can predict the AUC of the drug in a person depending on their baseline characteristics. So we can create an MIC over predicted AUC ratio and look for benefit of the new drug versus a comparator for patients who have the lowest value of that.

So look for a benefit of the drug in the region where it's most likely to be seen.

DR. SCHAENMAN: Hi, Joanna Schaenman, UCLA. I too agree with much of what's been said previously. And I also want to praise again the FDA for bringing us together to address this growing crisis and, again, for their longitudinal efforts. As the IDSA representative said, it is a somewhat fearful time, and it's nice to know that this problem is being addressed. I think that's an important message to send.

In terms of the non-inferiority, again, I think a lot has been said about it. I just wanted to add a comment that I think we can address safety within non-inferiority. Some of the study protocol designs that were mentioned include using broad-spectrum antibiotics in addition to the targeted therapies. So I think there's a lot that can be done to make these to be done safely.

As was mentioned previously as well, I'd like to echo this because I think this is such an important point. When the current standard of care

is such a toxic drug such as colistin, we'd be so happy to have any kind of alternative, even if it also had toxicities.

Right now, we're in a situation where if the patient has high risk for nephrotoxicity, we have no choice, and in addition, as was mentioned previously, we often see a slow acceleration of resistance. So to have even a single option would be a great boon to the field, and I'm encouraged that maybe there are things in the -- I forget what is the term -- the narrow pipeline.

So I think that the menu, or I would like to say the toolbox approach, is the way to go in terms of really being creative in a challenging situation where we really want to encourage and give guidance to manufacturers to pursue these non-inferiority trials because I think, as we're going to get to with question 2, we would all prefer to see human data leveraged as much as possible rather than relying on animals.

I think the idea of trying to reexamine that M2 target in non-inferiority is important. Maybe

20 percent is too high, but perhaps 10 percent is too low. I don't know if I've come away with the right number here today, but perhaps that's something that could be really addressed in a nuanced fashion.

I think the hybrid approach is very promising as well as the close attention to PK data, since that seems to be very predictive of outcomes. I think that combining multiple small trials that might have different sites of infection is also very clinically attractive as well as what was mentioned by Dr. Cox in terms of simplifying trial enrollment, or maybe embedding a trial within either an open label or an ongoing registry that has a certain standard of care.

Last but not least, the idea of composite markers or surrogate markers, as Dr. Ighov mentioned earlier, I think that also might be promising. It might even be a way to show superiority, for instance molecular tests such as procalcitonin or maybe clinical markers such as SOFA score, length of hospitalization, length of

intubation.

All of these things might be pathways to show improvements when the overall mortality, which of course is the gold standard and the most important thing, can be affected by all the co-morbidities of our patients.

As I mentioned earlier, I think the limited population pathway is attractive. Maybe I'm overly optimistic, but I think that centers, and hospitals, and antimicrobial stewardship programs would take this very seriously. And I'm optimistic about our ability within IDSA and in infectious diseases to provide guidance and not to overuse these agents. I really think the tide has turned in that way.

I want to end by saying, as Dr. Clark brought up, this difficulty of multiply resistant organisms is especially dire in the situation of a growing number of immunocompromised patients. Not only is the number of transplant patients and patients with cancer receiving chemotherapy increasing, but we are treating older, and older,

and more and more complex patients. And as I've mentioned to a few of you here next door in Ballroom A, there was an FDA panel talking about desensitization strategies in kidney transplantation.

So it's almost like a perfect storm where we've got these older and more complex with more co-morbidities receiving more innovative immunosuppression agents meeting head on with this growing tide of resistant organisms. So clearly, this is an emergency and something needs to be done.

DR. HONEGGER: Jonathan Honegger. I agree with many of the comments that were made and appreciated the excellent discussion today. The only one point I wanted to make at this time is that one advantage of this single-species drug development is that there are maybe unique opportunities for synergy. If there are networks that do HAPB/VAPB research and they take advantage of rapid diagnostics, they could run multiple studies concurrently, shifting Acinetobacter

patients to one arm and the Pseudomonas to another trial without having competition between the trials.

DR. LO RE: Vin Lo Re, University of Pennsylvania. I want to thank all the discussants. I want to thank the FDA for their efforts. I think we clearly have unmet needs for rare drug-resistant bacteria. We got Acinetobacter, Pseudomonas, resistant to many or all antimicrobials. We're faced with limited antimicrobial choices.

I think given the challenges of the relatively small pool of potentially eligible patients for studies, the uncertainty, and the diagnosis, the concomitant empiric antibiotic therapy that is a challenge, and then taking into consideration the seriousness of the disease and the mortality, I think we're asked here to consider the options mainly prior to approval that would provide the evidence that new therapies are efficacious and safe in humans, prior marketing.

I think given the challenges with superiority trials, I think non-inferiority trials

would be preferable for efficacy. I think conducting studies in pre-defined populations of patients with a single-species infection with more diagnostic certainty, particularly for example the bacteremic patients, would be important given the challenges in the diagnosis of clinical syndromes like HAPB and VAPB.

I would also support the development of a single-species-specific antimicrobial clinical trials network either nationally or possibly internationally. That could help to train investigators, to capture disease appropriately, and that would allow valid conduct of clinical trials, and pre-marketing and observational studies postmarketing.

I think the fact that the Infectious Disease Society of America was here, you could potentially leverage the Infectious diseases Society of America in a way similarly that the FDA leveraged the development of the mini-sentinel program for both pre-marketing and postmarketing purposes.

I think, if non-inferiority trials cannot be

conducted, I think to have maximum interpretability of the efficacy and safety data, that requiring data from animal models for efficacy and disease, PK/PD studies in humans, phase 1, phase 2 studies would be valuable; and then there would be some need for some global assessment of data to determine whether or not the drug should be approved.

I think if the efficacy and some degree of safety can be demonstrated pre-approval, I think if there are any safety concerns or signals that are observed pre-approval, then requiring postmarketing pharmacoepidemiological studies would be valuable for continued assessment of safety.

DR. GOETZ: Matt Goetz, UCLA, VA Los Angeles. I'm left for the challenge of being very near the end and of saying something more. Several of the previous discussants have really very well summarized the position. So again, I thank all the FDA and thank all the presenters. It's been a marvelous discussion.

In my mind, there is a very clear need for

drug development. We don't know when disaster will strike, and we wish we had the drug. It could be tomorrow. It could be next year. I hope it's never. It won't be never.

A single-drug model, I'm in favor of that. And as many have said, superiority is what we want. Non-inferiority is what we can get. Having trials that will test for superiority if non-inferiority is satisfied is clearly one way of melding the two of them. I wish to see superiority, but I know that I'm very unlikely to.

We talk about non-inferiority, and as many people have said before, we're likely to have thresholds or perhaps 20 percent. We want precision medicine, but it's a long time coming. It's not tomorrow's solution. It's not next year's solution. It's somewhere downstream. So we're going to be left with vulnerability.

To mitigate our vulnerability, a development of a strong animal model, several different animal models, that provide substantive supportive evidence will be very important, I feel.

Blending in data from other clinical sites will be important, and I think development of a prospectively collected registry or clinical trials network, where you can collect data on patients who may not be enrolled in studies now of these agents, where we can capture the natural history of a robust group of patients, and then look over time as what happens when patients get data, and we use this supplementary information in a fashion perhaps somewhat similar that was done for isavuconazole and the approval for mucormycosis. I think there's lessons that can be learned from that, at least, I hope there are. And I'll stop there.

DR. BENNETT: John Bennett, NIH. I've tried to study rare infections, and those studies tended to die. The people I wanted to look for in the intensive care unit, the microbiology laboratory, the emergency room, couldn't remember to tell me. So what's a solution for that? And I'll use urosepsis and Pseudomonas as an example.

So you tell the emergency room and the house staff you want to look for patients with urosepsis.

So they tell you this patient, and you don't know if the patient has urosepsis. It's a clinical diagnosis, so you enroll them and you randomize them.

Now, the blood culture, if it's going to get positive, will be positive typically the next day. And thanks to BioFire and MALDI-TOF, within a few hours, we know it's E. coli. Oops, well, we take them off the study or whatever the house staff wants to give them.

If it's Pseudomonas, we don't know if it's resistant, but we leave them on the study. And then the susceptibility's come back two days later. We'll have a subset of people with resistant Pseudomonas, and we can see how they do, and we can see how the other patients do.

So the idea is to keep the ball rolling. Unless you do this, you just won't find out about the patients. So that's my suggestion.

DR. BADEN: A quick summary of everyone's comments, I've been charged to integrate the integration. Tremendous unmet need. This unmet

need is increasing due to medical co-morbidities. Complex to do the studies because of background treatment, uncertainties of diagnosis. Event-driven analyses are valuable and may need to leverage composite endpoint.

We need to make sure we understand the disease burden in the population with the disease and potentially have synchronous contemporaneous populations not in the study to be able to show what the outcomes are doing. Diagnostics have been commented on, incentives for industry.

The statistical issues, I suspect we can never resolve between superiority, non-inferiority, and historically controlled, but those have been excessively discussed, and I think the issues are palpable.

Animal data are complex to interpret, model dependent. An NHP model might be of use, and it is worth considering about to ensure safety, not just in normal healthy people, but in those who are diseased with co-morbidity to better understand the safety signal. We need to manage expectations of

the community, of providers, of industry so that people understand the path of development in this space.

I think those are the major -- and then the comment of just networks, maybe networks that can be developed or leverage that could perhaps be enrolling in multiple studies, and just depending on what organism lights up the latest diagnostic machine. And then it's messy, which was Jack's comment.

So that's question 1. We now have question 2. I realize there are some who need to go to the airport sooner than others, so I would like to take them out of turn. And I don't remember; everyone who has to go to the airport around 4:00 or 4:30, but I think we can start with our California contingent.

So on question 2, Dr. Goetz?

(Laughter.)

DR. GOETZ: Now, after complaining about being last, I get to be first. This is wonderful. I just want to try to address A and B, types of

animal models and appropriate endpoints you think might be useful to assess the efficacy.

We've had a lot of discussion this morning about different animals are used for different purposes. I think that when we get down to the mouse model, I think of mice as being predominantly the utility for defining PK/PD targets. And clearly, if drugs fail in mice, we don't go further.

Then the challenge comes in, in the previous workshops in July and March. And I spent some time talking about this, and I looked into those materials. We obviously didn't have that discussion here. But we clearly have to be sensitive to every animal that we look at as different than man in pattern-receptor recognition, the inflammatory cascade that's set up. There's susceptibility to inoculum of organisms, innate immunity, adaptive immunity, and other ways.

We also have to be sensitive to the fact that animals don't have the same underlying co-morbidities that patients have when they get

these illnesses, so understanding how all these factors interact is messy or complicated to say the least.

But as has been pointed out by many philosophers or statisticians, while all models are wrong, some are informative, and that with sufficient animal models, which are sufficiently calibrated and validated, I'm willing to say that animal models can supplement and buttress to a large degree what we find in clinical trials.

If we have to go solely on animal data, the case needs to be made in a very strong fashion. And I don't think the case for the organisms we've talked about today has been made sufficiently strong to say that we rely solely on animal data for approval.

But that gets me to point B. Might clinical trials leave us with a signal that is ambiguous? We've said, as we talked before, a non-inferiority margin of 20 percent because that was judged to be doable, feasible. Why do a trial if you're never going to get to another trial? We're going to be

left with some syndromic definition, no matter how precise we try to be, which will bias us towards a no, as pointed out by others.

So in that situation, a panel such as this will be convened and will gnash its teeth for several hours debating it. The animal models won't give us that shining bright light that says, yes, obviously approved, but may give a very important signal that allows us to be sufficiently confident to say, yes, under limited conditions, we can go forward with this drug, or say go back and do it again.

Finally -- and maybe I should have brought this up with the first point -- I think that there's a postmarketing point still to be brought up here. If I understood the FDA right, if an accelerated model is used for approval, or if an animal model is used for approval, much more constraints can be put upon the manufacturer for postmarketing surveillance. And I would really like to see that be the case because I think it's going to be very important to network with not only

clinical studies postmarketing, but also network with large groups such as the VA, Kaiser, and other organizations to look at the efficacy of the agent, what's out there.

DR. BADEN: Dr. Schaenman?

DR. SCHAENMAN: I agree completely with how Dr. Goetz has put the answer to this question very eloquently, and I also appreciate Dr. Green's comments regarding some of the limitations about the animal models.

I just want to specifically address comments regarding trying to make analogies to the previous drugs that were approved under the Animal Rule that's been mentioned a few times by the FDA. And I wanted to suggest that I think that these two situations are not analogous.

I think it was an excellent approach for these potential bioterrorism agents, and I'm so glad that we have some drugs or monoclonal antibodies available for use. But if you look at those infections, such as plague and tularemia, compared to these MDR organisms, I think there's a

lot of differences that make the situations not analogous.

First of all, as we've mentioned, we had a lot of difficulty telling if a patient has pneumonia, let alone a pneumonia that's related directly to the MDR organism of interest. And that's in stark contrast to when you have a positive culture for tularemia, you're pretty darn sure that that's explaining the problem, and it's usually a mono infection as opposed to the polymicrobial situation.

Secondly, these bioterrorism agents tend to strike normal healthy adults out in the community. So maybe that would make animal models a better guide. And that's again in contrast, as Dr. Goetz just mentioned, to the multiple co-morbidity patient that we tend to see who have these MDR organisms.

Lastly, I think that although certainly these trials are difficult and challenging, I think that they are doable. And certainly the prevalence of MDR organisms and Pseudomonas is higher than

that of plague and anthrax, thank goodness.

So although it's very challenging, I think it can be accomplished. And I would encourage the manufacturers to really try to, in an ingenious fashion, leverage clinical trials using some of the techniques that have been brought up today rather than saying it's too hard, and here's our nice rabbit data.

DR. BADEN: Dr. Hilton and then Dr. Shyr?

DR. HILTON: Thank you so much. I don't really have comments on the animal model.

DR. BADEN: Dr. Shyr?

DR. SHYR: As a biostatistician, when I reach the animal model, I'm very nervous. Because people say, if we run an animal model, I don't need a statistician if I am going to see a difference.

(Laughter.)

DR. SHYR: So let me tell you what I think. First of all, I completely agree with previous comments. We do need a PK/PD, and we do need multiple animal models. But I will not feel comfortable based on pure animal models because

this is not like anthrax or any bioterrorism kind of drug development.

I do think, in addition to multiple animal models with appropriate endpoints, with clinical patients, we should at least have multiple single-arm studies to at least study safety and some efficacy data.

In addition to that multiple single-arm study, I also think we should have a rigorous randomized phase 4 that's also required with those two additional pieces of information and may feel comfortable to base it on the animal model.

But again, I want to echo one of Dr. Hilton's previous comments. If you are willing to move toward animal side, why don't you get more patients, even if it's not perfectly designed clinical trial data and use that patient data? It's still better than animal data. I will stop there.

DR. BADEN: Thank you. We can now start back on the left the way we intended. Even though no one else is racing to the airport in the next 10

or 15 minutes, we still can be pithy and to the point for the agency. Dr. Bennett? –

DR. BENNETT: There are two types of models for infectious diseases. One is looking at the colony count of the tissue, blood, or whatever, and the other is death. Now, ROIs [ph] people will not let your mouse die. A moribund mouse is the endpoint, not a dead mouse.

But looking at those two, I really don't like the colony count endpoint. The reason is, I can imagine going to the patient and saying, "Ms. Smith, the good news is this drug is going to drop your colony count 100-fold," and what the patient thinks, "I need a new doctor."

(Laughter.)

DR. BENNETT: So I really feel the animal models I think are essential but not conclusive, but of those, I like the ones that use the moribund animal as the endpoint. That's the end of my comment.

DR. BADEN: Thank you.

DR. LO RE: Vin Lo Re, University of

Pennsylvania. So I think animal models are valuable to examine pathology, the survival, toxicities at different doses of study drugs, but I still think that they should be supportive of trials in humans.

I mean, what's good for the mouse is good for the mouse, not necessarily good for humans. And I can't think really of a situation where efficacy is principally demonstrated in animal models with only limited clinical trials data in humans.

I completely agree with Dr. Schaenman, and this is why I had asked Dr. Cox the question about the diseases in animal rules. That was all with bioterrorism agents. This is completely different. It seems that, to me, the Animal Rule approval really would not necessarily apply here. That was approval of therapies of agents that had previously approved drugs. So I don't think there is a situation that I would consider for that.

DR. HONEGGER: Jonathan Honegger. In terms of the animal models, the one point that I was

going to make is pertinent to point B. If there was a drug that was to be approved based on limited clinical data but strong animal models, I could see this having particular restrictions and potentially being really limited to the dire situations with people with truly multi- or extremely drug-resistant organisms.

DR. FOLLMAN: Dean Follman, NIH. I don't know so much about these animal models. It seemed from the IDSA presentation and also the FDA that they felt there was room to improve those models. I'd like to talk a little bit about the animal models used for anthrax and Neupogen for radiation injury.

One key factor I think in those models was that there was a proxy or surrogate endpoint that they thought would predict benefit in a human. So for anthrax, it was anthrax antibodies in the bloodstream. So you could measure that both in human and in animal. You knew that an animal, if it reached a certain threshold, would be protected, and you tried to achieve a similar threshold in

human. And we know a lot about immunology and antibodies, how they protect against anthrax.

So there's this intermediate endpoint or variable that made us more comfortable going from animal to man.

Similarly, with Neupogen, which is meant for radiation injuries, absolute neutrophil count is a good intermediate endpoint. We know that's sort of related to the causal mechanism. We can induce that both in human and in animal. And when we give that to animal and they raise the neutrophil counts, they tend to survive.

So for this situation, I think, at a minimum, we'd want to try and have such a proxy or intermediate endpoint, and I don't know that there is one there. I don't think, for example, colony counts or change in colony counts is something that would be suitable.

I mean, every model is different, and it's something that needs to be investigated, but I think, in other arenas, looking at early bactericidal activity or early fungicidal activity,

looking at change in the slope of colony counts hasn't been very predictive.

So I'm more pessimistic for animal models here than for the animal models which were used successfully I think for those other bioterrorism agents. That's all.

DR. GRIPSHOVER: Yes. I also feel nervous about using animal models. I think that we would want to make sure that the models we chose had the appropriate organ and that they had positive and negative controls if you were actually developing a model.

But then more to question B, I share Jonathan's concern that I think that we need to be very restrictive about how we would let a drug that was just approved solely on animal models be used. And somehow, it'd have to be for emergency only.

I don't know, since we've heard it's pretty hard after a drug is approved, how we would do that, if we could go with the CDC or distribution by the CDC mechanisms. It seems like we would have to have some way to really make sure that we had

very restrictive use and were able to collect data on humans who then actually got it.

DR. GREEN: Mike Green. So unlike the bioterrorism models of animal-model-based approval, I don't think that we're in that scenario, and I think we should be able to get human data for at least these two organisms.

The information we were provided says 10 to 20 percent of hospital-acquired pneumonia, ventilator-associated pneumonia due to Pseudomonas, 5 to 10 percent do A. baumannii. I mean, those are not tiny numbers. You just have to be organized. So I think it's not unfeasible to do that.

I'd love to trust the animal models, but I'm not sure that the current models will be predictive. And then I worry a lot about approval that would then be based only on animal models. If we were to approve primarily on the animal model, I think we would need to require, for whatever it's worth, some sort of post-approval studies, and we have to be creative on how we could enforce that.

Finally, to item B, I think if we were in a

scenario that drugs had been approved primarily on animal models, you do need to have some control. But I think that the growing importance and role of antimicrobial stewardship programs in hospital settings really do provide that.

If you said pre-approval to get the drug and then a day 3 audit, but maybe do something really unique for a stewardship program, which actually gives bite for day 3 -- so you can't really get the drug unless we say yes, but once you start a drug, stewardship programs have a hard time of really making them go away. But perhaps in this scenario, we could just have it worked out, and with the help of the FDA so that we don't get sued for doing it, really say, okay, you don't need this drug anymore. It's gone. Thank you very much.

DR. BADEN: Taking the question in toto, I think approval based solely on animal models should be done with great caution, and it's not clear to me it needs to be done in this circumstance.

I think that if one has strong in vitro activity, broad number of strains, MDR/XDR, if one

has animal data disease, not just animal data, but a disease model that mimics the human pathology in some way, that would be supportive, very strong PK/PD, well-characterized in humans, human safety, not just healthy volunteer, but in those who are likely to be treated.

Then I think you need to have human efficacy data. Then the debate on how much human efficacy data depends on the severity of the condition. Rabies would require something different in my mind than skin soft tissue infection. And one needs to then have a way of managing the limited human dataset, and what is clearly known about the natural history of the condition in the generation of that limited clinical dataset, and the limitations on it will be greater the more severe the condition is. And then post-approval would have to have a mechanism for generating systematic data.

DR. WEINA: Pete Weina, Walter Reed. I don't know what's wrong with my colleagues. The animal models thus far, for drugs that have been

approved by animal models have a zero percent failure rate. I mean, these are amazing.

So that aside, animal models are never going to replace human clinical trials except where the populations don't exist, like we have with select agents, not just because it's tough to do. As has already been pointed out, there are ways of doing it in human models or human clinical trials, and they should really be required.

In the cases in which it's not required, and maybe we do approve something based strictly upon an animal model, how would the product be used clinically, I have significant concerns about off-label use of products and the fact that they would probably be misused.

Our profession is absolutely wonderful at doing that, and not just our profession saying infectious disease, but also all of our other colleagues in family practice, and surgeons, and et cetera, et cetera, et cetera.

So these drugs, if they were approved based strictly upon animal models, I think there would

need to be exceedingly strict controls put in place with a distribution network and accountability based upon that. That's all.

DR. CORBETT: Amanda Corbett, University of North Carolina. I'll be honest. I don't have one answer. Maybe you all felt the same way, and you just picked one. Let's hope. But I think this is just really complicated.

One perhaps obvious statement, but I feel the need at least to say this out loud, is at least I feel like there's conversation of -- this antimicrobial is what is going to allow someone who has a complex disease, including the syndrome of HAPB/VAPB, to cure them, and we all know that that's not true.

There are multiple other factors that contribute, other than the bacteria, to the survival and morbidity outcomes of that individual, so their immune function, their respiratory status, previous infection, concomitant diseases.

So I feel like we would almost be doing a disservice to say we're not going to consider

strong in vitro models, which of course we would, PK/PD to predict lots of different outcomes, so very strenuous PK/PD, including those in animal models. And I'm not saying no clinical trial data, but I would almost be okay with saying limited clinical trial data, especially ensuring that we can at least get in enough patients to show some sort of level of safety with the caveat that postmarketing has in some way -- and I know this is perhaps novel and perhaps never happened before -- but some sort of controlled distribution where there is a requirement for strenuous study of those agents.

So I'm not suggesting I would know how you would do this, but the distribution piece, I think, has been demonstrated. We could do that, but how do we ensure that the institution that gets the medication gives us the information back from this patient that can allow good data to come out. So not phase 4 commitments where it's really difficult to determine what that information is, but truly saying if you want this drug, this is what you've

got to do to get it, pretty much.

Then also along those lines -- I've said this before, but I still would agree with this. My opinion is not the case and not what happens, but there are strenuous clinical trials that need to be done, that we really do need to find a way to all work together.

I'm not sure who would lead this. Perhaps it is the FDA that would lead this effort in collaboration with industry. I know that's potential conflict, but I really don't think there's any other way around making that happen in a timely way.

DR. BADEN: Let me jump to Dr. Moore since I think he has to leave.

DR. MOORE: Thank you. To answer the first part of this question, I don't really have much more that has not already been said. I think that, in general, science and unmet needs are pushing us into the realm where clinical trials are becoming more and more difficult to adequately perform without having to enroll a prohibitively large

number of patients in order to find a margin, particularly for certain indications and certainly for pathogens that occur or cause disease a little bit more rarely.

So I think ultimately, some amount of animal data is going to have to be relied upon for these entities. So answering that, assuming that is the case and assuming that a product is released, how would it be used clinically?

I am in a state where the vast majority of hospitals in the state have an open pharmacy. There's no regulation. The only thing that limits prescribers' use of drugs is their own discretion, which I'm sorry to say in many locations is poor.

But the other big limitation to the profligate use of antibiotics is their price. So when a new agent comes out and it's prohibitively expensive, that actually serves the purpose of restricting its use for good or bad.

I really don't know quite how to -- I was thinking about the example with bedaquiline, which is the most recently approved anti-tuberculosis

agent. That's a drug which is not commonly used. It's obviously very restricted and as it should be.

But I don't think the same obviously level of restriction could be used for a novel antibiotic to target a specific pathogen, although it's kind of a thing you'd almost have to do to prevent its overuse.

I guess what I mean to say is that I'm not so concerned about limitations of its use as much as I am gathering data when it is used. In order to gather those data, there would have to be some well-controlled -- and I mean enforced -- clinical trials for postmarketing strategies in order to do that. It's easier said than done, as has been mentioned earlier, but I think that's the only way to gather those data. Thank you.

DR. BADEN: Thank you. Dr. Daskalakis?

DR. DASKALAKIS: Demetre Daskalakis, New York City Department of Health. From the perspective of question A, I want to echo the other comments that the animal model needs to approximate best the human disease state for which you are

looking at this drug as a potential treatment.

With that said, also to echo a lot of previous comments, the animal models I think need to be supportive of clinical data in humans. I want to, without taking a lot of time, just echo the comment that these are not the same as bioterrorism agents. We have people who do have these conditions and these syndromes. Therefore, we have the right folks that we can introduce these agents to.

So it's not a perfect study, but perfection shouldn't be the enemy of good in this scenario of getting more tools in the hands of individuals who need them to treat these resistant infections.

From the perspective of question B, I would hope that there would almost never be a scenario where this happens, where there is a drug approved only on animal data. In this scenario, the rare scenario that this happens, or that there is a combination of only a small amount of human data along with more robust animal data, I do favor the idea of some sort of restriction to access.

I don't know how well hospital stewardship would be at doing this. In my head, I can imagine the release of an anti-pseudomonal drug that targets one organism, and the next day it's used in prophylaxis on the oncology ward. So I can imagine that pretty rapidly without a lot of debate. So I would say that it's worth having a deeper regulatory block on access to the drug.

Finally, to summarize all of this in one sentence, I think that we know when these drugs are coming for evaluation and there should be a clear track, that once these drugs go in those tracks can say that some amount of animal data with some limited but acceptable amount of clinical human data will be enough to bring these potentially for approval. Thank you.

DR. OFOTOKUN: Ighovwerha Ofotokun from Emory. I agree with what has been said, and I'm just going to reiterate, as has already been mentioned, that I don't think in this scenario that dealing with the animal model will be adequate. I don't think it will be adequate. But I can see how

in the presence of limited clinical data, if you have clean animal data, it will be highly complementary.

So if I have a situation where you look at the animal data, there is no safety concern, and there is some evidence of efficacy within the animal data, and I have limited clinical data, I will have some confidence in moving forward with that drug than when there is limited clinical data but no animal data at all.

So I see the role for animal data as being complementary to whatever limited clinical data that we're able to get in this scenario.

DR. CLARK: Nina Clark, Loyola. I would agree that it would be difficult to support approval of a drug just on animal data. Regarding the animal models, I think obviously it would be important that they would be reproducible with different strains and perhaps even multiple types of animals, especially because it seems that there are many variables that could affect outcomes in these animals and perhaps even different virulence

factors or development of resistance over time during the infection.

As far as the second part, I would just agree that there would have to be some defined thresholds for use.

DR. ANDREWS: Ellen Andrews from the Connecticut Health Policy Project. I agree that animal models should be the last resort. And there is an unmet need, but I don't see the kind of immediacy that would push us to that point, where I do with bioterrorism.

While I give the FDA lots of kudos for being forward-thinking and realizing that this is probably going to become a bigger issue, if it does really, this should be a last resort. And then it should go out to those centers that will as a condition do the research to make sure that we know and understand whether this is better than what's out there or non-inferior, and whether it's the safety profile, and also would cut way back on off-label use.

MS. MCCALL: Debbie McCall. It should start

with animal models. It shouldn't end there.

DR. WEINSTEIN: Mel Weinstein. I agree with most of the comments that have been made. I think animal models are only part of the data package and should not end there. I think the use of the drug clinically will depend on the limitations of the clinical trial data.

DR. MARKS: Lynn Marks, GlaxoSmithKline. I think we need to continue to work very hard to make sure that we're not able to run superiority trials because that would mean that our comparator regimens are inferior up front, known not to be effective. So we need to keep that ever in front of our mind, that this is the world that I hope, because of new approvals of agents, that we're in.

Therefore, the package of data would be robust in vitro microbiology data focusing hopefully on new mechanisms of action, frequency of resistance, new combinations that are either additive or hopefully synergistic in the future, robust PK/PD, focusing on the animal model efficacy where we work together to share that information

across industry, academia, and governmental organizations.

So it reminds me of the '60s when we had MIC testing, everybody was doing it every different way, and nobody knew what that looked like, so we had to put some controls around that. I think the animal model world, since we're going to be relying on this increasingly, I believe, I think we're going to need to have conversations about what that looks like.

I appreciate Dr. Isaacs -- I know he had to leave -- coming forward with a clear example where he did not come forward with saying, "I only want to give you rabbits," or whatever animals. He came forward with what he felt like was a responsible approach to a limited clinical trial dataset.

We can debate the confidence intervals and non-inferiority margins, but it did include clinical data, and I think that's where the state of the industry is right now.

DR. BADEN: Summarizing the group's comments, significant concerns with animal models

being the sole arbiter of approval, though they can be quite useful. Clinical trials may be ambiguous. This is not analogous to the bioterrorism issues for a variety of reasons, including surrogates and other a priori knowledge of likely effectiveness. Clinical trials will be hard but doable, and we need to work together to enable them to be successful.

The issue of the post-approval is a complicated one, and perhaps access to the drug could be linked to a requirement to generate data in a post-approval setting until the dataset is robust enough to better understand how the drug may be used.

The limited clinical data can work, however, the definition of what the limited data may be will be the subject of significant discussion, but proportionate to the nature of the problem and the potential benefit.

So I think that summarizes the last round of comments. Before we adjourn, any final comments from the agency?

DR. COX: So I just want to thank everybody for all the discussions today. This is obviously a challenging issue, and we appreciate all the energy, thoughtfulness that folks provided to us today, so greatly appreciated.

DR. BADEN: Dr. Nambiar?

DR. NAMBIAR: I just wanted to add my thanks to the committee members. This was a very interesting discussion on a very, very difficult topic. And I also wanted to extend our thanks and appreciation to the speakers at the open public hearing. Most of them may have left by now, but I sincerely appreciate all the efforts, and safe travels back home.

Adjournment

DR. BADEN: I was going to make the same comment, that the speakers were terrific, and the committee has put a lot of effort into discussing what is a very important topic that we shall be discussing for some time to come.

We'll now adjourn the meeting. Panel members, please take all your personal belongings

with you as the room is cleaned, and safe travels.

(Whereupon, at 4:36 p.m., the meeting was adjourned.)