FOOD AND DRUG ADMINISTRATION

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FDA-IDSA-NIH-Pew Public Workshop

Enhancing the Clinical Trial Enterprise for Antibacterial Drug Development in the United States

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P R O C E E D I N G S

JOHN FARLEY: So good morning, everybody. I'm John Farley. I'm the Acting Director of what is now called the Office of Infectious Diseases at the Center for Drugs here at FDA. We want to welcome you to this workshop.

Next slide, please.

So I thought we might go ahead and start the morning by focusing on why we're all here. This is -- should look familiar to those of you who have taken a look at the recent CDC AMR threats report. We've had some progress from stewardship efforts, but the serious public health challenge continues with 2.8 million antibiotic resistant infections each year and 35,000 deaths.

How about this? Okay. I will lean forward.

So I want to begin the day by just thanking Ed Cox for his leadership here at the agency. As most of you are aware, he left government service after nearly two decades, and really a steady hand and focus on science and the data on his part played a key

role in the progress over the last decade, making safe and effective new antibacterial drugs available for patients in the setting of AMR.

I also want to take a moment to thank everybody who is sitting in this room for your steadfast commitment, your innovation, your positive dialogue, and your collaboration in the midst of what has been a decade of scientific and economic challenges.

So we at the agency really appreciate your commitment. Cindy -- I was telling Cindy Sears earlier, I come from the world of perinatal HIV where I felt like we built a strong collaborative partnership over time and there were major accomplishments. And I feel like the dynamic is the same here, and it's really an honor for those of us in the agency to be part of that.

I thought we'd begin today by just doing some brief introductions, and your disclosures are already listed in the program, so you don't have to provide any voluntary disclosures as you introduce yourself. But maybe we'll start with Aaron and move

around the table from there.

AARON DANE: I'm Aaron Dane. I'm a statistical consultant who's been working in the area of infectious diseases for about 20 years.

ROGER LEWIS: Good morning. I'm Roger Lewis. I'm the Chair of Emergency Medicine at Harbor-UCLA Medical Center and the Senior Medical Scientist at Berry Consultants where I focus on adaptive and innovative clinical trial design.

DAVID MELNICK: I'm David Melnick, the Chief Medical Officer at Spero Therapeutics, a small biotech based in Cambridge, Massachusetts. We have three active programs in the antibacterial space.

RIENK PYPSTRA: Hi, I'm Rienk Pypstra. I'm head of development for the hospital business unit in Pfizer; hospital business unit includes all the antibiotics. I have also some years of experience with developing antibiotics.

CHIBUZOR UCHEA: Good morning, everybody. My name is Chibuzor Uchea. I'm a science officer in the Drug Resistant Infections Program at the Wellcome Trust. We are working on a range of

different interventions in the AMR space to lead the program about combatting antimicrobial resistance in a range of different areas. And I'll be speaking later on in tomorrow's session on the use of clinical trial networks.

VANCE FOWLER: Good morning. I'm Vance Fowler. I'm the Contact Principal Investigator for the Antibacterial Resistance Leadership Group and the Chair of the Infectious Disease Society Antimicrobial Resistance Committee.

CYNTHIA SEARS: Good morning. I'm Cindy Sears. I'm past President of IDSA and Professor of Medicine at Johns Hopkins, and I'm an infectious diseases physician.

SARA COSGROVE: Good morning. My name is Sara Cosgrove. I'm a Professor of Medicine at Johns Hopkins also and also in the Division of Infectious Diseases, and I am the Medical Director of our Department of Antimicrobial Stewardship.

REBECCA REINDEL: I'm Rebecca Reindel. I'm a pediatric infectious disease physician by training. I'm a Medical Officer in the Office of

Vaccines in CBER.

LINDSEY BADEN: Lindsey Baden. I'm a Physician Investigator at Brigham & Women's Dana Farber, and an Editor with the "New England Journal of Medicine" focusing on infectious diseases.

WES KIM: Good morning, Wes Kim with Pew Charitable Trusts. I'm the Senior Officer of our innovation workstream our Antibiotic Resistance Project.

JOHN REX: I'm John Rex. I'm an internist trained in infectious diseases. I am currently the Chief Medical Officer of a company, a private company that has an antifungal in phase two, so not specifically a topic for this for today. And also, I work for Wellcome Trust as their advisor for their investment strategy and drug resistant infections.

HELEN BOUCHER: Good morning. I'm Helen Boucher from Tufts Medical Center in Boston, where I practice infectious diseases and I'm the Treasurer of IDSA.

SUMANTHI NAMBIAR: Good morning. I'm

Sumanthi Nambiar, Director Division of Anti-Infectives.

ERIN DUFFY: Good morning. My name is Erin Duffy. I'm the Chief of R&D of CARB-X. We're going to talk about CARB-X later today. But briefly, we're a global partnership that funds and accelerates innovation and antibiotic drug discovery.

AMANDA JEZEK: Hi, I'm Amanda Jezek with IDSA. I'm our Senior Vice President for Public Policy and Government Relations.

KEVIN OUTTERSON: Kevin Outterson. I might be the only lawyer around the table. I'm a law professor at Boston University, and I'm the Principal Investigator of CARB-X.

JANE KNISELY: Good morning, Jane Knisely. I am with the National Institutes of Health, National Institute of Allergy & Infectious Diseases.

DENNIS DIXON: Good morning, everybody. I'm Dennis Kixon, also from National Institute of Allergy & Infectious Diseases at NIH. I'm Chief of the Bacteriology and Mycology Branch. We manage all of the escape pathogens. And I've had a chance to

observe these challenging areas for nearly three decades at NIH as we've developed various mechanisms to shore up our defenses and had prior experience in academia, political lab, and briefly in industry.

MARK ALBRECHT: Good morning, everyone. My name is Mark Albrecht. I am the Chief of the Antibacterials Branch at BARDA.

AMY LEITMAN: Good morning. My name is Amy Leitman. I'm the Director of Policy and Research at a patient advocacy group called NTM Info and Research. We advocate on behalf of patients with pulmonary nontuberculous micro bacterial disease, bronchiectasis and other gram-negative pathogens.

NICK KARTSONIS: Good morning. My name is Nick Kartsonis. I'm an infectious disease physician, and I currently provide oversight for infectious disease and vaccines at Merck Research Labs at Merck & Co., Inc.

RYAN CIRZ: And good morning. My name is Ryan Cirz. I'm currently an independent consultant. But for the 16 years prior to the summer, I was a founder and the head of research at a company

called Achaogen.

SUE CAMMARATA: Good morning. I'm Sue Cammarata. I'm the Chief Medical Officer at Melinta. I've been involved in antibiotic and anti-infective clinical trials for twenty-some years since I first came into pharma.

MANOS PERROS: And good morning, everyone. Manos Perros, CEO of Entasis Therapeutics, clinical stage antibacterial company. I'm a Ph.D. scientist by training, worked in discovery most of my career. And I also believe we're on the cusp of something really big, probably as big as what we've seen in oncology in the last two decades, and I really thank the agency for organizing the day when we can hopefully usher that through.

JOHN FARLEY: So thanks very much. I want to also thank Pew, as well as IDSA for their co-sponsorship of this workshop, as well as our sister agencies within the Department of Health and Human Services, who are supporting this workshop and are focused on AMR. You've met our colleagues from NIAD, as well as BARDA, and we do have colleagues here from

the Assistant Secretary for Program Evaluation at HHS who are very much focused on the economic challenges that all of us face in this field.

Next slide, please.

So I think we've got a great agenda for this workshop. I'm very excited about it. I'm really looking forward to the discussion. We're going to start out talking about the current state and resources for antibacterial drug trials. We've got an industry roundtable focused on needs and challenges that I'm looking forward to hearing those perspectives.

Then we'll begin to focus on realistic options for enhancing the enterprise. Tomorrow morning, we'll talk a lot about new approaches and strategies that might better support the enterprise.

Next slide, please.

So I think there's a number of discussion topics that, at least from the government perspective, we really want to make sure that we get some good and open discussion about. The first is serious infections that are in need of feasible

approaches to obtaining clinical trial data. We're particularly thinking about pathways to develop products for infections caused by primarily gram-positive organisms. There, we certainly have a clear pathway for acute bacterial skin and skin structure infections, but there really are other needs such as staphorious bacteremia, diabetic foot infections, prosthetic joint infections. Let's talk through some feasible pathways for development in that area.

I think we'll hear a lot of discussion and ideas about labeling. But from our perspective in the gram-negative arena, what we'd really like to also include is a discussion on looking at the paradigm for how we develop products for gram-negative pathogens. We've got some ideas to throw on the table. Let's take a feasibility check, let's talk about what the feasibility challenges are, and maybe talk about some strategies to overcoming those in terms of the design that we would like to see going forward.

We're going to talk about feasible approaches to updating treatment guidelines. Cindy's very excited to share her perspective, and we'll look

forward to that discussion. We really want to hear from you what a clinical trial network might look like that would maximize impact in this area. And then we're going to talk about innovations and statistical approaches, design and end points that we might prioritize going forward.

So I think I have the privilege of chairing this session with Aaron, and I think we're going to maybe alternate introductions and it's my pleasure to introduce Sumathi Nambiar. We're both pediatricians, we both trained at Children's National Medical Center, but she's younger than me, so we didn't know each other. But it's been my privilege. She joined the agency in 2002 and kind of broke me in, and she has served as the Director of what is now the Division of Anti-Infectives since 2013. So Sumathi, thank you.

SUMATHI NAMBIAR: Thanks, John. Can you hear me okay? All right. So good morning everybody and welcome to this day-and-a-half-long workshop. Thank you for being here in person and also for some of you that have joined us by web. We'd also

want to thank our co-sponsors -- IDSA, NIAID, and Pew -- for helping to organize this workshop.

All right, so there are four main topics I'd like to touch upon. And we'll start with the history; how did we get here? So if you look back in this from the 1960s to 1980s in antibacterial trials, patients with a variety of infections -- those at different body sites -- were enrolled in the same trial. And there's really no plan for formal inference testing in these trials.

The indications that were granted were based on substantive body sites of infections from within these trials. Indications tended to be less specific; they were more broad. Early on, they were as broad as respiratory tract infections, and then they were refined to separate out the upper from the lower respiratory tract. And within the allowed indication, you had a broad spectrum of conditions, and those are commonly pneumonia to bronchitis.

Similarly, skin infections, they want separated out whether they were complicated or uncomplicated; and then subsequently, they were

refined further and complicated skin infections are now referred to as acute bacterial skin and skin structure infections.

So in the '90s to the 2000, the move was more towards conducting site specific trials. And the reason for moving to site specific trials was because there was a better understanding of the natural history of the disease, and the fact that it differed depending on the site of infection. There was a recognition that end points and treatment duration would differ, depending on the body site of infection.

There was also an understanding that drug efficacy may differ at different sites of infection, and the fact that the dosing regimens could also differ depending on the site of infection.

The two documents that many of you are familiar with, the 1992 IDSA Guideline and the 1992 FDA Points to Consider document, recognition of the aforementioned differences in these documents really represented an advance in clinical trial design.

Around 2005 to 2006, there was

significant (indiscernible) in the field and many of you really were part of the discussions at that time. One of the main questions that was raised was about the non-inferiority trials and whether or not they were scientifically justified. There was a lot of effort, not only on part of the agency, but with the stakeholders -- again, many of you were part of those discussions, and we were able to come to scientifically sound NI trial designs.

We were able to formulate evidence based anti-margin justification for some of the common indications that were being pursued. At the time, trials were typically conducted for these common indications, and we had two trial per indication, and that's what the data package used to look like.

Around 2012, the focus -- you know, while we continued the work on non-inferiority trials, there was a greater focus on unmet need, particularly to treat gram-negative infections, streamline drug development programs. There was a lot of discussion around that as well, and drug development programs followed the approaches that were laid out in our

draft guidance.

And under this paradigm, usually it's a single trial per indication, and the safety databases for the new drug applications tended to be much smaller; they were in a few hundred.

In the years ahead, we think there'll be continued focus on unmet need programs, including difficult to study indications and not just focusing on infections due to particular resistant phenotype, and also, the challenges associated with the development of non-traditional therapies.

So if you look back at the approvals in the last decade or so, the types of data packages have varied. For standard indications, say intrabdominal, UTI, pneumonia or skin, we might have had two trials per indication or at least one trial per indication. So the data package for a drug with gram-negative active -- activate against gram-negative organisms could be a trial in CIAI and a trial in cUTI.

For limited use indication approvals, it is generally a single trial with supportive evidence, which could include data from a phase two

study, invitro studies, and animal models of infection relevant to the indication that was being sought.

More recently, we've had two products approved under the LPAD pathway. For both, we had very small data packages. It was a single trial that was the basis for approval. The patient population for which the products were approved is a very well defined and limited population of patients. But given the unmet need, the seriousness of the condition, there was some flexibility in the benefit risk in situations.

So then why are we all here today? I mean, it's apparent that we've made progress, but there's obviously a lot more work to be done. And it does seem like we are right now at a critical juncture in antibacterial drug development, and we as a community need to think hard and formulate what our plans are for the years ahead.

We want criticism from different quarters regarding the clinical utility of some of the recently approved products and the trials that were conducted to support their approval. I think there's

also recognition that there continues to be an unmet need, particularly for difficult to study indications, and I've just given you a couple of examples.

I think it's very important that we work together. All of us have our own role to play, and we really need to work together because no one individual or one group here has all the solutions to the problem. We need to map out the needs and also potential solutions.

And we do recognize that labeling is an important component of the discussion. We understand it's certainly going to come up in many sessions today. But I think it's very important that we address the scientific and feasibility issues. Once we address the scientific issues, labeling just follows automatically.

So what do some of the criticisms about the recent registration of trials and, you know, I've listed a few. I'm sure there might be others, and we look forward to hearing them during the course of this day and a half.

The clinical conditions studied -- an

example is, you know, it was just a urinary tract infection indication that was studied. I think it's important to note that such trials are feasible and do demonstrate the efficacy of the product at the body site of infection. It also provides reasonable safety information in a population with fewer confounding factors. I think one has to understand that this is a new molecule that is being evaluated, and this provides a good chance to assess how the product behaves both from an efficacy and a safety standpoint.

And then starting with an indication like UTI or intrabdominal allows for a step up to a more difficult to study condition. I think it's also important to keep in mind that one has to balance the realities of drug development with the desire to study difficult indications or difficult populations. Certainly, trials in HAP/VAP are needed.

Now, all drugs are not suited for a pneumonia indication, given its spectrum of activity. These trials are often difficult to enroll. Often, there are a lot -- many more confounding factors making it harder to tease out the treatment effect of

the test drug. And from a drug developer's perspective, it's often considered risky for a first indication.

The other major criticism is there's lack of data on patients with infections due to resistant organisms, whatever the phenotype of interest be. I think we've learned over the last few years, conducting randomized control trial in patients with infections due to a particular resistant organism can be challenging. We've seen a few trials conducted recently in patients with infections due to carbapenem resistant enterobacteria, see gram-negative infections. And these have been difficult not only to conduct, but also very difficult to interpret, as these trials were descriptive and had no pre-specified hypothesis testing.

And as new therapies become available, you know, the resistant phenotype of interest will change and it will evolve. So one -- what might be potential study designs, if you're interested in such a study, is a demonstration of superiority over best available therapy, and we've seen the challenges with

being able to demonstrate superiority of currently available treatment options.

The other consideration -- and this will come up during the course of the discussion -- is, now that some treatments are available which have activity against a CRE, could one consider enriching the trial population in an NI trial, as long as an appropriate comparator is chosen.

The other criticism is that the trials conducted are generally NI trials, and so the new product is only non-inferior to existing therapies. We certainly welcome superiority trials; they're a lot easier for us to interpret. But I think the practical difficulties in conducting and demonstrating superiority is very obviously. Its opposition that well conducted NI trials are interpretable and provide useful information on the efficacy of a product.

And I think it's also important to keep in mind that having some redundancy is helpful to address patient needs and also to address potential drug shortages.

The other criticism we've heard is that

very few patients are enrolled in the United States. And so, I think it is imperative and we need to understand what are the reasons for this limited enrollment in the United States. We need to do better with the infrastructure here.

I think what's reassuring is that Steve, who will present after me one of our all Rice fellows, has reviewed the data from recently conducted trials, and at least they show that most disease and patient characteristics between US and ex-US sites are comparable. So that's reassuring, but I think we still need to identify what the issues are and how we might do better in getting data from patients in the United States.

The other -- one other criticism is that in these trials, patients with comorbidities or those with more severe disease are often not enrolled. It certainly would help if pharmacokinetics of the drugs in patients with, say, hepatic arena impairment or other comorbidities are evaluated early in drug development so one can include them in these clinical trials.

And on our part, we certainly -- we're willing to exercise maximum flexibility and inclusion/exclusion criteria, but we have to ensure patient safety.

So I just wanted to spend a couple of minutes talking about -- you know, I know we're all trying to find solutions to the problem. But in that effort, it's very important that we don't lose our focus on scientific principles, because that is really key here.

So even though the trials that have been conducted have a lot of shortcomings and there are a lot of criticisms about it, I think it's very important to keep in mind that well-designed comparative trials do teach us important and unexpected lessons. I mean, I've listed a few here that we've seen over the years with daptomycin and binding of daptomycin to surfactant, and this interaction was rarely identified after a trial was conducted in patients with cap that did not meet its non-inferiority margin.

We've seen higher mortality and lower

cure rates in trials of ventilate associated pneumonia. I've given you two examples, tigecycline and doripenem. Based upon the findings in these trials, I think there's a better understanding that pharmacokinetics can be altered in sick patients, patients with HAP/VAP; acutely ill patients can have augmented renal clearance and their dose requirements might be different.

We also have a better understanding of differences in drug penetration between animals and humans. So I think it's important that the body -- that we recognize that body site of infection matters. And the efficacy of drugs can be seen in one body site; it may not translate to efficacy in another body site. So I don't think -- I think we should keep that in mind and not ignore that finding. And some of you are familiar, you've got a list. And it's very unfortunate, but the list does keep growing.

Let's spend a couple of minutes talking about labeling. I mean, there are two key considerations when it comes to labeling. There are labeling regulations. There is a framework within

which we have to work, and that really helps in ensuring consistency, not just across anti-infective products, but across products that the agency reviews.

And it's also important to keep in mind that including information in labeling, if it's based on sound scientific evidence, it's helpful to all stakeholders, whether you're a provider, a payer, or a patient.

So these are the regulations, and I won't walk through them. So if you look at some recent approvals, what information have we included in labeling. The indications section will include the organisms for which we had adequate clinical data. There will be information regarding limited population, if that's applicable. The microbiology section provides information on invitro activity and relevant animal models of infection; there is a first and second list of organisms. And the clinical study section describes the adequate and well-controlled trials that supported the indication.

So really to summarize, I think over the last decade, we -- not just we, the agency, but we

as a community -- have made significant progress with development of antibacterial drugs. New safe and effective therapies are available to patients. There certainly is more to be done, but it's also very important that we learn from our experiences and continue to refine our approaches to address patient needs.

Some considerations to encourage as we move forward, and, hopefully, a lot of these will come up during the course of the workshop. We need to identify the types of infections or the patients in whom there is an unmet need, and how exactly do we do this is important to discuss. We should consider in all the study designs or end points, as long as they are scientifically sound.

We need to work to improve the clinical trial infrastructure in the United States, discuss the potential role of clinical trial networks, and need to identify barriers and also what we can do to stimulate/investigate the interest in participating and enrolling in clinical trials for anti-infective drugs.

So with that, thank you very much, and look forward to the discussion in the next day and a half.

JOHN FARLEY: Thanks, Sumathi. Our next speaker is Steve Bart, who's one of our fellows here at FDA in the Office of Infectious Diseases. Steve obtained his Ph.D. from the University of Pennsylvania. His research was focused on Ebola, but he's decided that antibacterial drug development is much more interesting, as well as gaining epidemiologic expertise to support that. His next stop is the Epidemiology Intelligent Service at CDD, and we congratulate him on that acceptance.

STEPHEN BART: Thanks, John. Can everybody hear me? So like John said, I'm going to be talking today about some of the work I've been doing over the past year and a half or so about antibacterial clinical trials and shifts in enrollment and what impacts that might have on general reliability.

So I want to first start off by talking about drugs in general. And over the past few

decades, clinical trials have become increasingly globalized. I'm showing this in two different ways here: on the left, we're looking at the percentage of investigators on INDs submitted to the FDA; and, specifically, the percentage based in the United States. So in 1990, the vast majority, 96 percent, of investigators were based in the United States. Well, by 2007, that percentage dropped to 54 percent. Similarly, in 2008, over half, 57 percent, of subjects in drug trials were enrolled from outside the United States were interested specifically going forward in antibacterial drugs.

And this is something that we've seen no specific data on, but over the past few decades, there's been a definite trend where new drug applications have included increasingly more non-US data. So these are excerpts from several recently approved antibacterial drugs labels. And you can see in all three of these cases an increase in enrollment from other areas, and a decrease where there are a few or no patients enrolled from the United States in these registrational trials.

The drivers for these enrollment changes are not particularly definitive, but these are some speculated drivers that have been brought up: cost, differences in clinical practice that might affect recruitment, and the desire to tap emerging markets worldwide. The second one, differences in clinical practice is something that I think is really important for antibacterial drugs, especially prior antibacterial drug therapy which may present a challenge to recruitment in some regions. And the length of hospitalization for IV drug administration, potentially dampening excitement by some -- for some sites to host these trials.

For my talk today, I'm going to focus on two major questions: how is antibacterial drug trial enrollment changing, and can we quantify that, and what impact does this changing enrollment have on trial generalizability.

So in order to do this, I looked at new drug applications or NDAs for antibacterial drugs that have been submitted to the agency since 2001. From these NDAs, I abstracted subject level data for

geography, demographics, clinical characteristics, and microbiology for four different indications; so ABSI, skin infections, CIAI, intrabdominal infections, pneumonia, and cUTI, complicated urinary tract infection.

I assigned subjects to one of seven different regions, and they're colored coded here. So each country that's filled in with a color had at least one subject in the trial. And we could use these classifications to determine different -- differences or similarities among these regions.

So let's take a look at some of the data we've looked at -- we've collected. So I found 42 phase three trials from 20 different NDAs, so there's 20 different products. There are 29,282 subjects in this dataset altogether, and there are 57 countries identified. So what I'm showing here is a timeline of these trials. So each one of the circles is a different trial, and they are organized on this timeline by start date. So the first subject, first visit; they're color coded by indication.

And you can see two distinct waves of

drug development activity from 2001 to 2009 or so, and then after 2010 with kind of a dead period in the middle here.

On the bottom, just to give a little bit of context, each one of these diamonds represents, and they're labeled, represent the publishing of a different draft guidance by the agency in a field important for drug development.

So in order to get a sense of how enrollment might be changing, I compared trials initiated from 2001 to 2009 with those 2010 to 2017. So those data are shown here, so I'll walk you through this here. So on the left side is 2001 to 2009, so the early trials; the right side are the later trials.

Across the bottom are the different indications we looked at with the number of trials for each one of these time periods. The proportions of subjects are on the Y axis, and they're color coded based on region, based on the legend on the bottom. So the bigger the bar, the more color from a specific region and the more patients were enrolled from that region.

So focusing on the left side first. You see a lot of diversity and where subjects were being enrolled from in the earlier trials. West Europe, South America, North American and Eastern Europe were all represented in all of the different indications.

But by the second half of the study period, after 2010, we saw a major focus in trial enrollment for CUTI, CIA, CIAI, and CAP to Eastern Europe. However, for ABSI, for skin infections, we actually saw the opposite where North American enrollment actually increased.

These are the same data just shown a different way; so these are divided by indication, instead of by time period. And you can really see the concentration in Eastern Europe for the first three indications here and in North America for skin infections.

So we found that for new antibacterial drug trials, there was a shift in enrollment towards either Eastern Europe for most of the indications or for North America for ABSI and skin infections.

We wanted to know what kind of impacts it had on generalizability, so we looked at demographics, clinical characteristics, and microbiology to approach that from three different lenses. Today, I'm going to focus on the clinical characteristics, especially those that may have some impact on recruitment and the microbiology.

So for these considerations, we used subject level NDA data again. But the data were pulled across the entire study period, so we're not looking at the division by date as we did in the previous slides. First thing I looked at was prior antibacterial drug therapy. So for some indications -- so ABSI, CAP, and cUTI -- FDA guidance recommends limiting the percentage of subjects that had received an potentially effective antibacterial drug immediately before study enrollment because of the potential difficulties that could be introduced with interpreting non-inferiority trials.

For cIAI, the FDA doesn't have that same recommendation. So we looked at cIAI patients who received an antibacterial drug within the first 72

hours before randomization to try to identify differences regionally in the percentage of subjects that are receiving treatment.

You can see, compared to North America, Eastern European subjects are much less likely to receive prior antibacterial drug therapy. So you can kind of imagine that if you're screening patients, if you have a subject population that has much less prior antibacterial therapy, you may be able to screen fewer patients in order to -- in order to recruit an adequate number.

So that, like I said, is looking more at the cIAI/cUTI side. But we found that ABSI subjects were actually becoming more and more North American over time as we looked at this, so we were trying to figure out why. We looked at different medical history aspects and found that North America subjects were much more likely to be IV drug users than their counterparts from other regions.

So I'm showing this here on the graph on the left. So across the X axis are the different regions that we looked at. The Y axis is the

percentage of subjects that reported current or recent IV drug use. Each dot represents a trial.

So you can see that in Eastern Europe to the right, there are very, very few subjects that reported IV drug use. However, in North America, an average of about 40 percent of subjects in ABSI trials were IV drug users. This is much higher than the estimated prevalence of IV drug use in the general population shown in the red line of about 1 percent in North America.

We looked at where these subjects were being enrolled from and specifically by zip code. So the bigger the circle and the deeper the color, the more subjects were being enrolled from that area. So you can see that most of these IV drug users were being enrolled from California and Nevada.

So we want to move on and now talk about microbiology. I'm just going to talk a little bit about that to give in a sense of the generalizability considerations that we did for this analysis. So we analyzed regional differences for cIAI/cUTI. We focused on gram-negative aerobes for

those indications and looked at all organisms for ABSI. We weren't able to look at CAP because the culture rate for CAP is much lower than these other indications.

And we used FDA recognized breakfronts for specific classes of antibiotics to identify resistant isolates and compare those among regions as well.

So I'm only going to show data from cIAI today, just for the sake of time. So these data are shown here. So we looked at gram-negative aerobes isolated from cIAI patients in all of the trials that we had. Across the X axis are the most common organisms that were identified. The Y axis is the percentage of isolates that that species is made up. And each one of the different colored bars, using the same schemes as before, represents a different region.

So E.coli was the most common species, perhaps not surprisingly. And it's set on its own axis on the left from 40 to 70, compared to zero to 30, just to point out for these less common organisms on the right.

So we did identify some differences. So South American isolates were more likely to be E.coli than their North America counterparts. Klebsiella pneumoniae was much more common in Asian isolates, compared to those from North America.

However, reassuringly, it seems that overall microbiology is very similar among the regions. It wasn't like in one region, there were no isolates of a species that was much more common in North America, for instance.

So as I said, I'm only showing data for cIAI. However, we did this same analysis for cUTI and ABSI and found similar results.

We also looked at resistance phenotypes, so these data are looking specifically at Enterobacteriaceae and the cUTI and cIAI trials. And we used FDA recognized breakpoints to assess the susceptibility of these different isolates.

We focused on three different classes of antibiotics: third generation cephalosporins, which are sometimes used as a marker for ESBL production in this family; carbapenems, which, of course, are going

to give an idea of carbapenemase production; and fluoroquinolones. So these data are shown here on the bottom: so the indications are across the X axis; the Y axis is the percentage of isolates that are resistant, so not susceptible, not intermediate, but resistant according to the breakpoints.

And you can see some regions are much more -- there's a much higher prevalence of resistance compared with North America, which we made all of our comparisons to. And these data, I think, would be helpful in the future for people perhaps trying to enrich for organisms resistant to these different antibiotics.

So in terms of the conclusions. We found that enrollment trends differ by indication, so cUTI, cIAI and CAP trials increasingly enrolled from Eastern European sites, while ABSI trials became more dominated by North America enrollment.

For the sake of time, I didn't talk about demographics today. But characteristics such as age/sex didn't differ significantly for most comparisons. Perhaps unsurprisingly, there was one

difference we found; that North America subjects had a higher average BMI than subjects from other regions. And this is important for consideration when reviewing drug exposure data that's collected elsewhere.

We did find that certain clinical characteristics, especially those that we think might affect enrollment, vary by region. I didn't show these data, but we didn't identify any large differences in disease severity regionally, which is an important factor to consider.

Eastern European subjects exhibited the least prior antibacterial drug therapy for cIAI, and this could either be a result of differences in the prescribing practices or standards of care, or it could be that Eastern European sites are more efficient at enrolling before the initiation of antibacterial drugs.

North American ABSI subjects were disproportionately IV drug users, and this is important to consider based on differences -- potential differences in infection types. So ABSI subjects who inject drugs are more likely to have

wound infections, for instance, and microbiology.

I didn't show these data, but IV drug users were more likely to have infections caused by oral flora isolates, potentially because of the practice of licking needles before injection.

We found that microbiology was probably similar among regions, but we did identify regional enrichment for some species and resistance phenotypes.

So overall, the conclusions of this study are that demographic, clinical and microbiology similarities between regions, less than generalizability concerns for antibacterial drug trials. However, U.S. participation is still important in these trials, given known and unknown regional differences. Some acknowledgements. Thanks.

ERIN DUFY: It's my pleasure to introduce Helen Boucher, who is our next speaker. Helen, as she said, is the Chief of Geographic Medicine and Infectious Disease, the Director of the ID Fellowship Program at Tufts, and a professor of medicine at Tufts. I think I met Helen first in 2005 when we were just starting (indiscernible). She was

on our clinical advisory board and she's been a mentor of mine ever since, for which I'm very grateful.

HELEN BOUCHER: Thank you so much, Erin. That's very kind. It's very nice to be here. And as is my usual disclosures are shown here, I'm wearing the hat of the clinician today. And I'm going to start us off just coming right back to why we're all here at the beginning of World Antibiotic Awareness Week, and I'm really grateful to our colleagues at the FDA, the NIH and Pew for making this happen. A lot of us have been talking about it for a long time, so we're really grateful.

But we'll start right away with a couple of cases. So this is a very typical case that many of us see routinely in 2019. This is a 47-year-old lady, schoolteacher, totally healthy, who initially presented to her primary doctor with pain on urination and some lower abdominal pain, and she was started on standard oral therapy with ciprofloxacin. But, unfortunately, she got worse and came back two days later, now sick with chills, nausea and back pain. She had a high fever and her exam was notable

for some tenderness in the right flank.

Her urine appeared infected, and they got some blood work that showed an elevated white blood cell count with a left shift. And they advanced her therapy appropriately, according to the guidelines, and she looked, despite this, you know, well enough to go home. She was an otherwise healthy lady, so she got one dose of intravenous ceftriaxone and then was started on oral (indiscernible).

So it got a little worse. So two days later now, four days into the illness, she's really sick -- high fever, low blood pressure -- comes to the emergency room and needs to be hospitalized for support with hydration because she couldn't eat because she was vomiting. She had a fever and low blood pressure, as shown here. She had an elevated heart rate. She looked sick. She was in pain over her right kidney.

And despite the antibiotics that I mentioned, her urine is growing greater than 100,000 colonies of klebsiella pneumoniae that was subsequently identified as being ESBL producing, and

was resistant indeed to the ciprofloxacin, ceftriaxone and (indiscernible), with which she had been treated. So she was admitted and treated with a carbapenem, which is the drug of choice for ESBLs. She got better. So that's one kind of a patient, sort of outpatient who gets sick.

Another patient is a lady I took care of recently, a 60-year-old lady wit leukemia who had had chemotherapy induction and was in remission. She was in the hospital recovering when she developed a fever and a cough. Her chest x-ray showed pneumonia. She had pancytopenia. Her cells hadn't recovered yet. The hematologist, though, thought she was going to recover. You know, they were very encouraged with her prognosis.

So she was put on standard empirical therapy with meropenem and vancomycin at our hospital. And then we got this result; this is about when we were called. The result came back, elizabethkingia meningoseptica, and the lab reports that ID consultation recommended this is a multi-drug resistant organism and this is what we got. And you

can see all the Rs and you can see a couple of other things. So you see plasmolysis NIS, (indiscernible), with numbers in NIS and that means no interpretative standard.

So those drugs are so new and this bug is so weird that the lab can't even tell us. So what do we do? We look it up, we call people, and we realize that that's not good either, those probably mean resistant.

So I had to go talk to this patient who was sitting in her room relatively comfortable actually. She's on minimal oxygen at this time, and she said, how could this be; surely, you're going to find something to treat this. So, of course, we tried our best. We added ceftazidime, avibactam and (indiscernible) in hopes that that combination of avibactam (indiscernible) would do something for this organism.

We rushed it off to Dr. Bonomo's lab in Cleveland so they could do some fancy testing, and we called the FDA. And ultimately, a company who gave us compassionate use of (indiscernible), under

investigational new drug status, and everything was done as fast as possible. It was incredible, you know. Great thanks to everybody. But the drug got to us four days later; that's about as good as it gets. And we changed her background therapy based on the results of Dr. Bonomo. We added minocycline. It was quite a combination.

And sadly, despite all those efforts, she deteriorated. She ended up in the ICU on ventilatory support and succumbed 10 days later.

So, you know, these cases and many others tell us that the crisis of AMR is here, and we all know that in this room. We all know that this can affect you and me. It threatens our modern medical care and we have to do something about it now.

I think I'm here to talk about the fact that we physicians often make decisions with limited or even no data. The data we have is often much less than what we would want. We have data on infections at standard body sites, as Dr. Nambiar told us, which are a great foundation for us to build from, but we have to extrapolate to the patients who we see.

Patients don't always present with a UTI, skin infection, or pneumonia. And every day, we work with data from a variety of sources and a variety of observations.

So one message that I hope I'll leave you with in these few minutes is that, you know, we do this every day. We extrapolate a lot from PK data, from invitro and surveillance studies, right, what's going on. And that crazy bug I just told you about, we had never seen in our hospital, and we haven't again -- thank heavens. But, you know, surveillance can sometimes help us. We take data from different indications and we take case reports.

You know, I'm here to tell you that I've treated patients based on one case in literature. And then our pediatric colleagues -- I'm really glad that we have a pediatrician here -- they rarely have any clinical data, right. They have PK data and adult data from which they have to extrapolate into children, like mine and yours, and little tiny babies, right, which aren't the same. So this is kind of where we are, and I hope we won't let, in these two

days, perfection be the enemy of the good or the good enough, at least for us.

So back to what we need antibiotics for, for all the things I mentioned in those cases, but really everything we do, right? Every surgery -- cesarean section, joint replacement, the most common surgery in America -- and the intensive care that our hospitals are becoming, right -- our hospitals are becoming one big intensive care unit so that all of our patients require support with antibiotics.

So Dr. Farley started us off with the CDC threat report, and I wanted to come back to that for a minute because I think there's an observation that's really important. This is a 2013 threat report that we all know and love with our escape pathogens and the other pathogens that we've been working so hard on the past five years.

The 2019 threat report came out last week and lo and behold, there was a new friend on the block; candida auris is an urgent threat. It was nowhere on the 2013 report, right? So the message is that all this work that we're doing and all these

trials that we're designing have to help us be ready for the threats we know about and the ones we don't know about.

So we need to think about going after drugs and indications in big buckets so that we have the robust and renewable pipeline that will meet these challenges. And thank heavens there are a few people working in this space that might work for candida auris.

So what about oral antibiotics? So the presentation we just saw -- and if you look at the Pew, which we're going to look at a little bit later, the Pew report -- most of what's been happening in the last 10 years is in the IV space. But we really need oral antibiotics, right, because every time we have to put a long IV catheter into somebody for two weeks, we put that patient at risk of yet more infection.

And so, I didn't want to miss the opportunity again to highlight the importance of thinking about pathways for oral, as well as parenteral antibiotics to get our patients back to work, school, and being productive.

So then this -- I wanted to make a quick comment about the U.S. patients. And I know we heard the great presentation on this before, which is encouraging, but I just picked one study that was kind of -- that I was called on about recently, the study of nosocomial pneumonia for ceftazidime avibactam. And a group was considering, you know, putting this on their formulary and I was asked the question of, how can I put this on the formulary when we don't have any U.S. patients.

And, in fact, when you drill into the paper, and you do have to kind of drill into the paper, which I would submit not everybody does, you will see that this trial, this big trial, right, of over 350 people per arm had zero U.S. patients; it had a third from China, almost a third from Eastern Europe. It was a great trial and it led to the approval, but I think it does leave us where we're making recommendations in the United States perhaps without all the information we would like.

So what do we need? So we need a diverse renewable pipeline of both IV and oral

antibiotics. We'd like to have some efficacy and safety data from patients like ours, and that includes big ones, as was said earlier. We'd like good surveillance data to inform our empirical therapy. Susceptibility testing to guide our therapy; it's really hard when you get results like what I showed you where there's no criteria.

Data from various sites of infection in various types of patients; it's already been alluded to that we have patients with certainly skin and urine infections, but also bloodstream infections, bone infections, young and old, obese, pregnant, people whose organs don't work; that was alluded to earlier. And PK data really does help with antibiotics, and I think that can't be stressed enough.

We also need the data fast, and this is a message I really wanted to spend a minute on. You know, we hope to see data as close to real time as is feasible, right, because we have patients now who need this help.

So FDA labeling I think gets a bad rap from a lot of clinicians, but it actually is used by

physicians. It's used by our pharmacy committees, it's used by payers increasingly, and I would submit that what's in the label does matter to docs. And we get an idea saying others have been advocating that CRE data and other multi-drug resistant pathogen data really should be in the labels, even when it's imperfect, especially in the setting of LPAD, because it's useful to us when we have to make these decisions. The limitations can be clearly stated, and I think we'll see some very creative ideas on this in the next two days.

Publications. I'm so glad my friend, Dr. Baden is here. And the question there is, can pivotal trials be published faster, especially when the data becomes public as part of the FDA process. It's great to see these publications in top tier journals, but the sooner the better for those of us on the front lines.

And then we're going to have some conversation, and Dr. Sears is going to talk to us about guidelines. We know that it takes a while for guidelines to be published and sometimes up to 10

years. So the question is, can we expedite that process? Should we consider alternative processes while imperfect, something like the guidance that was done for Hepatitis C perhaps, to help clinicians get data lacking the perfection of a true guideline more rapidly, so thinking about the risks and benefits of that.

So finally, I'm circling back to where I started. We physicians do work with incomplete data every day. We can't care for our patients without a steady stream of new drugs. And I don't think we can insist on or wait for perfect data. We need every piece of information we can get about new drugs, susceptibility testing, along with good stewardship and linked to good data so we understand how the new antibiotics are being used to optimally use and preserve the new drugs that we have.

So with that, I'll thank the colleagues who helped me and all of you. Thanks very much.

ERIN DUFY: I'd like to introduce Sara Cosgrove, who is a professor of medicine in the Division of ID at Johns Hopkins. She's also the

Director of the Department of Antimicrobial Stewardship and an associate hospital epidemiologist at Johns Hopkins.

SARA COSGROVE: Thank you so much, and good morning to everyone. Thank you for inviting me to speak today. The official title of this talk is the role of antibiotic stewardship programs and the utilization of new antibiotics, but I feel like the subtitle should be, we should all just get along, because I recognize that on occasion, stewardship is viewed as not a helper, but a hindrance, in terms of new antibiotics. And I really hope to show that I don't think that way. How do you advance? Here are my disclosures. I keep advancing in the wrong direction. Can you advance for me? Okay. You can go to the next slide.

So I kind of wanted to talk about two issues today, and one is to discuss real-world challenges with positioning the use of new antibiotics in hospitalized patients, and that will be my focus today -- hospitalized patients; and then discuss the role of stewardship programs and implementing the use

of new antibiotics to improve patient care and minimize emergence of resistance.

So I'll start with a little bit of data. I think this paper, which is published in OFID, was one looking at essentially why is it taking so long for newer agents to replace polymyxins, which are clearly not very good drugs. And this is one of the images from this paper with the number of CRE infections, or carbapenem-resistant Enterobacteriaceae on the Y axis. Polymyxins show up three times; they're light blue, dark blue and gray. And this is because the authors estimated proportions of the numbers of CRE infections treated with polymyxins before ceftaz-avi was available; and those are their three different estimates -- 45 percent, 32.5 percent and 20 percent.

They also note that in the data they were using from IQVA that the data on route was not provided. There is a fair amount of colistin that is used in the inhaled form in the United States. And so, they estimated for the purpose of this study that 65 percent of the use was IV.

And so, if you look at the red, which is ceftaz-avi and (indiscernible) and plazomicin, they note that using that mid-range estimate of colistin that it was around December of 2018 that we started to see more use of newer agents compared to colistin.

So that's a little late. And, you know, I think we would all agree that we really should have been using newer agents, instead of colistin and polymyxin before that. Can you go to the next slide?

These are some data that came from Anthony Harrison and Katie Goodman, looking at data from the premier database. And these -- we just kind of ran last week; this is a dataset that we have, and I was curious what it looked like in premier. Premier is 576 U.S. hospitals; about a fifth of them are teaching, you know, more academic and the rest are more community oriented. And in this, the Y axis is days of therapy for 1,000 patient days, the blue are the polymyxins, and the green is ceftaz-avi, (indiscernible), And we have (indiscernible) in there, but there wasn't any (indiscernible) being used in this time period, which is 2016 to '17.

So in this dataset, we see the cross more in the Spring of 2017. So, you know, where we get our data from, you know, may indicate that there's different uptake in different settings across the U.S. And this data does include inhaled colistin, but only 3 percent of the use was inhaled colistin. It doesn't change the graph at all if you take those out. Next slide, please.

As part of the study in the first of the graph that I showed you, there was a concomitant survey done of pharmacists on guidelines for anti-CRE infections that they had in their individual institutions. The survey was 110 pharmacists in 41 states, and it was done in December of 2018. And what I thought was interesting in this is that when surveyed -- and it was 2018 when we saw that crossover, but still a fair amount of polymyxin use. But when surveyed, ceftazidime-avibactam and (indiscernible) bactium were actually positioned in these hospital survey to be first line therapy in the majority.

So if you look at that pneumonia

column, for example, of 54 plus 32 percent, that's pretty high. So most of the hospitals surveyed here were saying, yes, these are first line agents and we should be using them. They also asked about polymyxin and aminoglycosides, and the one area where aminoglycosides were still first line was in urinary tract infections.

I added below this, ceftolozane tazobactam and (indiscernible), which they did not ask about in the survey because they were focused on CRE, but just to remind us that those are two other drugs.

And then we've talked already in the session about what things do get approved for. But in the FDA approval column, as everyone knows, there's a lot of complicated UTI approvals, which is a bit of a stewardship issue sometimes. Next slide, please.

So why is uptick slow? We've talked about this already today. The primary studies for FDA approval are non-inferiority studies in patients without resistant organisms, and pneumonia indications and dosing information is late or doesn't exist. And, you know, a lot of the patients who are dying of CRE

infections and resistant pseudomonas infections in the hospital have pneumonia, and so that is a challenge.

I would say that this is not particular a challenge for stewardship programs because we seek to have access to these drugs as soon as possible. We have people coming to us saying what can I do, what can I do, as Helen demonstrated in her cases. And so, we work around this, but it is potentially an issue.

We've also discussed low numbers of patients with CRE and MDR pseudomonas in studies for fast-tracked FDA approval. And I will say that we don't actually want in the United States to have a robust number of patients to enroll in studies with CRE and multi-drug resistant pseudomonas. So, again, you know, I don't want that. I think it's good that we have trouble enrolling patients, to some degree. But when you do show these data to people who are, you know, data driven, they say, whoa, those numbers are pretty small.

So you can see in this little graph here, you know, the numbers for the new agent with Mero/Vabor and (indiscernible) were 32 and 21, and

best available therapy were 15 and 10. So those are pretty small numbers. You can see I put in parenthesis the success rate with both of those. They still do look better than colistin.

Post approval studies, which I think we ultimately rely on, and I think it was really the publication of studies that showed that these newer agents were better than polymyxins, the post-marketing studies that really started pushing the use more, but they take a little bit of time. You know, even if you adopt these drugs as soon as you have access to them, it takes a little time to gather up enough patients to publish that data.

Obviously, these agents are expensive, and I can't leave that off. So there's always a little bit more, you know, cajoling, negotiating that might have to be done in some institutions to make sure they get on formulary. And then initially, there were difficulties with susceptibility testing. This is largely resolved, which I think is a huge win. But many will remember the time when you really couldn't get ceftolozane/tazo testing done easily at all; and

that, of course, limits our ability to use those drugs. But, again, I think it's a win that this has been improved. Next slide, please.

So what are some of the stewardship considerations with regard to new agents? I think that stewardship programs recognize that these are the agents of choice for resistant gram-negative rods. I think ASPs are often the primary driver of formulary additions of these new agents. We are watching the studies, we are trained in infectious diseases, we push to get these things added to formulary.

And then clinically, we often coordinate issues with micro-testing, selection of the optimal agents, selection of combinations of agents that may or may not work, and also advise on duration; that's kind of all in the role of stewardship. And I think we're also critical in recommending optimal dosing strategies. And so, you know, when an agent comes out at a lower dose approved for complicated UTI, I think we all in the hospital have to keep in mind if we're going to use it for pneumonia, probably need to use higher doses. And so, that's what we pay

a lot of attention to, what actual dosing do we want to use in our patients in the hospital.

I think we also desire to ensure that agents are used in a way to preserve their utility though, and we have a lot of concerns about emergence of resistance. We don't want to see resistance to these agents across the population. We don't want to see emergence of resistance to these agents within a patient that we observe under our own eyes.

And we want to avoid treatment of colonization, because treatment of colonization leads to resistance; it's the best way to get resistance. And I worry a little bit about some of the studies that poll just data on CRE infection reports that a lot of that may actually be colonization, and we need to be very mindful of that.

And I think ASPs at this time, just because we view these agents as so precious, are unlikely to support routine empiric use. And I know that that is a problem in terms of getting hospitals to put these drugs not so much on formulary, but getting them to be used and support the market. But I

fear as a steward that if we use these routinely for empiric use, we will see faster emergence of resistance. So next slide, please.

Just a little bit on this resistance topic because I do think it's a major concern for us clinically. I just have some examples of large-scale data that show there is some baseline resistance to all of our new agents; not bad, but it is something that we still have to keep in mind we do need to test. We can't, you know, assuming a hundred percent susceptibility with all these agents.

And then some data from our own institution, which is just pseudomonas ceftolozane/tazo susceptibilities in 2017 to 2019, and there was a huge difference depending on the population we looked at in terms of baseline resistance. So amongst CF patients, cystic fibrosis patients, our susceptibilities at baseline were 38.5 percent, which is, of course, exactly the population we want to use this drug in. And then in non-cystic fibrosis patients, much better at 75 percent. Next slide, please.

There's also some data on emergency of resistance during therapy for both ceftazidime-avibactam and ceftolozane/tazo. For ceftaz-avi, this was a series from Pittsburgh of 37 CRE infections of mixed etiology. In the study, clinical success was seen in 59 percent of cases, but there was macrobiotic failure in 27 percent of cases. And there was resistance seen in 3 of 10 failures that developed at a median of 15 days, so resistance is a reality for us.

Data from my own hospital using ceftolozane/tazobactam looks pretty similar in a way. We had 35 resistant MDR pseudomonas aeruginosa infections, saw clinical success in 46 percent of patients, micro failure in 26 percent of patients, and resistance. You know, so when I say resistance emerging, I mean, we had a susceptible isolate and then we went on to have a resistant isolate in that same patient in 6 of 10 of our failures developing at a median of six days. Next slide, please.

So why does this matter? Most of the patients that we're treating with MDR gram-negative

infections have significant medical complications. Many of them have major issues with source control, particularly when the infection is intrabdominal. And many of them have future medical needs, a need for a lung transplant, a need for a stem cell transplant, a need to undergo chemotherapy and become neutropenic.

So often, we're in the position of having to say when should we pull the trigger on the use of these new drugs so that we get the person over the hump, so that we -- we can't just start it if we have concerns that resistance is going to develop. We have to time that in a way that we get them through the procedure that they need to get through. Next slide, please.

One other challenge I wanted to mention was paying for new agents after patients are discharged from the hospital. So insurance often does not cover outpatient antibiotics; sometimes, it doesn't cover any outpatient antibiotics regardless. But when they're used off-label, that can be a big issue that you have to fight with insurance companies about; and sometimes, they still say no, even though

it's clinically obvious to you.

And then nursing homes, where sometimes we have to send our patients, don't have these agents on their formulary, and they often balk about obtaining them due to the cost. And then changes to the inpatient perspective payment system and the long-term care hospital perspective payment system for FY2020 don't actually address these problems. So this is a constant battle in patients that are in the hospital that stewardship teams and ID clinicians are dealing with. Next slide, please.

I just wanted to mention briefly stewardship's role in agents that are not directed at MDR gram-negatives. As we know, these are approved on the basis of non-inferiority studies for infections that we don't have a big problem with, you know, that we have a lot of cheap existing drugs to treat, and they cost 10 to 25 times more than standard therapy. So I struggle with this as a steward because, on the one hand, it's hard for me to advise the hospital to bring these un-formulary and use them for CAP or skin infections.

But I also recognize that these agents may have a lot of promise for future treatment of infections that we don't even know about yet. And just as an example, a metacycline may have a significant role in treatment of (indiscernible) or perhaps (indiscernible). And so, we don't want, as stewards, to have these drugs go away. We want to have the ability to see future studies that show that they work for these rarer issues, but it's still financially a hard sell to a hospital to bring agents that cost this much onto formulary. Next slide, please.

So what can be done? I think we're going to spend the next several hours talking about this. I do think that there's still a proportion of ID clinicians, of critical care clinicians and so forth that may still be using polymyxins, and we need that to stop. And so, what do we do about that? And I think the idea of guidelines or probably guidance, because we don't have tons of clinical data, are a good idea to really push forward the idea that these are the agents that we should be using and getting

those messages out to our colleagues.

I think we need to continue to push for post-approval data on utility for multi-drug resistant gram-negatives from all sites and think about new study design, such as adaptive clinical trials, to really get at which agent should be used for what and how. I think we need to develop approaches to predict which patients may benefit from empiric treatment with these agents because we want to avoid overuse. We need to think about predictive models that might help with this, the role of surveillance cultures, and then the role of rapids, because if you can get rapid diagnostics and say use it quickly, then that helps.

I think that the change in colistin and polymyxin B breakpoints will change; basically, nothing is susceptible anymore to colistin and polymyxin B. CLSI did this on purpose, and I think it is a real win that they did this because clinicians will see intermediate or resistant now every time they send the test for colistin susceptibilities.

And then I think we need to continue to ensure and keep going the good work we've done with

ensuring that we can get susceptibility testing for the new agents. Thanks.

JOHN FARLEY: Thanks very much, Sara. So it's my pleasure to introduce Amy Leitman, who's the Director of Policy and Research and NTM Info and Research. It's a nonprofit patient advocacy group with patients with non-tuberculous micro bacterial lung disease and related comorbid diseases. I've had the pleasure of working with this organization for about the past decade in the NTM space. And in my view, we need more organizations like this in the AMR space. So thanks very much for joining us, Amy.

AMY LEITMAN: Thank you. Thank you for having me here today. I'm going to touch on various aspects of the patient perspective in clinical trials. Some of them I'll go into more detail and some of them I know we will hear about later from CTTI, so I'm going to leave those parts alone for the other experts. These are my disclosures.

So I'm going to start with what do patients need and want in therapies. So we've heard some already about the antibiotic challenges, the

challenges in developing antibiotics. And one of the things that I've noticed is patient-reported outcomes are not really integrated into the development of antibiotics, and I think that this is something that we should be looking at more carefully.

There are other areas of drug development where the pipeline is much more robust. They've started to integrate PROs much more, and they've had better results because of it.

So what do patients need and want? To start, they need better options, especially, you know, we're facing this rising tide of multi-drug resistant organisms. They need more options. They need other therapies: sometimes, they are allergic to a particular therapy; sometimes, they have a pathogen that's resistant to one and not another; and sometimes, they have a susceptible pathogen and the therapy simply fails. So having more options is going to be better for patients.

They also want new and creative options. Antibiotics just, they're not going to be enough, I don't think. We're facing -- we're up

against evolution. To put it bluntly: these bugs are just better at evolving than we are. They're smart, and they're designed to evolve to resist. There are other areas that should be explored; some of them are already being explored and developed in combination or adjunct therapies.

So I've seen some of the early research that has been done on sort of these compassionate use cases for bacteriophages. It suggest that bacteriophages working in tandem with antibiotics can be effective. It's a very difficult area of development, but I think it's something that we should be looking at. We probably should have been looking at it sooner, and I think it could be a huge step forward for the use of antibiotic therapy as a combination.

Targeting the bugs themselves, and specifically those mechanisms that confer drug resistance, is another possible avenue, as is developing antibiotics that essentially trick the pathogens' defense mechanisms and avoid resistance. And I know there are a couple of companies that are

sort of in the early stages of looking at these things. But overpowering a mechanism of resistance is a therapy that might be useful in terms of allowing an antibiotic that was previously resistant to go in and work effectively.

And tolerating treatments is also an issue, and this is a big challenge in clinical trials, because it's not enough just to get them into the clinical trial; they have to be able to take that therapy through the clinical trial and get through it. So I think this is an area that we don't address well enough. I think there are other disease states that do a better job of addressing it, and I think there are valuable lessons to be learned there.

One of the biggest frustrations I've heard from patients is about clinical trials themselves. The criteria are often exclusionary to the point of hampering the enrollment. The design doesn't take into account the impact that the therapy might have on the patient and whether that should be measured.

And the end points don't often enough

include patient reported outcomes from tools that assess this patient over an appropriate period of time. And that's another question that we need to ask and it's really going to depend on what is the infection, where is the infection, and how is it being treated. So determining an appropriate length of time to assess that is important.

So what else helps them? Better and faster diagnostic tools can help make a difference in clinical trial enrollment, and identifying a pathogen sooner can help determine that they are eligible to enroll in a particular clinical trial.

Likewise, being able to identify susceptibility of the pathogen can make a difference, particularly if you need to explain to the patient or their loved one that they have an infection that is drug resistant and will be extremely difficult or nearly impossible to treat.

Only focusing on the pathogen in the tube, we're missing critical information. We need to also learn more about the infection in the patient and how that patient's body reacts to it, in order to

properly determine and understand how we figure out what the susceptibility is to the drug.

So I touched on the first two, bacteriophages and other adjunct therapies. But I want to talk a little more about what else is going to help patients, particularly when we're talking about clinical trials. One of the objectives I mentioned is to get that patient to stay on the therapy because that's how you see if it works. So this is often call retention, but patients actually usually refer to it as enduring or endurance.

So the cancer community has actually become quite adept at this. A lot of cancer treatment centers offer a variety of supportive therapies to help mitigate or manage some of the more severe side effects, including gastric effects, and resulting dehydration and malnourishment. It's actually routine to pretreat a patient with an antiemetic, and the American Society of Clinical Oncology has a clinical practice guideline actually specifically regarding this.

And I know that some of the key opinion

leaders in NTM now have actually started in their presentations talking about the fact that when they have to treat with a drug like triglycine, they've started pretreating with ondansetron because it helps the patient better tolerate the therapy, and they're getting better results with that.

So one area we need to better understand also is the relationship between our own microbiome and immunity and inflammation. The gut microbiome has historically not been that well understood, just that it's there and it serves a purpose, and disrupting it can cause gastric and other issues.

More recently, our understanding encompasses the idea that as part of a whole system, this microbiome is a valuable part of the body. We emphasize to our patients that they must take a probiotic while they're on an antibiotic. The literature that we put out, what's on our website, emphasizes this as well. But it also tells them something else; it tells them how to take a probiotic.

We tell them don't take it at the same

time as an antibiotic because you're effectively neutralizing it. This sounds pretty basic and simple, but you'd be surprised at how many people go, oh, right, okay. You have to actually communicate to the patient in a way that they're going to understand, and you have to make sure they're getting all the information threat they need, especially when you're dealing with life-threatening infections. There's a lot coming down at them.

So we've talked about respiratory infections as well, and I'll get into that in a little more detail afterwards. I want to talk now about some key challenges. Time is the first one when we're talking about critical infections in particular. This doesn't allow of time to determine enrollment; that's why rapid diagnostics could be very useful.

Another issue is that 24-hour rule. Sometimes, you have this concept where if a patient is on therapy for more than 24 hours, they can't enroll in a clinical trial. But I guess, you know, one of the words we're used to using is refractory, when the infection is refractory, and we've seen clinical

trials where they have to have refractory disease before they go into the clinical trial.

But, you know, if you're talking about different kinds of infections, what defines refractory then; when do you determine that a UTI or a skin infection is refractory? What defines failed therapy? Because even if it's more than 24 hours of antibiotics, at some point, if they're not responding to therapy, then the therapy has failed and it's probably time to consider something else, and you may want to think about enrolling them in a clinical trial at that point.

And I want to emphasize here the wording because this is something we hear a lot and, again, this is about how we talk to patients and talk about patients. The patient doesn't fail therapy; the therapy fails the patient.

Decision capability. As a health crisis increases, the patient or legal representative hears things more through this, what I call, a filter of fear. So, again, they've got this information coming at them, and they have to make these often, you

know, life critical decisions. How you word things and how you say things may also matter, but identifying early risk factors to infection and having rapid diagnostics together, I think, would be a very powerful tool to enrolling.

Pre-consenting for a clinical trial would mean that as soon as it's apparent that a patient is or may be an appropriate candidate, they can be started on the consent process, so that if they become more critically ill, you don't have to wait for that process to start. It already takes a little while to get them enrolled; you start that sooner.

Exclusionary criteria are another issue. Two major populations of patients who need antibiotics -- diabetics, cancer patients -- are often excluded. They're more prone to infection. I know of several patients who, when they were starting their cancer treatment, were told don't go for a manicure or pedicure because you might get an infection that we can't treat. So that really tells you there's a whole population out there of patients that could be pre-consented to enroll. That's how great their risk is,

but they're routinely excluded.

One more point to make about barriers and issues. Financial challenges are a barrier and that was touched on earlier. This is also a challenge in clinical trials. If you're running a clinical trial, you should be prepared to bear the cost of the patient testing because, oftentimes, their insurance won't. They think about other things: they think about, you know, how much work am I going to have to miss; how much will I need to do for this trial, what's the time commitment; will I be able to afford this, how far do I need to travel?

I want to present a case study now. So this illustrates how at various points intervention, better treatment options, and early consent might have helped this patient. This information was provided by his closest friends and family, who were present throughout the course of his illness, and it includes their observations on measures which might have helped this patient. They've given their consent to have me share his story.

The patient in question was a 43-year-

old male with multiple comorbidities, including obesity, poorly controlled diabetes, and corresponding poor dietary habits. And based on their description of increasingly antisocial behavior, probably undiagnosed and untreated depression.

The patient developed pain in his left foot, but did not seek immediate treatment. After 10 days, he was taken to the hospital where a severe MRSA infection was identified. Over the course of a 10-month in-hospital stay, the patient underwent extensive treatment with antibiotics, had his pinky toe and surrounding tissue amputated. He had multiple treatments with a hyperbaric chamber and, overall, had approximately 50 surgeries to degreed additional tissue and muscle. He was discharged after approximately 10 months of treatment.

About six months later, the patient once again developed symptoms, including discomfort in his foot and leg. Motivated by his previous experience, he sought treatment quickly and was hospitalized for two weeks, receiving additional antibiotics and more hyperbaric treatment.

Four to five months after his second hospitalization, the patient became symptomatic again and sought treatment, receiving additional antibiotic therapy. After approximately three weeks with failing treatment and showing symptoms of sepsis, the patient lost consciousness. He was comatose for two weeks and died of multiple organ failure at the age of 44.

As they related this story to me, his loved ones and his friends made several observations that I thought were really critical to talking about critical trial design for antibiotics. First, that lack of treatment option certainly contributed to his death, and had there been better treatments available, he might be alive today. This speaks to the growing need for therapies that fight this rising tide of drug-resistant bacteria.

Another observation they made had to do with the clinical trials. At no point had anybody discussed with them or his family enrolling in clinical trials. But they noted that for someone with comorbidities like obesity and diabetes where the patient is not taking proper measures to control them,

simply being at risk might not be enough.

Their observation that fear was a motivator for the patient to seek treatment faster the second time the infection presented prompted their observation that prior history of infection could be used to identify at-risk patients who will be more amenable to the idea of early consent for clinical trials, and this is particularly true when you're dealing with certain comorbidities.

Finally, when discussing the totality of care, his loved ones observed that at no point in his treatment was he given psychological counseling, despite the physical trauma he had endured, that included again more than 50 surgeries.

Interventional therapies are necessary for many different patients for many reasons, and they increase the chance of a positive outcome. In clinical practice, these interventions are often used and desired. So, again, I want to raise this possibility that they should be considered in a clinical trial setting. It helps reflect a more real-world practice that you would want, and it helps to

possibly optimize an outcome. It helps possibly increase positive outcomes for the trial and for the patient.

So what else should we be measuring? We've talked about microbiology and symptoms. Some of these things are obvious, symptoms such as fever, swelling, redness and discharge; these things can be measured clinically. But there's another set of measurements that we've discussed briefly. I want to get more into that now, and that's patient reported outcomes.

So what can patients tell us about their illness? This is a host of symptoms that infection patients, including those with sepsis, chronic respiratory infections and acute respirator infections such as pneumonia, have reported. They're generally difficult to measure in a lab, but there is an entire area of science dedicated to developing tools that measure these things. These symptoms range from pain and fatigue to respiratory symptoms and mental symptoms, among others.

This is a table showing the use of

patient reported outcomes, more than 500 in oncology clinical trials. These data were collected through clinicaltrial.gov postings over a six-year period from September 2006 through December 2012. A good example was a trial for small cell lung cancer using a particular symptom list. That looks remarkably similar, doesn't it, to the previous slide displaying symptoms reported by those with respiratory infections.

So there are a number of PRO tools that are validated for various diseases and, in particular, for oncology. And instead of reinventing the wheel, these are possibly tools that we could be looking at for use in infection disease spaces.

How far out do we measure with a PRO? So, again, that's really going to depend on the infection; where it is, what it is, and what outcome we're looking for. We need to answer those questions. They're going to be difficult to answer, but this is part of developing a good PRO.

Sepsis survivors have reported similar experiences to other respiratory infections, and

patients with chronic respiratory infections, the matter complicated even more by their prolonged course of treatment. And it means that their symptoms may not resolve for a long time, and it also means that their side effects may be confused with symptoms.

So I want to talk a little bit about messaging, messaging matters. I've not really heard of many patients walking into the doctor's office and saying, hey, doc, I have dyspnea. But they do say things like, I'm short of breath or I'm having trouble breathing. And to a doctor, that means dyspnea. And actually, when we conducted a patient survey on preferences in treatment and so forth back in April, when we talked about their side effects and their symptoms, we put shortness of breath and then the word dyspnea in brackets, making sure we use patient-focused language.

So messaging matters. Patients and their loved ones want to gather as much information as possible, so talking to them is important. Speaking clearly and plainly without making them feel confused or uneducated makes them feel valued and that they're

doing something valuable; it can help them feel empowered and that their loved ones feel that they're helping -- something helping the patient as well.

And just as an example. We actually had a meeting last week for one of our research consortium projects, and I believe the word was borborygmus or borborygmi. There were 12 of us in the room and 6 of us were wondering what it meant. It means a loud stomach, in case you're wondering.

So I just want to leave you wish this little anecdote about messaging. This is the Panthera Tigris, that's what the scientists named him, he's very cute is a lovely creature. He's renowned for his -- yeah, he's very fuzzy and cute, isn't he -- renowned for the hunting prowess, largely due to a combination of the powerful legs, strong jaw, razer sharp teeth and claws, and those claws are curved and retractable. So this tiger is beautiful and everybody loves a fuzzy creature.

But when the ordinary citizens of the internet started renaming animals, we came up with very big cat and danger kitty with murder mittens. It

sounds ridiculous. But my point is this: when you're trying to teach someone who doesn't know what a tiger is about the risks associated with them, this might be as good a place as any to start. Thank you.

ERIN DUFY: Thank you very much. Okay, now I'd like to introduce Wes Kim. He's a Senior Officer of Innovation at Pew Trusts. His work is focused are research and, in particular, policies that help to drive antibiotic research and development.

WES KIM: Great. Thank you, Erin, and appreciate the opportunity from FDA for me to present our work in the antibiotics analysis.

So I think most, if not all, in this room know that Pew tracks a global pipeline for both small molecules and non-traditional. Today's presentation will be strictly focused on the small molecules, and we started tracking in 2014 and have continued to do so up to today.

And about a year ago, we said wouldn't it be cool if we took a five-year historic analysis and see if we could identify any trends or something that would inform future R&D, advocacy, investments.

So today's presentation will dive into what we found in the past five years, and then our most recent updates.

So overall, there were 67 total small molecule antibiotics in the clinical development. Additional notes for the scope: this doesn't include TB drugs and doesn't include antifungals. Within this five-year timeframe, we saw 20 new entrants with an output of 10 approvals. Also, there were 15 discontinued products or candidates, and 10 that stalled, which are essentially those that started -- where we tracked, started tracking clinical development in 2014 and there weren't substantial updates to that program.

So this is a snapshot of what we found in 2014 to 2018 analysis, so let's take a deeper dive into what individual types of the candidates. So as I mentioned, 67 to start with. Now, if you come a gram-negative to a gram-positive, we see about a 40 and 60 percent split across the 67. About 17 were targeting against CRE, another 11 were targeting against C.diff.

And so, it will be interesting over the

next 5-10 years how this balance between gram-negative and gram-positive pans out. Certainly, there's a lot of -- there's a big spotlight on gram-negative pathogens, but also as we've seen in the prior CDC report and current CDC report, that C.diff is still an urgent pathogen.

Now, I want to talk about the novelty of drugs, so let's take a look between the gram-positive and gram-negative and how they break out between a candidate that has a novel component versus those that are candidates that are building off prior generations or prior scaffolds.

On the gram-negative side, you see about 4 out of 26; if my math is correct, that's about 15 percent on the gram -- sorry, that was g gram-negative. On the gram-positive side, 13 out of 41; I think that's about 30 percent. It's hard to say if that's a coincidence or a correlation. We don't have enough data to make that kind of distinction, but I just wanted to share what we've been seeing.

And then in terms of those that ultimately came out on the end for either approvals or

for those that were in development or stalled, you see, as a mentioned in the previous slide, there's 10 total approvals, 6 of those are targeting gram-negative and 4 are gram-positive. So for those who are all in on the gram-negative team, then that's not too bad.

But let's take a look now at the approvals specifically. So as I mentioned, 10 within the 2014-2018 timeframe, and then the bottom three, I updated with the recent approvals this year, including the one, (indiscernible) that was approved last week.

If you look at the column that has novel components, you see three that has a checkbox: two of those are the beta lactamase/BLI combinations, the BLI components being the novel component; and then (indiscernible) was a (indiscernible) that was discovered in 1950s and is novel in the sense that it's for systemic use.

I will note that what we saw in the remainder of the pipeline that there's a six other candidates that are beta-lactamase/BLI combinations. Whether we'll see more of those in the pipeline, it

will be interesting to look at. We don't track pre-clinical candidates. I know WHO in their forthcoming update will provide a summary on the pre-clinical landscape and looking forward to that.

If we look at the column with activity, again, it's gram-negative escape pathogens, I think there's a pretty good distribution of and the checkmarks, so, you know, we should celebrate these wins.

In terms of those that are indicated for WHO critical pathogen, how many of you guys think -- or how many checkmarks do you think we'll see in this column? Actually, none, and I think that's part of the discussion that we'll continue to have today. And, you know, this is something that we track, of course, in our pipeline, and we would hope to see some ways to -- obviously, some of these drugs are being treated -- or being used empirically for CRE infections and other critical pathogens, but they are not indicated per se.

So those updates were from 2014 to 2018, the cutoff being December of last year. And

since then, we've updated our clinical pipeline. So as of June 30th, you see a total of 42 in the clinical development. So if you count, the numbers don't add up, that you see 37 total in pill bottles, but those are the ones that are in phase two -- phase one, two and three.

There are four NDAs at that time under view, and one complete response. Since there, there are three approvals and, unfortunately, one company is seeking a development partner after their phase three trials.

We did not see any new entrants. And year over year, total number of candidates have been steady. So over the past five-six years, it's ranged from upper 30s to low- to mid-40s, so we haven't seen a spike or a complete downturn in terms of the total number of candidates. So we've -- this seems like over the past five-six years, about 40ish is kind of the steady state.

I do want to focus on the phase three clinical development candidates. There are 13: three are based on novel candidates, so that's excluding;

but, unfortunately, one has since been now discontinued. So that highlights the kind of challenge of phase three or clinical development.

For those who are well steeped in the probability of success in phased clinical development, generally speaking, phase one is pretty high, then you see a dip in phase two. But once you show that proof of concept and have successful pivotal trials, you're probability of success for phase three does tend to come up a little bit. However, that's no guarantee, as we saw from one of the drugs that had been discontinued since. Six within the 13 are expected to have activity against CDC threat -- or urgent threat, according to the most recent publication.

So we talked about activity against gram-negative escape pathogens. 17 of the 42 have activity, so that's a decent percentage, but we still need more. And I had mentioned, you know, if we think about the call for action for more novel candidates treating these escape pathogens, particularly gram-negative escape pathogens, one of them had activity, one that was novel and activity. But, unfortunately,

as I mentioned, this has been terminated since. So we don't, at this point, have a novel candidate that's targeting gram-negative escape pathogens.

So to wrap up, I'll just tee up some questions that, you know, keeps me up at night: How do we reinvigorate the antibiotics pipeline; how do we populate the pipeline with more differentiated antibiotics? And by differentiation, I'm not -- it'd be great more novel scaffolds making these actions.

But to what Dr. Boucher talked about earlier, you know, a product can be differentiated based on the route of administration. So the more we have clinical tools for our ID docs, the better.

And then other than financial push and pull incentives, this has been a hot topic for the past few years. What other levers are available to facilitate and reinvigorate in the clinical pipeline?

And with that, just quick acknowledgements. My colleague Cara Lepore, she does the grunt work and the heavy lifting in our clinical pipeline, and then our expert reviewers who we pick their brains and help us characterize accurately each

of the individual candidates. So thank you.

JOHN FARLEY: I want to thank all of our speakers from this morning. We wanted to quickly get some data updates and different perspectives on the table. We do have time coming for clarifying questions and discussion with the audience. We're going to take a 15-minute break at this point. And why don't we make a point of all being back here at 10:35, so 10:35. Thanks.

(Break)

JOHN FARLEY: Thanks, everybody, and for our next workshop, John Rex and I have decided on a different coffee plan, so, we apologize for the long line. John will be buying coffee for everyone. No, I'm just kidding.

So we're now going to turn to a review of the current federal efforts to support antibacterial drug development and our first speaker is Dennis Dixon, well known to many of us, who's the chief of the bacteriology and mycology branch at NIAID and the National Institutes of Health. Thanks, Dennis.

DENNIS DIXON: Thank you. Thank you,

Leslie. So I think most people know that the NIH is their research agency within the federal government and we do research that's basic in nature, translational, and clinical.

And if you want to look at our strategy for antibacterial resistance, you can use the search engine of your choice and put in NIAID AR PDF and you should see this pretty document which goes through a lot of our activities from years -- several years ago and the resources available and the philosophies on what new strategies we need to do.

This will be updated shortly. It's been revised, updated, even had input from the community, and will be appearing in a similar spot on the web when it is released. So basic research. Well, what's that got to do with product development?

It certainly provides seeds for new targets, for new drugs, vaccines, and diagnostics and that's what all of the research is ultimately aimed at, as you can see from the graphic, but that is truly what we're focused on in NIAID is looking for better means of diagnosis, prevention, and treatment of disease.

And I'll cite just one R01 that's pretty remarkable and within the group that I oversee, and it was by Andrew Myers for total synthesis of tetracyclines which led to the spinoff company, Tetraphase, which led to one licensed drug and several other candidates in the pipeline.

That went through a number of other grant awards in NIH and then moved on to BARDA and on to licensure. So right out of an R01 grant. We have a lot of translational opportunities that I'm going to spend some time on and some clinical opportunities that I will also talk about.

So a lot of stuff on this slide. I'm going to turn it into a story momentarily, but a couple of points to make first are that this doesn't require a grant application. These are free services for product development for someone who has a bona fide product development plan and wants to move toward a product.

So these are things you can request for free to assist with product development and just to look in the lower left, you can see that the kinds of things available are MIC tests, animal models, too,

synthesis and CMC, ADME assays, pharmacokinetic safety/toxicity. These are administered through individual service contracts.

They're in place to conduct these services and they are at the ready for bona fide customers to come and use. Just in my branch alone, I see several of the people who are involved with this who have written these task orders under the contracts or who oversee them or meet weekly as we hosted last year, 58 different calls and meetings, to talk about these services.

And the story I would tell about these services is back when I had the privilege of living in Basel, Switzerland and working at Hoffmann-La Roche for an extended two-year sabbatical, a beautiful campus spanning two sides of Grenzacherstrasse and overlooking the Rhine, my lab where I worked had a beautiful view of the cathedral. It was 60 feet from the Rhine.

The point is, this campus housed labs for screening for running MICs, an animal suite where you could go and put these same experiments through animals, larger animals up through non-human primates.

The animal tissues you could get back and sent to histopathology and have the fungal stains or anything else you want run on them, the histopathology and so for, and have them interpreted.

If that compound wasn't quite right, you could meet with the chemistry labs over on the other side of the street and talk with them for optimization. And so structure activity relationship could be defined, new discussions with chemists on how to go at this a different way.

Pilot lots could be manufactured for screening in all of these assays, and ultimately there was a section on the campus where large-scale material was made for distribution. We've sort of disassembled all those different parts, all those different labs, and all those different services and provided them under contract for people to ask us to use.

We also provide clinical services. These are, of course, early phase development -- Phase 1, some Phase 2 -- and we have done some post marketing studies that you would probably call a Phase 4. Our typical point of handoff is after Phase 1, maybe Phase 2, and help for the proof of principle to

have been made by that time so that this could be picked up in more -- more totally by a company.

And so we have a similar process where presently, these services are awarded under contract and they're in two types, Phase 1 clinical trial units or vaccine and treatment evaluation units. Both can test antibiotics and just to show the map here, the point here is that these are either existing academic centers with experts or existing companies that provide CRO type services to conduct a Phase 1 and get the first inhuman data.

And these are provided free of charge. Sure, it might take a little longer than if you were in the company and raised the money and did it yourself, but free is pretty good and if you're really stuck and can't get forward without this assistance, this helps to de-risk the enterprise by providing those services and giving the data back to the intellectual property owner.

Not only do we assist with the development of new antibiotics, but while we're waiting for them, we also work to optimize existing drugs and to use them in new ways, and so I wanted to

include that a little bit because there are some lessons learned here that I think will be relevant to the discussions we'll be moving into for the rest of today and tomorrow.

And so in 2007, we started a series of what we called strategy trials. These are not efficacy trials. These are not A versus B to prove a drug. It's to see if a particular practice has a comparative effectiveness in the community and so back in the beginning when the CA MRSA epidemic was sweeping the country and people were (indiscernible) worried about seeing patients in an emergency room setting and sending them back out before you had susceptibility testing data.

Is it okay to give them last -- the last line agents, the off-patent drugs? Or do you need to give them something like IV vancomycin or linezolid? And so we answered those questions by conducting, in one instance, the drugs such as trimethoprim sulfa, clindamycin, and even a cephalosporin in things like abscesses or cellulitis and so forth.

And those are published now

(indiscernible) England Journal but it's basically, which drugs to you use, how much to you give, how long do you give them. Or even if you can drain an abscess, do you need to give a systemic antimicrobial at all, if you've got proper wound care and proper drainage?

And it looks like, much to our surprise, you probably do if you want to get better faster and don't want a relapse, don't want to have as much pain.

The only one I'm going to talk about is one that's still underway. We had eight of these total. I believe we're going to complete six, so that's pretty good success rate for a large, basically Phase 4 type studies in difficult situations and I think this is the toughest of them all.

The title of the study is OVERCOME. I think one of the challenges was coming up with this acronym and I think by doing that, we'll probably come to the end of the study and we'll get an answer. You can look it up in ClinicalTrials.gov. The principal investigator is Keith Kay. It's been a labor of love.

We started the award in 2009. It took

us three years to get it through launch and starting to enroll. These are all done, by the way, under I&D. They're a little bit different in that I think the FDA is kinder and gentler when you're not going after a label indication. You're looking at off-patent drugs to see how they work best.

And the question here, and I think still, is what's the best available therapy for MDR gram negatives and the model we arrived at through competitive review was colistin alone versus colistin plus a carbapenem in the populations where that tough population of pneumonia -- hospital pneumonia, HAP/VAP, and bacteremia, and we took sort of an operational approach.

These are the microbes that don't respond to anything but colistin, so it's the MDRO, XDROs in some instances, starting off carbapenem-resistant Enterobacteriaceae, pseudomonas, and A. baumannii. They're flipped in order now because during the long conduct of this trial this has become an Acinetobacter trial instead of starting out as a carbapenem-resistant Enterobacteriaceae trial because of the shift in the epidemiology at the centers.

And so it's good we provided that in our target organisms at the beginning. So the reason I want to talk about this is what we learned and a drive for this is, if we can't figure out how to do this with a model study, we'll never figure out how to do it with the newer agents. And so that -- please consider it from that aspect.

I'll also be very pleased when we get an answer because there are people around the world that tell us the answer, do you really need to add a carbapenem? If you don't, we need to know that because it's driving carbapenem resistance in many places of the world. And if you do, we need to know that, too because we want to use it to benefit the patient. So there are large places in the world that this is a really important question.

And so as you can see, the first -- we started enrollment in 2012. Didn't really start until 2015. The first 12 sites in the United States that had a CRE epidemic saw that epidemic and had no more real population for enrollment moving forward. So where do you go to find the others? That's what we spend the remaining years to try and find.

It's not straightforward. We started in (indiscernible). All of the U.S. sites except for one was closed. We now have added 12 in other parts of the world. In my opinion, the most lucrative in terms of density of patients in a small number of centers is Asia and so what is it about other parts of the world that are better than America?

Most of these sites outside of the U.S. have 2,000 beds per hospital or more. I've heard that the average hospital bed size in the U.S. is 80. So right there, you're going to need a lot more hospitals to equal 2,000 beds to generate the risk population for your infections and the gram negatives are particularly concentrated in Asia, in China, for example, in Thailand -- always one of our high-enrolling countries -- and in Taiwan.

And so we've had to resize the study because although it was set at 444 in the beginning, colistin resistance has emerged. It's still low in the United States. In Greece, it's high. We've got Greek sites. And in some places in Italy, it's high and we've got Italian sites.

And so we did not have the end points

and the procedures to screen for that in the beginning of the study. We do now, and we screened out and now have to replace the patients who have colistin resistant isolates.

Some other things we ran into along the say is, you know informed consent is going to be tough in intubated patients and the -- most of the VAP patients were -- and so legally authorized representatives are not permissible in several countries, including those in our trial to that pretty much means that we are skewed toward bloodstream infection or those who are not incubated to get those patients involved.

Other thing is prior antimicrobial use. We started out like we should with no more than 24 hours of prior antimicrobial therapy. Nothing was happening, so we realized we would still keep our I&D if we just said, okay, we're going to allow 48 hours and we tried that for a couple of years. We're now at 72 hours because that's what is -- basically, what you're going to find in ICUs in places like this on what people get.

And so our answer will apply to people

who want to use it that way, so I think that there's a certain logic to a comparative effectiveness kind of an answer in this population.

These targets trials were pre-ARLG and ARLG, the Antibacterial Resistance Leadership Group, you can see Vance Fowler is here and he may talk more about this later. I've stolen here from the cover of the 2017 CID article that describes what the group is. You can see here they've been quite productive. And the reason I put this up here, first of all, is to show the value of the MDRO, Multi-Drug Resistant Organism network, for access to population planning.

In my opinion, the two biggest limitations in succeeding an antibiotic, licensure and survival, is access to the populations. Few enough hospitals with enough patients to test and answer your question in a financially feasible and timeline fashion and the second, I think, is after marketing, after licensure, is access to the revenue flow to keep them on the market so they don't go down and void all the use of the prior development.

And so this study will help with that because it started by David (indiscernible) who was

looking at let's do a laboratory based starting point. MDRO is identified in the laboratory. Pull the case records for that patient. Do a thorough evaluation to work up and follow the course of that patient to determine contaminant or infecting agent.

What are the conditions in that patient, how do they get treated, and how did they do? You, essentially then, can know when inclusion/exclusion criteria would work in that environment and you'd also know which environment would work for enrolling the trial you want to work.

So that was expanded to, as you can see, 91 hospitals in the U.S. and then expanded and first to South America and then into China, and I'm particularly proud of the entry into China where we have visited 10 hospitals, we have about half of them in a study that is going through the enrollment data to get this information.

The ARLG has also produced some statistical value in terms of desirability of outcome ranking, DOOR -- I think people may talk more about that later -- but some very clever statistical manipulations to help with some of the challenges in

interpreting the data.

And you're probably going to hear Kevin Outterson talk next about CARB-X. The things I described about our preclinical services are our role in CARB-X, so I'll stop there because this red light is flashing in my face.

JOHN FARLEY: Thanks very much, Dennis. You're actually going to hear Erin Duffy talk about CARB-X and Erin is now chief of research and development at CARB-X and we're looking forward to her presentation.

ERIN DUFFY: Okay, hello, everybody. Again, my name is Erin Duffy. I've been at CARB-X for 2.5 months, so it probably would've been better to hear from Kevin about CARB-X, but here we go. And as we talked, John suggested I put myself in context here.

Prior to joining CARB-X, I was the chief scientist at Rib-X and then Melinta Therapeutics until we closed our research site last year. We were a CARB-X awardee and so this is a pretty personal thing for me to see antibiotic research continue.

So thank you, Dennis, for introducing

this slide. So what is CARB-X? I doubt anyone in this room doesn't know, but in the event that you don't, we are a global partnership led by Boston University that's accelerating science in the discovery and early development space to fight drug-resistant bacteria.

You see on that first and second row we have a collection of very strong backers and funders including BARDA and ASPR, the Wellcome Trust, NIAID, in a form of preclinical services which we'll talk about later, very valuable to our drug developers, the UK government and the German government as well as the Bill and Linda Gates Foundation.

I'll come back to this topic of accelerators at the end, but we do want to introduce here that CARB-X is more than a funding mechanism. We feel -- again, you'll see this -- a lot of our companies are very small companies in come cases, and less than five people who are doing everything. And in those cases, we've put a strong shell around them of business and scientific support to help them really transition from a neat idea to something that can be clinically valuable.

So we have a lot of money to invest, about half a billion dollars between 2016 when CARB-X was first founded and 2021, and we're really focused, again, in that discovery to early development space and I want to stop here for a second because early this morning we saw a slide where you started to see a bunch of acute bacterial skin and skin structure infections.

New drugs for those trials come to market sort of in the early teens up to and including this year. And there are they who say, you know, we don't need any more ABSSI drugs and, you know, MRSA. You know, let's focus on priority pathogens. And, you know, for those of you who don't do research it's not like you go back to your shelf when your CEO comes and says, hey, you know what we're going to do today, we're going to focus on Acinetobacter.

Okay, so you don't just, like, go back to the shelf in the lab and pluck something off -- I know you see that in movies, but it's not true -- and then it goes into clinical trials. It can take for even, you know, an improvement on an existing class, 10 years to get to the clinic let alone something

novel.

And so what we're doing today is building a pipeline so that when that next -- I can't even pronounce the bug that Helen introduced to us today -- but when that next weird bug comes, we have a variety of solutions that are there.

The other part of this is the cynical people in the room, and I've certainly been among them at times, would say, you know you're building a bridge to nowhere, given what Kevin's going to talk about next which are the market challenges and I know some of us feel this very acutely. And the answer is no, because again, we're building something not for today but for the future and we believe -- and I think for the good of all of us -- there has to be a solution.

Okay, so let me just go on. So what do we fund? We do fund traditional and non-traditional therapeutics. We've brought in one recently to our portfolio, vaccines, microbiome approaches in antibodies. And we've also added a diagnostics arm that in the short term has been focused largely on bacterial ID and AST, but we're going to expand that and part of how we do that, I think, is listening here

to what might be helpful.

Again, the emphasis is on pathogens of high priority, both in the CDC list and the WHO list. So we do focus early. We're not focused on basic science, so there needs to be a hit and then we will fund everything up to and including a Phase 1 program. Our goal is to have these programs Phase 2 ready.

Likewise, in diagnostics, different terminology but we certainly fund, again, from early feasibility demonstration up to and including system ID and testing. So I'll give you a look at what the portfolio today looks like and I'll do this in a couple of slides.

So when you think about direct acting therapeutics, these are the companies in our portfolio. If the company is named in green, that's because they've graduated our program which typically means completion of a Phase 1 trial. In the case of that very first box on the left, that's Idera and we supported their product which is now in Phase 3.

And so you can see as we go across from left to right, certainly we have representation in all of the very well validated clinical targets with the

exception of RNA synthesis. We don't have a program in the portfolio there. We have other targets like fatty acid biosynthesis being conducted at Debiopharm. And then we have some innovative programs where the mechanism has yet to be determined.

Also in these boxes next to the company names are their date when they jumped into the portfolio, probably less important piece of knowledge, but also staged, so again, you'll see population (indiscernible) optimization, preclinical, Phase 1 if you hit to leads.

And then in each box to the right is the pathogen set that they target, so if the letter is in black, that means it's something they target so we tried to use the ESCAPE acronym there and so you can see representation. We have a lot of CRE. We have some that are aspirational for really broad coverage. We have some Neisseria gonorrhea programs and as you'll see also some C. dif programs.

So again, a lot of diversity, we think. A mix of novel -- truly novel targets or classes as well as some next generation classes. And here, again, I'd like to say beauty and also novelty is

often in the eye of the beholder.

As I mentioned, we do focus on nontraditional approaches as well, so we have some anti-virulence programs, (indiscernible) programs, bacteriophage, and (indiscernible), which are, again, new to us -- we will be growing -- microbiome as well as some other approaches. And again, you see a diversity in pathogen coverage and also stages of program.

As I said, we're starting to embrace vaccines and immunotherapies so you see we have three vaccine approaches under the hood right now, one antibody-based program. We had a very successful call this year in this area where I believe we'll be adding a lot more innovation into these boxes.

And then we also have a growing diagnostics portfolio. We've had our first graduate there, T2 Biosystems, and T2 is now partnered with BARDA so that's a very exciting thing for us as well as companies coming through, again, at several stages.

So I'm not going to belabor the point. This is that same collection. I do want to say, if you can count up the rows there, that we have now had

50 programs come through the portfolio and that's really exciting and I must credit Kevin and certainly John Rex who's in the room as well, Barry Eisenstein, and people who aren't here, Karen (indiscernible) and Rich Lawson for bringing us to this stage that we really have 50 programs that are innovating for the future, and the haven't just started and sort of stalled.

We've seen a lot of progress and that's what the dark blue bars mean and then goal is graduation because it matches that tassel on your cap.

Okay, so we did have four funding rounds this year, the last of which opened last week, last Tuesday to be exact, and you can see we really span the range of things for which we were looking. We had a very healthy nontraditional round as well as vaccine and biotherapeutics and a really dynamite diagnostics round and I'll be very excited to see what comes out of all of these.

We have a poll internally for how many direct acting small molecule therapeutics we're going to have. Kevin and I are going to duke out our position because we chose the same number, but suffice

it to say, I think this is also going to be a very large pool from which to choose.

So as I said, CARB-X is a lot more than funding and one of the things that we're rather proud of is this global accelerator network that we've built and again, you can see the little dots and the names around the world and these are places that both have scientific expertise and business expertise, so again, for those companies where the CEO is also the chief bottle washer and the bathroom cleaner and maybe the CSO, too, having groups that can really help them understand how to build the business and drive programs, gain funding, in addition to the funding that we are giving, all very important.

I didn't say this, but of course we do have a cost-share element and so helping those companies to navigate that very important. But through our advisory board and also through these networks, there's a strong scientific focus as well and I'll call out two groups in particular, ILSE which is led by Keith Bostian in New Jersey and BaselArea Swiss, where Malcom Page is a very large figure, certainly very helpful. Lot of years of experience in

the area of antibacterial drug discovery and development.

And they bring teams to bear that can really support holes in any of our programs and very important for us to do. I'll call out (indiscernible) which is a federation in Germany which is really quite terrific for not only our European colleagues but also U.S. colleagues who are looking particularly for guidance in the EU and FIND, of course, in the area of diagnostics, very large.

So again, what they offer is a range of services. Here again, I do want to call out the NIAID preclinical services. Dennis mentioned them to you. I can tell you again, not only in my own case when we were CARB-X awardees, but also our company's case, having access to assays that you just can't do internally or, frankly, are very weighty in terms of budget, having that access, having the flexibility, I know both Ann and Anita are in the room here.

They work with the teams to really come up with the studies that you need and this can be activity, efficacy, safety, all to support your clinical development package.

And I want to end -- so we built this R&D group and we're actually still building it at CARB-X, because we wanted that internal capability as well to drive programs. And one of the things that we're lucky enough to do now here, having had a few years in the portfolio, is we're starting to see some cross-portfolio challenges but also opportunities for us.

And these become very important when we think about how these data packages and these molecules are going to move through these clinical trials that we're going to spend the next day-and-a-half talking about.

Certainly gives us an opportunity to establish best practices among our network and to guide our developers, and in some areas, to really lead the field -- and I'm going to talk about a few of these -- and again, an ability to provide information within our portfolio in a way that's actually very difficult to do across competitive companies.

And so we've identified a number of areas here, so when Wes talked about the current portfolio and certainly expressed some sadness about

the one program in Phase 3 for priority pathogens that was a novel class, that fell out because of a safety concern, and this is a safety concern across many programs and companies and this is nephrotoxicity and so we're looking at how might we get involved in identifying or at least clarifying what the right models are that can really help us so that when we transition into the clinic we at least have a better sense that this isn't going to be an Achilles heel that you're not going to uncover until Phase 3.

Areas we do have some programs looking at CF, so translation of preclinical data into the clinic there, the animal models of questionable utility and this might not just be true for CF. Some of our portfolio companies are targeting GC and I'm going to be very excited to see how Zoe (indiscernible) work here with GAR-P. we're certainly cheering it on.

My colleague, Sue Cammarata, and I certainly were in the wars there and it's a difficult thing. There aren't really good animal models because of the nature of the condition and then the single dose in the clinic. How do you translate that? And

so these are things we're thinking about. We have some virulence programs, anti-virulence programs into the clinic. Again, animal models and regulatory path, very unclear.

We'd like, really, to work with people in this room on those, and then other areas, working with our product developers to really be honest about the microbiological profile and look at preexisting trends of resistance. This is an area where we can study all of our developers' compounds in large surveillance panels and really help educate them and educate us on what the portfolio looks like.

Again, PKPD, we talk about this all the time but in areas where you're looking for single pathogen indications, this is an area we'd like to contribute to as well as ways that we might leverage our diagnostics portfolio with our therapeutics more creatively. I am at the end, but this is a shameless plug and an important one.

So if you know anybody who would be really interested in joining our team -- look at how happy we were. We're a happy team. We also could use a little more testosterone, okay, so we've got this

great Richard Alm on our team and -- anyway, that's a little facetious, but we are looking for people to build out our team. Thank you very much.

JOHN FARLEY: Thanks, Erin, and our last speaker for this round is Mark Albrecht from BARDA, who's the chief of the antibacterials branch there.

MARK ALBRECHT: Well, good morning, everyone and thank you for having me here today. It's always a pleasure to know that so many people are interested in the work that you're doing, particularly within the antibacterial space.

As was highlighted a moment ago, there are definitely a lot of products that are in that early stage of development. BARDA is the bridge to bringing those products into the clinic and hopefully transition them out into use and into a physician's hands.

So with that, I -- introducing our program here that I am managing. As you can see, this highlights our mission, really revitalizing that antibacterial pipeline through innovation as well as focusing them on reducing the morbidity and mortality

cause by multi-drug resistant infections, particularly those that you see during a mass casualty event.

Of course, BARDA was initially stood with the focus on a variety of different threats: Chemical, biological, radiological, nuclear threats; pandemic influenza; and emerging infectious diseases. This branch is focused on those bacterial threats and this includes anthrax, plague, tularemia, melioidosis, and glanders.

We also look at the fact that following any one of these mass casualty events, you're likely to see opportunistic infections that are going to complicate that response and really be a challenge for our first responders. That's why we focus in on both that biodefense as well as public health and focusing particularly on products that span both those spaces.

Now, in order to accomplish this, we have to have a holistic strategy, one that focuses on novel products, novel mechanisms, those that overcome a lot of the drug resistance that we're hearing about, that we've talked about this morning, and looking at new technologies, new modalities, whether that's a vaccine, a nontraditional therapeutic like a phage,

microbiomes.

And, of course, we're also partnered internally with the diagnostics branch of BARDA to understand and help develop new diagnostics for AMR.

Now, in addition to having that holistic strategy, you need to have a holistic pipeline and we've heard a little bit about carbaxin -- I'm going to also labor that point in a moment -- but you can see that BARDA now is supporting product development in an end-to-end capacity, starting with carbaxis as our early-stage program and portfolio that we're supporting and really excited to see the level of innovation within that portfolio.

That brings us up to our bread and butter. That's our advanced research and development portfolio that really takes over at that post-I&D Phase 1 stage and brings products all the way through clinical development, hopefully to NDA approval and out into the commercial market.

And then finally, we have project BioShield. This is really our acquisition and advanced, advanced development, Phase 4 clinical trials and eventual product development and

procurement of those assets. Now, I highlight a variety of our interagency and international partners at the bottom, really to highlight the fact that it's not just one organization doing this. It's an entire city of organizations that are supporting product development.

You cannot do this alone. It takes both our interagency partners, our international partners to solve this problem. So when you do a little bit of a deeper dive into the -- each of those individual components starting with CARB-X, as Erin really well highlighted and drove home the message, that this really is an amazing portfolio of innovative products.

You can see some of the highlights here. We're equally excited about the fact that there's been 50 different products that have been supported by CARB-X and there's been an unprecedented level of innovations within this portfolio, as Erin talked about. The one thing that we're really excited about is the fact that six candidates within this portfolio have entered the clinic.

This has really helped us realize one

of the goals for CARB-X, to see that early stage clinical pipeline become repopulated with new candidates. We're also equally excited about the fact that we see T2 Biosystems now showing up within the BARDA portfolio, another metric that we had for CARB-X, is kind of that graduation of products from CARB-X into our advanced development portfolio.

Now, this gets us to the advanced development portfolio that BARDA manages. Right now, we have 11 different partnerships that are highlighted here on this slide and they're developing 16 different candidates. Now, it's important to note that five of these partnerships are occurring under BARDA's other transactional authority.

This is a flexible authority that enables us to enter into a partnership with a company to support not just one product but multiple products that they are working on, kind of a portfolio within a portfolio, if you will. Now at this time, there are seven different products within this portfolio that are in Phase 3 clinical development and we're hopeful to see some of these products transition through a successful NDA and out into the market.

This brings us to, really, a lot of the successes that we've seen, noting VABOMERE, Zemdri, and Xerava. Each one of these approvals really highlighted the fact that the BARDA model is working, providing non-diluted funding that's multiyear, subject matter expertise within that technical space covering clinical manufacturing, nonclinical, as well as ensuring that each one of these companies has access to our interagency partners to really support this product.

That model, that mission, is successful in bringing products to market and it's exciting to know that there's going to be future product approvals.

Now, having said all that, I would be remiss if I didn't highlight the fact that there are definitely some commercial challenges that we've been witnessing. I think this is something that everyone here in this room is thinking about and definitely trying to come up with new solutions and new ways to overcome this challenge. BARDA has heard all of you.

We recognize this problem and are internally discussing different avenues and different

approaches to solve this. In fact, two of those strategies I'll highlight right now, one is Project BioShield. As I introduced earlier, this is really our acquisition fund within BARDA. This enables us to procure products for our first responders.

This year, for the first time, we're going to be using Project BioShield to support that advanced development and eventual procurement of a product into the strategic national stockpile, the idea being that through this mechanism we'll be able to either bring about a supplemental indication that further advances that product within the commercial market but at the same time, those procurements create a level of a commercial market for that product.

The next effort that we're beginning to look into is a clinical trial network. Clearly, as has been discussed, there are several challenges surrounding product approvals. Number one, it's really easy to get an indication for cUTI and inter-abdominal infections but is that showing the true measure of value for that product? Are we actually deriving clinical value for that indication, and is it really enabling that product to adequately enter the

commercial market?

Clearly, this criticism argues for the need to investigate these products in new ways, in new structures. So this has brought us to this idea of a clinical trial to try and reduce the barriers for product development, both in time, risk, and enabling each of the partners that would use this to have adequate access to different sites that would have the patients that they're looking for.

At this time, we're definitely reaching out to our interagency partners to kind of discuss the challenges that they've seen with clinical trial networks in the past as well as their lessons learned and what they would like to see in the establishment of another network. Clearly, there are several advantages with a network such as this. It has a multiplier effect.

You can have multiple products going on in one trial. This would, of course, also require a centralized oversight system that would definitely involve the FDA as well as all the partners supporting this effort. And we believe that it would enable a more efficient startup of the program.

Basically, with a clinical site already on board, already under contract, you'd be able to immediately begin to bring a product developer to them. And finally, this is ultimately going to improve our understanding of these antibiotics, their use, and yield us with additional data to help us know how to better use them and how they could be better advantaged within the clinic.

So in closing, BARDA is going to continue to invest in the development of products. We're going to continue to support CARB-X, that early stage pipeline, continue to be in the space of the advanced development pipeline and leveraging Project BioShield to begin to create more of a commercial market for new products.

This isn't going to change. We continue to see these challenges and we're listening and supporting you and everyone within this space. And in closing, I just want to thank Marina Kozak, Tina Guina, Brian (indiscernible), Oksana Sovanova, (indiscernible) Hawk, for supporting this program. They are the project officers behind this program and really are there to ensure its success. Thank you.

ERIN DUFFY: Thank you, Mark. Okay, it's always questionable to introduce your boss in a talk, but I'm going to do that. So now we're going to hear from Kevin Outterson. As you know, Kevin is a law professor at Boston University. He's also the PI and executive director of CARB-X.

He teaches health law and corporate law at Boston University and my personal goal is to be able to say a sentence in legalese with the same facility as he does in AMR.

KEVIN OUTTERSON: You know, you're working in law school. We can work that out. So my name's Kevin Outterson. I stand between you and lunch. You've heard a lot about CARB-X already. I'm not talking about CARB-X now. Here's my disclaimer. I'm going to talk about other economic issues within the industry.

So just think about systems. How do you know when one is broken? How do you know that something is mixed up? One way is to look at the outputs. Maybe the rate of output is too slow. If you have a machine designed to create one widget per hour, it's giving you one per week, so the rate or the

number or the type or the quality is different from what you're expecting or hoping for.

And we have some data for this on antibiotics. Surely, the approvals were down prior to 2002 and I'm talking about the article from CID that several people in the room were part of and everyone here probably knows, but then we also had issues with the withdrawals and the second article there -- either subsequent withdrawals or products that were discontinued because the companies couldn't support it in the market.

And so there is something going on with the outputs to the R&D -- antibiotic R&D system in the world. When you think about another way to look for whether the system is broken is that you look for smoke. If the toaster is smoking, it's a problem. If a patient is febrile, it's a problem. Something's wrong with the system.

In your car, you get the check engine light, right? And that check engine light doesn't tell you exactly what's wrong, but you know that something is wrong. You really need to go take it in and have it diagnosed and find out what's going on.

So I'm here to tell you that the check engine light is on for antibiotic R&D. Everyone here understands that, but just to use that language explicitly.

Some of the inputs going into the system, I have green check marks. I think we're doing a pretty good job on the inputs. CDC report 2014 said we need more gram negatives. Let me tell you, the preclinical pipeline has responded. The GAIN Act gave some clear direction.

The whole CARB process, the combating antibiotic resist bacteria program throughout the U.S. government gave clear signals and mobilized things within HHS and other agencies, all the things that were just discussed as well as everything the CDC is doing and everything FDA is doing, rolls into that CARB process.

All the basic research funding -- so, Dennis, thank you. All the things that are in preclinical that we see in CARB-X, a lot of it just wouldn't exist if 1,000 R01s had not been funded and everything else that NIH and other basic science funders around the world do. It's important, and so we've done some things well.

On the output side, I've got some red marks and some green and I'm going to cover a couple of these in some more detail. The clinical pipeline is fragile. Wes, is that still a good word for it? He's shaking his head yes, let the record show. The preclinical pipeline, I want to say, is actually working. And there's an article coming out, Ursula and myself and Andres Carlin and Alec Ingle -- should be out next week, I'm told, but I have a slide for that coming up in a moment.

The question is, what should physicians value? What do they want? I have a little bit of discussion about guidelines. And then more to the topic that I was given, what does the market want. And let me tell you, what the market wants is inhaled amikacin because that is the product that is driving the most market response in the entire antibacterial field today.

And the market caps for everybody else is pretty low and they have to raise money for commercialization, these companies, even after market approval. If they're popping a cork for Champaign, it's a very inexpensive bottle because they have to

save every nickel to commercialize and they're unable to raise with small market caps the funds that they need to do that commercialization to where is that money going to come from.

About half of the recent approvals in the U.S., new approvals of antibiotics, are being threatened with insolvency today. So there's a lot of things on outputs. I'm going to run through a couple of those, not all of them.

So the preclinical pipeline. It's must more encouraging than the story that Wes told on the clinical pipeline. This is from that forthcoming article in Nature Reviews Microbiology, supposedly out next week. But look at the little green dot. This is -- the WHO did a similar analysis but WHO required that every preclinical company release their data into the public.

And so a lot of the companies didn't want to do that and so we used the enable data, the repair data, CARB-X data. We collected it, preserving the confidentiality of the companies and then published the summary results here. So 46 percent of that preclinical pipeline is direct acting and within

that, 70 percent would qualify for the novel tag that Pew Charitable Trust -- we were talking about earlier.

There's a lot of excellent things going on in there and the vast majority of it also targets gram negative bacteria, so we can say that lots of good things are happening in the preclinical side, but Erin mentioned this. A lot of this is very small companies. The smallest, I think, we've had is three in CARB-X, three FTEs, and lots of nontraditional products with an article that John and I wrote together.

There's a lot of questions about the regulatory path for some of those types of nontraditionals, shortages of funds. The BARDA money for Phase 2 and 3 right now is the lifesaver in this space. So more encouraging, but still some challenges.

On guidelines, what do physicians want to know and when do they want to know it? I had to go back to a different impeachment era. We have -- guidelines may actually help physicians who are busy people and having to see patients every, I don't know, 10 or 15 minutes or less. I'm looking at the

clinicians, how much time you actually get with the patients.

They cut through the noise and you see this data from C. dif here and when the new guidelines came out, the sales move up. And then down below for oral vanco, you see that when the data is published, there isn't an increase, but when the guidelines finally came out several years later, there's a significant increase.

So we know this. Physicians do rely on expert guidance. They do rely on this sort of material. Let's get that out more quickly. Everyone, I think, here agrees with that.

On the economics for the companies, 17 public (indiscernible) companies, small companies today in the space -- it was 18 but (indiscernible) is bankrupt. The most valuable of them, I show here, their main product is inhaled amikacin. Melinta filed a 10K with the Securities and Exchange Commission last week that openly discusses the potential -- the grave potential of bankruptcy. Go read it and see the language specifically.

And several of these other companies

listed here would have stock prices below $4. In that sort of setting, they have difficulty -- that's the nicest word I can put on it -- raising the necessary funds to do commercialization. And so the market side, the market signals that they're sending, are very fraught in the system today.

So what could be going wrong? There's a couple things. It could be a bad signal. We could be -- have encouraged companies to bring the wrong sort of product to the market. If we were running a Soviet-era socialist economy with a five-year plan, that could be a problem. But if you have functioning markets, they send the right signals back -- that's the market system working -- that is the problem, I think, not so much that we're sending a bad signal.

The signal could be distorted. The companies misinterpreted it or (indiscernible) circumstances change. You feel bad for the companies that thought that some specific bug was going to be a bigger problem and five or 10 years into the program it turns out that it's not as big of a problem. That's not really the company's fault; the ground shifted under their feet.

You might have some questions about the (indiscernible) drug. We have plazomicin. And be those as they may, but if everybody in the industry is in the same boat, then it's really a system problem, not really a fault of any one particular team. And then finally, the market distortion which is where I think the largest issue probably is.

The market is not valuing the products that we actually need appropriately, partially because these products are designed not necessarily for just today but today plus tomorrow. So some lines of action, some ways that we can respond. We could improve the inadequate signals to physicians and I'm only going to talk about labels out of that list.

We've already had discussions about these others. There's some frictional things, you know, just delays in formulary option, delays in getting the diagnostic integration and the break points updated with good news lately on that. And then just the fact that the market is responding inappropriately and we cover two of those items in bold in the next couple of minutes.

So on the labels. So we have a couple

of labels that I'm just going to look through and the question I want you, in your mind, is what can we do to account for additional clinical information -- I'm not talking about microbiology, but clinical information -- in an LPAD environment in a way that could help move forward some of our goals and objectives here?

So here's plazomicin. They start off with a black box which is just based on the safety data, obviously. And here, this is not the label because the label is a package of all sorts of written materials, but this is the thing at the top of the label and this is really, when people colloquially call the label, they think about this.

And this is what they got, and obviously, it's urinary tract infections and they limit that with that really LPAD sort of sentence in the second sentence. And then at the bottom, something akin to a stewardship sort of moment and this is the main message that goes out to physicians and to hospital committees. Lots of data to back it up as well, but this is the summary that the FDA puts out.

Here we have for (indiscernible) you see something similar and I just want to not go through the whole thing again, but they do have the stewardship provision in there as well but notice the updates. So they went in with supplemental new drug applications. They got additional label extensions.

This is a drug that's actually making money. They can afford to do that, but that's obviously where we want everyone to go, is to come back with more data later. And the most recent drug on this list, approved only -- I think they've been in the market now seven or eight weeks in terms of actually available in the market, and here again, different community acquired bacterial pneumonia, but also with the stewardship sort of message.

And so my question is, is there a way that we could get some additional clinical information up in that part of this FDA materials, but in a way that is true to the science but also helps advance -- the way that we know the physicians are actually going to be using these drugs, because we don't really want them to be using the drugs, necessarily, for the conditions that are described on the previous couple

of slides.

And so this is just a thought experiment. It's just my idea to throw out into the room, but instead of a black box warning, a gray box statement that's based on clinical information. It's not sufficient for approval, but it's still clinical information to guide what you -- the sort of patients you actually think are going to use the product.

And maybe there's some way to do something there. I know that FDA surely has lots of questions and comments on this. I want to note that let's sunset it; give the companies some time to get this supplemental new drug, the label extensions worked on so it's not there forever because we don't want to disincentivize them to actually do that work, but sunset it. All right.

DRGs, diagnostic related groups. A clever idea from the Reagan Administration to try to reduce hospital costs, inflation in Medicare. It bundles all the things together that happens in a hospital. You get a single price. So antibiotics, if they're $1 or $1,000, the difference is that the hospital will have to eat the $1,000 and I believe

Sara said that antibiotics are expensive.

I still think these new agents compared to the oncology world or the orphan drug world, for somebody that cares for somebody who would otherwise die from -- I think they're still very cheap. But that these DRGs did, they did their intended job well. The drove down costs to Medicare.

They drove down the average length of stay, LOS, but then the clever hospitals discharged people quicker and so the Medicare had to respond with additional rules to fill in the gaps in the things that people were doing to respond to these economic incentives. It's a cautionary tale. Any time we lay out an economic incentive, somebody will follow it in a way that's unanticipated -- DRGs is an example -- and we might need to modify it as a result of that.

There's been some efforts, something called a new technology add-on payment, NTAP. Give two or three years. There's reasons why it doesn't work for antibiotics, because if they're not actually used in those first two or three years, it never gets baked into the DRG recalculation. And the companies themselves are asking for a carveout, either through

legislation from Congress or through the IPPS 2021 rule.

Go look at the most recent blog post from the administrator of Medicare, if you want to know more about that. But just to put it in perspective, this is daptomycin, allegedly the most successful antibiotic in the last, whatever, couple decades, and this is its launch curve to loss of exclusivity, and then we have Keytruda, okay?

So in most of these sales, these sales were largely in Part B because a clever thing that's not as well understood is that (indiscernible) did a lot of its sales in OPAT which got it outside of the Part A bundle, enabled them to sell, but even with that being marked out, they weren't exactly tearing up the world in terms of shifting volumes or prices.

The prices actually got something close to 2.75 percent increases from the beginning to the end, so they did have price increases. But you can see the overall effect on revenues is rather modest.

The last thing I want to say is that the social value of antibiotics is huge, and that was true in the ERG report done for ASPE, the Department

of HHS, or a part of HHS in 2014. The social value is greatly in excess of what we're paying for them now. Some of the work done for the UK (indiscernible) model at the University of York, has some out with this, what we call study.

These different ways to think about other values for antibiotics, namely the spectrum value. Everyone says do narrow spectrum, but you're going to get fewer sales. You need a premium if really what you're going to do is a narrow spectrum. And transmission, you prevent other cases. But how does the company make money on prevention of other cases?

Good luck with modern medicine without antibiotics. But who will pay for this enablement value? There's nobody that's going to step up and volunteer to do that. The industry, actually, is thinking about this in a broader level. Diversity. Choices are good. Clinicians would like to have two or three choices, not just one.

And the insurance value, the fire protections in this room, it will save our lives if this room burst into flames. They didn't make the

company or the workers who installed that or built that equipment wait until the fire started before they got paid. The optimal number of fires in this room is zero and yet, they got paid.

But for our companies, we put them on the shelf. We're very careful with the drugs and as a result, the companies are moving towards bankruptcy, so a lot of the things that I could talk about are well outside of the FDA's purview and these are my concluding remarks, summarizing what I've said before.

But let's advance the conversation, the pieces the FDA can help on. I'm grateful for your help and thank you (indiscernible) and John for inviting all of us me to be here today.

JOHN FARLEY: Thank, Kevin. I think we have a little bit of time before lunch for clarifying questions or topics that you want to get on the table that aren't on the table yet, so I'll invite the -- start out with the panel, invite you to put your tent card up on the side so that Erin and I can see you and take a few minutes for questions and discussion.

WOMAN 1: (indiscernible).

JOHN FARLEY: Thanks, John.

JOHN REX: (indiscernible) too slowly writing my notes. Dennis, the OVERCOME trial, how much -- what's the whole study cost of that project? (indiscernible) that I have -- I'm currently holding an email from somebody that says, well, we could do a 400- or 500-patient study for $2 million.

DENNIS DIXON: It's under $15 million.

JOHN REX: It's under 15. And the -- under --

DENNIS DIXON: Between 10 and 15 and it's closer to 10.

JOHN REX: And does that include paying for the people who do the data collection, the study coordinators, the --

DENNIS DIXON: Yes.

JOHN REX: -- site audits?

DENNIS DIXON: Yes. It is the most efficient of all of the targeted clinical trials that we have done. They generally run two to three times that.

JOHN REX: All right. And in that study, are the data being collected, are the data being audited? I mean, is this a pivotal trial

quality dataset?

DENNIS DIXON: It's not a pivotal trial. It's not --

JOHN REX: A distinction, the quality of it.

DENNIS DIXON: PPD does the monitoring and they make regular return visits with data quality. And they all did, so there were -- we also, I should say, we partnered with the combat network overseas and that helped us to identify sites to survey and from that site survey, we filtered down to only a portion of them actually had the numbers they could deliver.

And even with this, by the way, our screening rate is 1,000 screened for one enrolled. And only patients who get enrolled, does reimbursement go to the enrolling site. So that's one reason this is cheaper.

JOHN REX: So you don't pay for screening?

DENNIS DIXON: And there's also money to a local staff person to pay them and the coordinator there, so there's infrastructure support costs for that and so there's the combat site visited

the places, we site visited the places, then we did startup visits and then we do monitoring visits to them. So it's pretty close to what you would do in a registrational trial, but not -- a lot cheaper than what you do for an actual registrational trial.

JOHN REX: That's it.

DENNIS DIXON: If we'd spent more, we might be done, so -- and we do expect to be done within a year or by summer of next year.

JOHN REX: And the rule of thumb estimate for a 400-patient trial would be that it's $40 million. I mean, that's -- so you're saying you're about a third of the cost of a study of that size, because you're leveraging other resources.

SUE CAMMARATA: Actually, I had a question for Kevin. This is regarding your question around a gray box and I assume we'll get into this discussion later. You put that forth as a potential for the FDA, but my question is, since guidelines and guidances from professional societies are so well followed, especially in the ID world, why not a group of ID physicians, pharmacists, and not the FDA as far as the black box? Their remit is different. It's

really efficacy and safety versus use, to me, is a bit beyond that and that would need a wider input from a different group of folks, so that's my question is why could a gray box have to be in the label versus part of a guidance in more real time than what we're getting right now?

KEVIN OUTTERSON: So it's a thought experiment to see if people think it's helpful.

If we had our perfect, you know, really quick guidance system, then maybe we don't need those but I've heard from a lot of people that more information on the summary section of the label would actually help in market penetration and help with all the hundreds and thousands of decisions that people have to make with stewardship and getting on formulary at hospitals.

So I'm not trying to make any work for anybody. It's only if companies and the FDA think it's a worthy and helpful thing.

HELEN BOUCHER: So I'll just pick up on that. I think that having information in the label is important. First and foremost, it's information from studies that were done to a registration trial

standard and a lot of studies that we publish are not.

And that's not to say they're not important and they wouldn't be included in the guidance documents, but if people go to the trouble and I think one thing that wasn't said out loud, but I'll say it out loud, is we have at least three companies, if not four, who've gone to the trouble to do these CRE trials and screen many, many, many patients, spend a lot of dollars to get small numbers of evaluable patients but they're there, and those data are not in the labels.

And to me -- that's the problem to me as a physician is that they should be because I think that the payers and the pharmacy committees and everybody else will recognize that those data were obtained in the process of doing registration-level trials, if it's there. And that's just one -- my personal view, but I think it's important.

SUE CAMMARATA: Can I just make a response to that? I think one of the challenges is that for a lot of these trials, since they are descriptive, they're hard enough to get -- there are challenges to getting those published because they're

not randomized, regular trials. So to ask the -- again, I'm fully supportive, but then to ask the FDA to put stuff on the label that you actually are having trouble getting published because it's a descriptive trial, that's something we'll have to get to later on in the discussion is, it's a challenge which I can understand why the FDA has that issue.

JOHN FARLEY: Sure, I think Cindy was first. Do you want to --

CYNTHIA SEARS: Ann was --

JOHN FARLEY: Ann was -- okay.

CYNTHIA SEARS: I think I would say both of these approaches are likely complimentary, providing different information. The gray box would not be likely to provide sufficient context; whereas, a rapid guidance or whatever you want to -- words you want to attach to that, could provide more guidance. There is a way to rapidly publish results.

They are not peer reviewed, but the medRxiv system, whatever you want to call it, is specifically set up for the health sciences. Now, that may preclude review by some journals. I tried to look on the website this morning. I couldn't figure

it out, but the number of journals that will accept papers that are posted there has expanded greatly since that started. So there is a way. I don't know if the New England Journal allows that, but we can get that answer.

JOHN FARLEY: Since it's specific to publication, why don't we go out of turn and have Lindsey respond and then Pam and then John.

LINDSEY BADEN: No, I mean, I think that this group is very provocative which is the intent. I think that the, how to get quality information to the community is what we all want to have happen and have it happen quickly. And I think Kevin was trying to provoke that in how to think about different ways of doing is.

And the challenge is, what are quality data and what is the value of vetting of data and a positioning of data and completeness of data and then the temporal cost of that versus the need for it to be correct?

If we think that is a valuable parameter to sort of weigh, but not correct at the point where it's an eternity and so I think our

balances and ways to get information, I think part of what Helen was raising is the issue of also payers and other collateral groups are incredibly important and the data are not acknowledged somehow, then it may not be accessible even if we as a community think that it's appropriate.

So there are many metronomes we have to balance as we try to get information to the community rapidly and correctly, and bioRxiv is a complicated matter that is worth discussing at another forum.

PAMELA TENAERTS: So, hi everyone. So the issue I wanted to bring up is something that I'm sort of surprised doesn't come up more when I come to infectious disease meetings, and we do a lot of clinical trials work everywhere, so I'm not an ID person at all, but sort of, Rob Califf told a couple of us over and over that I would not want to have a disease that does not have a patient advocacy group.

Well, you're kind of in that group. You kind of don't really have an easy patient advocacy group and they can advocate for things and I've heard a lot of woe is us, woe is us a little bit in this community which I understand. It's frustrating and

I'm sure -- just sent my daughter a text.

Go get your flu vaccine. I'll pay for everyone for a drink of all your friends who goes with you, so they have herd immunity. But what I would like to say is maybe -- I mean, even in the outputs today, you talked about what do physicians want, but what do patients want? You know, sort of that question, I feel is missing here sometimes and I think -- I don't know if there are ways to harness them to -- there really isn't a disease that is just infectious disease that you could -- sort of like cancer, right?

They advocate for their -- and you don't have that, but to maybe organize a better effort around that. I don't know. That could behoove -- I mean, that could help you guys because you have -- you're missing voices, both for advocating for all the things you want economically and all those things but also in looking at your diseases and what matters to patients.

HELEN BOUCHER: So I'll just take a stab from the IDSA perspective. It's a very valid concern and one that we share. I think there are some reasons why we don't have the patient group that

breast cancer does, for example. Some of our patients can't speak because they're not here.

And the whole issue of drug-resistant infections is still somewhat complicated in that no hospital wants to be known as a center of excellence for antibiotic resistance. And any time there's a question of a patient speaking to the press, we have to clear it and then there's a whole process because that infection can't be obtained at a -- you know, it has to come from somewhere else.

So those are issues that are complicated. I would say that there has been some progress and IDSA has the faces of antibiotic resistance campaign which is a group of 14 patients and their stories and there is a big effort underway to grow it. But the fact that antibiotic resistance undermines a variety of types of medical care is really catching on and I think that's the good news.

There's going to be a big summit about geriatric infections and the problem of AMR and we're sort of working on that in terms of sort of collaborating with other groups to get the message across because if it's -- as the problem is impacting

our ability to do surgery and take care of these groups, it's becoming more real, but it's a huge issue so thanks for raising it.

JOHN FARLEY: Amy, did you have any comments that you wanted to interject at this point?

AMY LEITMAN: Yeah, sure. Yeah, you don't need one patient advocacy group. You need all of them. It's going to affect everybody, so they all need to be made aware. I mean, when I was preparing for this workshop, I come from a disease of basically one space and related comorbidities. So I started talking to all kinds of different patients.

I talked to, you know, somebody who's had skin and soft tissue infections. I talked to somebody who had pseudomonas UTIs repeatedly throughout pregnancies. I talk to somebody -- I talked to the friends and family of someone who was diabetic and died of a multi-drug resistant infections, so that was diabetes. I've talked to several cancer patient advocates. I've talked to a sepsis patient advocate. I talked to a neurology patient advocate.

So I cross as much of the spectrum as

possible because -- and there's no question it's something that most of the general public aren't aware of. It's something that I, frankly, bang on social media all the time about. My friends are just starting to get it, and it's been over a year since we lost a friend to an MDR infection, and it's like the lightbulb is starting to go off.

But in order to get the message out, the message has to be very plain and very clear and it has to go out to where the people are, and frankly, as much as we hate to joke about Dr. Google and Dr. Facebook, that's where they are. They're online. And when you want to find patients and build networks of patient advocates and networks for clinical trials, you go find them where they are, and they're online.

They're finding support online. If they've survived a critical infection, they've been through something incredibly traumatic and they're finding support from each other online. We had an incredibly robust patient network. We have two online forums for our patient. We have our own Facebook page.

Each one of our support groups, and we

have more than 30 of them, has their own private Facebook group in addition to more than 30 of them actually meet in person regularly. It didn't happen overnight. When we started, there were maybe five or six patient groups in the United States, one in Canada. Now we have one that's across Australia. We have one forming in England. We have one in the Netherlands.

I mean -- and you have to put the information out there in a patient-focused, patient-friendly manner, and that includes information about the antibiotics because we've been talking about labeling and labeling scares people when they don't understand what they're reading. They don't understand the datasets the way the medical community does.

So part of what we do is we bridge that divide with language so on our website we have a patient pamphlet. It's what our patients call their (indiscernible) bible. It's a 36-page patient pamphlet. It's in 11 languages now. There's a medication chart and it lists the most important side effects in plain language and it talks about the

screening that should be done and at what intervals to make sure that they're monitoring for side effects.

And that's talking to patients, but this is a network that has to be built and I know that we are short on time with this, for this kind of problem, but the messaging has to get out there and every patient advocacy group across every disease state and every patient state should be involved in this. We should be going out to every single one of them and saying, we're out of time, you guys.

This is going to hit you and it's going to hit you now and then it's going to hit your kids even harder and then your grandkids and if they need an appendectomy, good luck. And that's really how I put it to people. There's going to be a very high mortality rate for something like a simple appendectomy. It doesn't occur to them that that's a high-risk surgery but it will be.

JOHN FARLEY: Great. I think we're going to do comments from John and David and then we're going to break for lunch.

JOHN REX: All right. Well, and just to finish that line. A few years ago when IDSA was

trying to pick up cases to tell the story, there were a lot of (indiscernible), but you look at the really great stories and unfortunate stories like in the CDC's new report, the language that Wellcome Trust has developed about how to talk about this in cultures around the world -- it's everybody's problem -- and maybe, Amanda, it's time for IDSA -- it might work differently this time.

You tried hard before and I know how hard it was to find those patients. So my question is really for Dr. Nambiar. You put on one of your slides something that, I think it's a language issue and I want to be sure that we are all saying it the right way. You said there were three types of data packages. You said there was a standard approval, two good sized trials.

There was a limited use approval where the wording was one good sized trial. And then an LPAD approval where you used the word small. Now, I'm not asking you to define small, but I think I have heard some blurring of the words limited use and LPAD and I think that's going to come up and I wonder if you might take a minute or two and just be -- explain

it to us in a way that we can all use the words correctly.

SUMATHI NAMBIAR: Sure, let me try. So as our thinking has evolved and as drug development has proceeded over the, say the last decade or so, early on we just had the standard development programs. We had two trials per indication. And we did not have the LPAD authority, right? LPAD didn't exist.

But we already were providing guidance on how smaller development programs can be conducted and that they would suffice for approval if safety and efficacy was demonstrated, as long as the product had the potential to address an unmet need. So we had that information in hand.

Then we were advising companies that they could potentially do smaller programs and smaller programs could be a single trial with supportive evidence which had come from either a Phase 2 study or -- and/or in vitro studies, studies in animal models of infection.

So if you look at some of the products that were approved since 2015, and I think

(indiscernible) might have been the first one approved under the paradigm, it is a very different approach and there was language included in the labeling which said that only limited efficacies and safety data available -- I don't have the exact verbiage, but something like that.

And then subsequent programs came along which also had a single trial as the basis of approval and they got the limited use language. It's very important to understand that each of these drugs, there was a potential drug to address an unmet need so it just wasn't a mechanism for people to get away by doing one trial for a standard indication.

And then we have LPAD, within the last couple of years, so the difference between the two is for it to be an LPAD drug, the population for which the product is being approved should be very well defined and a limited patient population and it would still be a single -- could be a single trial but I think the key is defining the population.

So it has to be very well defined, limited patient population in whom, because of the small database, there are a lot more uncertainties.

We have a little more flexibility in the benefit/risk considerations. So that's where it gets a little complicated, so there is limited use but there's also limited use with LPAD and I think what really is key is defining the patient population because it is really a limited population antibacterial, antifungal drug pathway.

So it's really in defining the population, but the underlying requirement that you have to have at least one adequate and well controlled trial does not change. So just want to make sure that that's clear and I think early on, in the early days of LPAD, there was a lot of confusion that one doesn't need to meet the statutory standard's effectiveness, and that's not true.

You still have to have an adequate and well controlled trial along with other supportive information. What's different is that the population is very well defined and it should mean something to clinicians. We have seen attempts at defining patient populations that is really not relevant to clinical use, so one has to be able to define that so it means something to physicians who are treating these

patients. They can identify those patients in whom there is no greater uncertainty but the risk/benefit calculus might be a little different. Did that explain? Thank you.

DAVID MELNICK: Yeah, I wanted to come back for a minute to the subject of stewardship. I don't think there's anyone in this room who does not believe in careful and targeted use of new antibiotics. We work awfully hard to make these drugs and the concern is to maintain their utility for the longest possible time.

But too often, from the perspective of a drug developer, stewardship programs really come across as cost containment and I was wondering, Sara, if you might address whether you think there's a role in stewardship programs for careful instruction within the hospital setting and potentially outside of the hospital about the appropriate uptake of new antibiotics?

I mean, for example, you look at the data for (indiscernible), I worked on that program, and the slow replacement of the polymyxins by the beta lactam and beta lactamase combination. It's

incredibly frustrating.

SARA COSGROVE: I think first, stewardship programs probably did originally come about -- and I'm talking 20 years ago -- as a cost containment mechanism, largely conceived by pharmacies and lots of discussions of picking the cheapest thing to put on formulary and that kind of thing. But I would really say that that really shouldn't be the conception of what stewardship is now.

And I do think that has evolved. I do not think that most institutions consider their stewardship program as having the primary goal of cost containment, but rather that that's a possible good side effect of a stewardship program now, and so I do think that we should try to reframe that notion that stewardship is really all about cost containment.

I, personally, don't think that the new drugs that are for gram negative resistant -- gram negative organisms that are highly resistant are expensive, but if you look at them compared to their antibiotic friends they are expensive, relatively, and I think we should think about, from a societal stand point, redefining that because if they can save lives,

if they can get you to a lung transplant, if they can do good things, then we shouldn't keep saying that they're expensive, but we still have to say they're expensive right now because they are more money than pip tazo and I think we should think about how to reframe what is the worth of these drugs.

And as I said in my discussion, I struggle with the drugs that are pretty -- not to pick on anything, but omadacycline is expensive for what it is approved for, given the other drugs that you can use for those indications, but it has a lot of potential, as do all these drugs. (indiscernible) may have potential for abscesses.

There's all kinds of exciting things that often take us five, six, seven or more years to figure out. And we also need to determine how do we make sure that we're not losing drugs that may have excellent value and importance but we just don't know what it is yet.

But I do think that to say that we have to rely on the existing market approach where the hospital puts it on formulary and their use is encouraged is not necessarily optimal. I don't know

if I answered your question, but, just some more comments.

JOHN FARLEY: Great, thank. So great presentations. Great discussion. We're running a teeny bit behind, but we will catch up. So we're going to take a lunch break until 1 p.m., so 1 p.m. be right back here for an industry round table that will definitely keep you awake.

(Break)

KEVIN OUTTERSON: Great, thanks. So, great presentations, great discussion. We're running a teeny bit behind but we will catch up. So, we're going to take a lunch break until 1 p.m. So, 1 p.m., be right back here for an industry roundtable that will definitely keep you awake.

(Break)

MODERATOR: But I'm turning the chairs over to Kevin Outterson and Amanda Jezek. So, take it away.

KEVIN OUTTERSON: So, thanks for coming back. Amanda and I are pleased to have this panel of industry to be able to speak. The thought, if you turn and look at the program at the top of Page 3 is

that each of these folks are going to speak for about five minutes in the order shown. They're going to stay in their seats so that we don't have a lot of time shifting up and down.

And after that group is done, then Amanda and I will -- we may have a couple of questions of our own and then we'll moderate some questions from the panel and maybe -- I don't know, John, if the room as well after that.

So, that's the plan. We're going to start with Ryan. And let's hear from what the companies, especially the smaller companies, have to say about what they need today.

RYAN CIRZ: Great. Thank you, Kevin. So, as a reminder, I'm Ryan Cirz, formerly from Achaogen. Just as a disclosure, I am a paid consultant for Cipla, who markets plazomicin under the trade name Zemdri in the U.S. But, obviously, all the opinions I formed were really my own at my time at Achaogen for, basically, 16 years watching a molecule go from first synthesis through approval last year.

Also another disclosure: I'm a little bit of an outsider, and I was honest with the panel

about that, that I'm not what I would call a trialist, the person that understands the nooks and crannies of every inclusion and exclusion and how that can affect the outcomes.

I am a scientist and enjoy applying first principles to a lot of the problems we're solving, so, hopefully, can add some value there. And obviously I was in the rooms on the core team as we were thinking about things like superiority mortality trial, so watching the teams struggle with those issues.

You know, as an advocate for the field and continue to be, despite my non-employment in the field currently, you know, I have to say just as an observer, there's been a clear focus from my perspective on the patients for the last 15 years in that no matter what I say, I think there's been a lot of movement as one team to actually make progress.

I mean, there's always frustration and there's always restrictions on what we can do, but overall, if I look back 15 years ago, I think we've certainly advanced quite a bit. And maybe we're not quite at perfection but I'm pretty proud of some of

the work that was done in combination with the companies, our partners in the government, like CARB-X and BARDA especially, and obviously with the regulators.

So, my early years were sort of formed around the -- the biocreep thesis, which I think is a strong thesis and a concerning one, but it was also the era, as a scientist, where I first heard the phrase “placebo-controlled HAP/VAP study” uttered, and I think we’ve evolved a long way from that sort of line of thinking.

Achaogen was one of the first small entities to enter forth with a drug that we thought was for a severe unmet need. Our foundation was really centered on gram negatives. Plazomicin just happened to be the first of the four programs we put through INDs in our history that went into the clinic, and we were really challenged by the idea of being able to attract the funds to run a 6,000-patient, you know, total Phase III program that eventually led to the Care Study, which was our mortality superiority study, meant to be registrational and run predominantly in places like Greece and Turkey, where

the rates of KPC Kebsiella were almost 40 percent at the time. This was several years before any new agents were approved, so Colistin was essentially standard of care.

There's a whole workshop dedicated to the challenges enrolling that study that I don't want to dwell on too much because it's pretty well-documented. As a scientist and sort of an advocate for the space and wanting to see your creations be studied in a rigorous way, I think obviously the frustrating challenges were things like the Apache Range issues where you had patients that were either too sick or too healthy to be entered. That was a big challenge.

Ultimately, it was a superiority study for severe infection, including pneumonias, but obviously having -- not only having cultures but having non-polymicrobial cultures to get a confirmed CRE was a big challenge.

But the most frustrating to me as sort of a long-term scientist in the space was the emergence of Colistin resistance during the study and that forcing -- not forcing but enabling the opening

of an open label cohort, which to me as a scientist is the ultimate test -- is basically, again, that we're year before AVYCAZ's approval. You've got Colistin-resistant CRE in an open-label cohort. And one of the bigger challenges, which I fully accept, again, not being a trialist, but it was frustrating to watch that data be largely ignored at later stages when it was being evaluated by advisory committees, etc., because of the lack of a control.

And I think that's really influenced me as a scientist and a developer to think about the fact that that's just not going to happen. The only way we do superiority is if we have inferior therapies on market, and there's effectively that last chance of showing an open label, this is what happens, didn't really support any sort of data or approval -- it's a time to move on. That said, the Tier B, what we call the Limited Use Indication appears to be open. And it looks very clear to me as someone that would have to take quite a bit of risk and spend 5-7 years of my time to get something back in the clinic as a viable path. But there are clear consequences in the marketplace that I think we just have to think

through, and, again, just sort of serving some of my peers.

Obviously, the study itself I think was required to sort of open the discussion about doing limited population development. So, there's nothing you can do to change that history. But if we were where we are today then, we would've been to market three to four years earlier and had saved between 30 and $50 million.

If we ever got these drugs to where they need to be, which is peak revenues around $300 million to make the enterprise work, that's over a billion dollars in money that I lost for my investors in that delay. So, then you have to look at the up side. And, of course, the publication -- I'm sure the team is incredibly proud of in the New England Journey -- Lindsay stepped out. But ultimately one of the challenges is that data from a severe population such as therapeutic drug monitoring, which didn't occur in our standard NI study, appeared in the label for a CUTI drug. Probably because it's really important to inform when you're treating severe populations, but this hybrid sort of issue of a standard trial with

this descriptive data managing its way into that label with that context I think set some challenges for the team after the launch.

And then, finally, there was a comment earlier about dosing that's really interesting and it may be unique -- and it was Sarah's comment -- to the way we developed. Because we designed the drug to be able to treat things like HAP/VAP, the dose was actually set with that in mind. Now, when we did the supportive study secondarily, the UTI study, to provide the safety data for that same dose, you don't change the dose.

And so when you actually show up to market, you can imagine the dose that's appropriate for HAP/VAP in reality approved for UTI. And so I think as we think through of people doing this prospectively, which we did not, that's something to just think about with the new unmet pathway.

KEVIN OUTTERSON: I didn't warn you that I had my timer going, which, you actually finished with 27 seconds left, so I appreciate that. And I guess Manos will take your 27 seconds.

MANOS PERROS: Yep. And also those

from Sue and the others. So, Manos Perros, Entasis. Once again, thank you for the opportunity to participate. Let me start my timer and then we can compare.

So, I will start by disagreeing with Kevin. I agree with most of the things, probably everything else that Kevin says, but actually I don't believe that the system is broken. I think what we're witnessing is a change, a very rapid and radical change in the way in which antibiotics are being used. And that's because we've been successful as a community in inventing, and developing, and commercializing good, safe, effective drugs.

And I'm thinking of drugs like Cubicin, I'm thinking of all the carbapenems. And if you think back 20-30 years ago, when these were not available, it was a very different picture.

So, the place that we are today when we're thinking of what is clinically relevant for a clinical trial or for a label, what is clinically relevant was on some of the slides that were shown earlier today. The WHO, the CDC do not call UTI or HAP/VAP, the medical need. The medical need is in

drug-resistant pathogens. And yet our labels speak to polycyte indications.

Now, these are important -- the points that Dr. Nambiar made -- you can't extrapolate from the test tube to a human being. But also you can't extrapolate from one bug to another or from a drug sensitive to a drug resistant. And without having the solutions -- I introduced myself earlier, I'm a chemist -- we need to find the solutions that would make our labels more relevant to the way in which antibiotics are used today, which is for a far more targeted patient population than we're used to.

I think Dr. Cosgrove showed earlier, data from her own institution, 30-40 prescriptions. These are not the thousands that drugs written with antibodies would treat. These are much smaller numbers. And there comes the challenge: How do you actually trial the kind of patient that needs our treatments today? The kind of patient who failed Daptomycin, who failed carbapenems?

And I believe that the solution has got to be scientist. We need to dig into the science and we need to think as scientists, which is what we are

today, and put the clinical data in the context of the microbiology, put the microbiology in the context of the mechanistic biochemical data that we have, and put the whole thing together when we're considering how a drug is going to be labeled, how a drug is going to be licensed and offered to physicians to use.

I think the agency does an amazing job pooling the data together from each section. And for those physicians who bothered to actually read the entire label before they decide to use an antibiotic, they will find all the information that they might wish to have and make the connections. But I believe we need to do a better job at helping them make that connection.

Where there is an outcome where physicians spend almost an hour trying to cut data from 45 patients through four different ways to make sense, and there is no connection back to the preclinical science to try and put in the context -- I think we're missing an opportunity. When looking at microbiology and we don't make the connection backed by chemistry to interpret data that might not be clear, we're missing an opportunity.

So, I'm calling for a rethink of how we use the totality of the scientific evidence, clinical and nonclinical, within the boundaries of what the agency has to deliver to get labels that are more relevant for the way in which the drugs are going to be used. We heard numerous times today that this is important. This is important because it will drive use, this is important because it will drive formulary inclusion, this is important because it will drive pricing differentiation. Nobody compares modern oncology treatments today with the price of chemotherapy of 30 years ago. No one. And there is a good reason for that -- it's because the labels are actually very different labels.

But we compare today's modern antibiotics in price to the antibiotics that have been on the market for 30 years, for which their (indiscernible) costs have been amortized and which cost pennies to produce.

So, it's important that I think we have that conversation. I think as an agency obviously your role is to regulate, but by regulating you're also driving the way in which we, as developers, do

our work. And I think it's important that you help us do our work in a way that's going to be more relevant to what patients need today. I'm giving you another 25 seconds back.

KEVIN OUTTERSON: No, I think we're good, thank you. Not all the companies that are going to speak today are small companies. And I think Nick is next.

NICK KARTSONIS: Yes. So, I'm from Merck, as you heard earlier. And today I was going to talk about the challenges in doing difficult to treat studies such as HAP/VAP. HAP/VAP, as many of you know, is a very common condition and it's probably one of the conditions that we probably want to have these drugs available for to treat patients who need the most. And, in fact, I mean, I think we can all agree that since the 10 x '20 Initiative has come forth, we've now had 14 new drugs come to the market, which is fantastic. But there are few companies that have actually been involved formally in actually doing studies in HAP/VAP.

Streamline Development has afforded a quicker path to do studies in UTI and IAI. Of the 14

drugs approved, I think there are five that have done HAP/VAP studies. And I guess fortunately or unfortunately, depending on what your perspective is, I've been involved with three of those five studies, so I figured I'd share with you a little bit today about what we've learned regarding sort of the lessons learned and the challenges that are associated with those, to help sort of form a broader debate on the particular topic at hand.

On the surface, HAP/VAP's a great indication, right? I mean, there's a lot of cases that you see. Over 150,000 per year in the United States. My marketing colleagues salivate over this indication. This is the indication they really want because it shows severe infections. But if you actually look at the review of data from 2006 to 2010, before these companies started doing it, the average recruitment time for these studies was on the order of about 3 to 3-1/2 years.

So, there are many challenges as to why companies kind of shy away from this area, putting aside all the issues around diagnosis of pneumonia. Obviously, the fact that -- we've actually done a

pretty good job, within infection bundles and infection control, to reduce the number of cases of HAP/VAP, and as a result of that there's been less cases of HAP/VAP that are easier to identify in particular trials.

And as you had heard -- I think it was Helen who said it better yesterday -- the market research we get when we seek out investigators is "No, thanks. I don't want to be the center where I enroll the most patients in a HAP/VAP study." And so that's really something that you have to keep in mind in terms of that as well.

The FDA guidance has been great for HAP/VAP but there are still challenges with that. We talked about the 24 hours of antibiotics, the need for a Gram stain, if you're going to do both HAP and VAP, they need to have 50 percent of your patients in VAP. These are all necessary evils but they do come at a cost in terms of recruitment and what have you. Consent for ventilated patients is not easy. We've tried early consent but that didn't work very well in terms of that. The different regulatory differences between the U.S. and Europe -- you all know about

that. But the biggest issue probably is cost.

So, of our three studies, two of them were outsourced and the cost of those outsourcings were $130 million each. So, just the outsourcing of it. If you add in the internal resources, it goes over 150 million. The one study we did do in-house cost $40 million. So, it's a lot easier to do it in house but if you're a smaller company, that would be very difficult to help make that work.

So, we did three studies with Tedizolid, Ceftolozane/Tazobactam, as well as more recently with Imipenem/Relebactam. I'm going to share with you some statistics, so hang onto your seats here. Each of these were sample sizes of 536-726 patients. Each study had at least 200 sites involved with it. And the total recruitment for each of these studies, the mean was 47 months, so four years. And that was 42-53 months to get those studies done from first site ready to last patient, last visit.

U.S. recruitment was 4-8 percent in these three studies, despite having over 30 percent of the sites allocated in the U.S. The actual patient site per month was .05 patients per site per month,

which over the course of the studies, only 2-3 patients per study.

Screening randomization at best was 10:1. And the monthly recruitment was on the order of about 10 patients per month -- of site per month. And you have to deal with all the issues like drug supply challenges that you often face with the comparators. Each study had an average of two of those study issues on top of that.

But we learned a lot, so I want to also not just kind of be doom and gloom. I figured I'd share with you some of the lessons we learned from that. First is we did try using a clinical trial network in Europe. It was really challenging to get them on board contractually, but when we did, even then recruitment didn't really come up. It was one of our rescue mechanisms and it didn't really help us that much in terms of that.

The long IRB times also makes it hard to get started. And you're often having issues with different IRBs telling you different things, and trying to manage that across a large study is never easy.

We did almost all of our recruitment in Eastern Europe and there's a lot of reasons for that. You heard about the less prior antibiotic use. But another reason is those patients there, their standard of care is not a carbapenem. So, everybody's getting something that's good and above what their normal standard of care is so it's easier to recruit in those particular places.

It's also cheaper to do the studies there. Our closure site rate was on the order of 30 percent. So, you know, if you're going to do these kind of studies, prepare for rescue sites because I think they will go a long way in terms of that. We strongly implemented 24-hour around the clock at each of our sites and we actually paid for people to be available. Because the patient usually comes in on a Saturday night, and waiting until Monday -- too late in terms of making that work.

We also had a fully committed recruitment team at headquarters, which, basically, their job was to do things like refreshers, and regional meetings, and repeat site visits, newsletters, gratitude messages, inspirational

tagline. We had it all, to try to get people... Every time somebody would enroll a site, we'd get down on our knees and thank them for doing that because it was always a major accomplishment to meet that in terms of that. So, it was a big issue in terms of that.

I'll just close by saying that there were two other things that I would plan on. One is that know your investigators. Make sure you're finding the right investigators in your institution because they're not always the infectious disease doctor. In fact, I would tell you they're never the infectious disease doctor, or rarely the infectious disease doctor.

And the final thing is expect site fatigue and data overload. Sites get tired so they will go on holidays, a little bit of breaks. They need it just to kind of get on top of that. So, in the end, we completed these three studies -- and there's my timer, but I'll just leave one more message if that's okay and then we'll go with regard to that -- which is that it does differ whether or not you do a VAP-only study versus HAP-plus-VAP.

VAP-only -- our mortality rate was 27 percent, actually. HAP and VAP, our mortality rate was 20 percent. But it was because it was 10 percent for HAP and 27 percent for VAP. So, in the end, we were able to make it out in terms of that but that needs to be balanced in that regard.

And one of our studies, of course, as many of you know, we presented ID Week. We met on the FDA endpoint but we didn't meet on the EU endpoint so we are not moving forward with that approval going forward. So, I'll just close on that point.

DAVID MELNICK: Nick, you're (indiscernible) from a big company to a small company and -- does the 27 seconds still move on? So, we are a small company and I think the key points that I wanted to raise is whether or not we can do a better job in terms of both time and cost efficiency by making use of networks and potentially platform trials.

So, our Phase III compound is an oral carbapenem that's currently moving through its pivotal trial. And we have a Phase II program, a DNA gyrase inhibitor that's being developed specifically for

patients with pulmonary manikin faction. Being one of those small companies where everyone wears a lot of hats, efficiency is just key. You know, we don't have the luxury of an endless timeframe and endless resourcing.

In terms of trial networks, these two trials pose a very, very different challenge. The Phase III compound -- again, in CUTI, we've customized the trial but basically it follows a well-described path. There are numerous investigators, the CROs have experience, we know the trial sites, and there's a clear path to follow.

The second candidate is going down an untrodden path and we've had the challenge of developing a regulatory pathway, and we thank our colleagues around the table here and in the NTM community who've helped us develop that pathway. But, again, patients are uncommon, they're difficult to identify, care is highly concentrated in the hands of a few investigators, so it's a very different situation in terms of potentially utilizing a trial network. But that would seem to be the sort of disease entity which would be very well-suited to the

development of a platform trial.

In terms of platform trials, you know, we've seen wide utilization of platform trials for targeted therapy in the oncology space, and even though antibiotics are perhaps the prototype for targeted therapy, we've not really made much use of that approach in our trials. You know, we can potentially utilize an adaptive design both to explore the potency of individual candidates and potentially move toward combination therapy downstream. And, you know, I think that's going to be increasingly important as we move toward the use of combination therapy for suppression of treatment-emergent resistance. So, I think there's a great opportunity here.

In preparation for this meeting, I pulled together my Spero colleagues and sort of asked them their opinion about this idea of utilization networks. And I was surprised that there was a fair amount of pushback. The first priority that was raised, and maybe it's off target for this meeting but we've certainly discussed it so far, is that fixing the efficiency of trial design and delivery isn't

going to make much difference until we fix the marketplace, that we need a new commercial model. And until we do that, we're going to have trouble.

There are certainly some good precedents for these trial networks in the AI space -- the ACTG, the TB Trials Consortium. And in addition, as an example, in terms of antimicrobial surveillance activities now, multiple sponsors have gotten together to use a common system where they share data from a single vendor. So, certainly we can learn to play together in the same sandbox.

But, you know, despite -- you know, as others have pointed out, despite the fact that we're really focused on the activity of these novel compounds versus resistant pathogens, we're still stuck in the world of doing indication-based trials and there, a master protocol could potentially be of great use. You know, we go through this exercise with every trial of reinventing the wheel. We go through the same exact steps, We go to CRUs -- CROs that do feasibility studies. You know, based on their last trial, they charged us an arm and a leg. My number for comparison is that about 40 percent of our total

trial cost turns out to be CRO cost. So, finding ways to share that across sponsors would be very useful. You know, there's the obvious benefit of decreased cost and time.

In terms of drawbacks, the obvious one of confidentiality and IP, the risk of antitrust inclusion issues being raised if we join forces to work through a platform trial. The obvious intercompany competition for sites -- what do we do if there are two patients in the queue who are doing similar trials?

Probably the biggest concern was the concern about increased bureaucracy -- that interposing another level of administrative oversight between the sponsor and the site would be difficult. I think that the quote I like best from our pre-meeting discussion was, quote, "The idea of a central CRO makes me absolutely crazy." So...

So, I think the last point -- no offense to anyone sitting at the table -- the existing networks in our space, ARLG, excuse me, Combat Care, you know, the IMI networks have been cumbersome to use. They've been slow. There is a lot of

administrative bureaucracy involved. And as we move forward toward looking at new networks, we need to find ways to make that more user-friendly.

RIENK PYPSTRA: You can leave it on. So, I'm Rienk Pypstra. I have indeed some also 25 years of experience in developing drugs since working on new formulations for Augmentin in the mid-'90s. And, yes, things have improved significantly since, so that is the good news.

But let me first address one of your points. I don't have unlimited resources either, and I am competing with my colleagues in other therapeutic areas such as cardiovascular and oncology, who can do more with more money than I can. So, it is important for us as well to get this environment right.

But, as I said, the environment has been improving but it has been improving at different paces in different places in the world, and that is a topic that I would like to highlight here -- that doing a clinical development program is an expensive endeavor and you want to make sure that whatever you do suits as many regulatory authorities in the world as possible.

Now, again, there has been good progress, and the FDA and EMA in particular have come together. Their guidelines are not identical but they don't contradict each other. Still, there are some problems in the sense that the endpoints are not the same. And so you're supposed to take two endpoints and you won't get a statistical penalty for testing two primary endpoints because each one will look just at one, but you get into difficulties that the same study, as Nick just alluded to, the same study is acceptable for one area and not for the other area.

It was still one dataset. And that is only for Europe and the U.S., but we also have difficulties in convincing other authorities, and the big ones are China and India, Japan. Those are the big authorities to negotiate with. But we are also submitting in hundreds of countries all over the world and that is a typical big pharma problem. Small pharma companies just don't have the resources to do it. But for every agency, you have to submit a file that has different formats and you get different questions, and some questions are more relevant than others.

But coming back to the design of such a global program, ideally, you make one program that works everywhere but then you need to implement it. So, imagine that you found a way forward, you have a study design, it is accepted by EMA, it is accepted by FDA, it will probably be okay for the other ones. You start to implement it, and then you see that it takes you about one year to activate the sites in China. And you have all the practicalities that the pathogens that you're connecting in China and India or any blood samples, you cannot get them out of the country. No central lab possibilities. Again, practical issues that make it pretty difficult to implement good quality data.

Now, we saw this morning in the presentation as well, and I was fascinated by that presentation -- there was some stuff that I really didn't know, but it does resonate -- the pathogens are not the same everywhere, the resistance patterns are not the same everywhere. And what was not mentioned, the patients are not necessarily treated in the same way. Sometimes they get different antibiotics because different antibiotics are approved. But besides

antibiotics, there's also a standard of care. What do they get besides the antibiotics? So, that brings a lot of background noise in those trials that you're trying to do because you have to do them globally in order to be able to have a single program that works.

So, given all these difficulties, the question is -- and one more point I wanted to make about difficulties. This is just for the standard antibiotics as we know them today. IF we go to the next generation of products with novel mechanisms of action where we don't even know whether an MIC is predictive of what happens in the patient, you can imagine that the expectations from the regulators will be even more widely different and it will be even more difficult to test -- to demonstrate something homogeneous and meaningful scientifically.

So, what would we want to have? Well, first of all, the science comes first. We have to make sure that whatever we demonstrate in a global trial can be interpreted. And so as we heard this morning, that it is important that when you do your clinical trial you have to limit yourself to one body site, I would argue that you would also try to

homogenize the type of medical setting where you're in. And certain settings, it probably will not matter too much whether you do the study in Southeast Asia, in Africa, or in Western Europe, or in Northern America; but in other settings, the standard of care is going to make a big, big difference. And so I think we should try to make sure that, from a scientific perspective, we have a homogeneous population. We have homogeneous pathogen description, homogeneous type of infections that is also by body site. But from those datasets we have also to interpret them cleverly and smartly.

It is not because there was no U.S. patient involved in a certain study that the study would not be applicable to the U.S. situations. So, we have to dare to extrapolate from the data. And sometimes we'll have to generate additional datasets -- PKPD datasets, additional surveillance data, in order to be able to make that translation from the clinical data that have been generated, that have demonstrated something, to extrapolated, to the relevant populations. That is about interpreting the findings and then coming to that, how do you interpret

that? How do you put that in a label?

Is it important to have in the label just what you did, what has been studied? Yes. But it's also important to say what can be deducted from that. The agency has been working for months on those data. They have come to a good interpretation, and in case of doubt, they have a scientific advisory panel meeting to give additional guidance.

The physician who is facing the latest new bug has got a couple of hours or a day to try to find out what might work in that situation. So, it's not comparable. The agency is in the best position to do a meaningful interpretation of that data and to translate that ideally in a label and, of course, within the constraints of the current code of federal regulations.

But the gray boxes that Kevin mentioned I think are a great idea. You could give your indication based on the data that has been generated and then interpret within the constraints and within the risks that you have identified how this drug could also be used such that these other uses that seem perfectly appropriate to people who are well-versed in

the art would not become dismissed as just “Oh, well, that’s off-label, we cannot reimburse that.”

So, the dichotomy between being indicated and off-label, that is a problem, and if some of the off-label is perfectly appropriate -- and if it is appropriate, it has to be considered somewhat like an on-label indication. Thank you.

KEVIN OUTTERSON: Thank you. And last for the opening statements is with Sue.

SUE CAMMARATA: I’m Sue Cammarata. I’m the Chief Medical Officer at Melinta. And I came onboard at the company about six years ago when it was going -- transitioning from Riesbeck’s to Melinta and how I met Erin Duffy. That was when Riesbeck’s was recapitalized. So, for the last six years I’ve been there.

We went from 30 people at that time, around that -- and now about a couple hundred people with four products. So, Melinta has attempted to roll off products. There’s been a lot of discussion about that -- to be able to consolidate, so that’s what we’ve attempted to do.

I’ve been involved in anti-infected

trials for 20-plus years. I started out -- my very first study was a HAP/VAP trial for Zyvox way back in the day when it was in Phase III. And I have been affected by this rollercoaster that has been antibiotic clinical development. So, for the folks that have been here during that time, you've seen it wax and wane and it almost died once before. So, most of my comments have been -- are going to echo what other people have said to some extent.

Drug developers, all of us, have some understanding of what clinicians need. We're clinicians and we hear from clinicians, so I think we understand what you guys want. But, as been mentioned, we have to design clinical trials that meet the regulatory needs globally. So, we have to meet the requirements to show efficacy and safety. We also have to think about standards of care that may be different in different regions. So, those are all considerations that we have to take in that makes it very challenging for the companies.

In the days of big pharma -- so, when I did Zyvox, that was Pharmacia, which wasn't quite big pharma but got sucked up by Pfizer -- in the days of

big pharma, you had a lot more money and you could remember that there could be many trials that you could do for registration as well as post-approval.

With the exit of most of big pharma, it's now all the small pharma biotechs. And I think almost every single product that's been approved recently came from some small company. So, they're doing all of the antibiotic discovery and development.

But that takes people, and time, and resources, and when I say people, time, and resources, that all equates to money every single... So, I've tried to cut down saying money in my talk but really time, and resources, and people equals money. And they're not often internal to a biotech. So, if you have a small company, as been mentioned, you have companies that have 30 people, five people -- they may not have an in-house toxicologist, they don't have an in-house pharmacologist, they don't have a formula person.

So, when I was at Pharmacia, I could turn and say, hey, let's have a project team where a bunch of people come. When you're in a small biotech, no, you have to go find those consultants, you have to

find the CRO, you have to find the contractors that are going to work for you. So, you don't have the personnel in place to easily do all these studies.

So, we've contracted those. You may only -- you'll see one study done at a time. You do a HAP/VAP trial that may cost you $100 million if you're a small company, depending on the number of patients you enroll; you can do a UTI CAP trial that will cost you $50 million, hopefully, not too much more than that but it all depends on the size of the trial.

And this is the cost of doing trials where there is agreement in how to do the trials. So, we're not even talking about doing osteo, we're not talking about prosthetic joint -- just to do UTI and HAP/VAP trials -- their guidance on those approach. (sic)

So, do I want to do another UTI trial? Do I think we need another UTI drug? I don't think we need the indication, but for a small company with no money who can only do one trial at a time, you're going to put a bet on something that you know you can do that there's a clear guidance it can get approved, and that you can probably successfully complete it.

And maybe in the past get investors to invest.

So, we're also going to talk to some extent about, you know, all the issues of things we -- how we can go forward. But I would point out we're not in the big pharma era. We're not going to be 15 trials for 10 indications. It doesn't happen like that anymore. As you may remember, it has happened like that before. So, we have to be creative within the confines of regulations and statistics, but we're always up against the specter of time and money.

We have the tools. I think Dan's going to talk about stats and how we do various things. A lot of this has been discussed in many venues before, so we have some of the tools. And if you've been in the rare disease space, there are tools. The rules are no different for rare diseases as there are for antibiotics. So, they're not getting a special dispensation particularly.

So, in the words of the Rolling Stones, you cannot always get what you want. We have to be honest. It is unlikely that one or two registration trials will answer all the question that every clinician has about an antibiotic. It's just not

possible within the construct of a non-inferiority trial, which is what we typically are dealing with. It's very rare to be able to do a superiority trial.

I think everybody here that antibiotic development is currently imploding. We're not going to solve that today. But the economic reality that is killing antibiotic development is behind many of the challenges that you -- that we're going to be discussing today. Pharmas having difficulty funding clinical trials. And I also have heard that academic investigators are seeing money drying up. They're not getting money for grants, they're not getting money for investigational trials that they used to be able to explore, some of the questions that were out there.

So, I'm looking forward to discussion options regarding antibiotic clinical trials. But I'd also like to understand the options to gather and disseminate information that clinicians and patients need that are not specifically funded by pharma and are not reliant on registration trials. I think you just have to understand the paradigm is changing and we have to come to grips with that. Thank you.

AMANDA JEZEK: Thank you to all of our

speakers for this session. I will start us off with an initial question. So, a couple of you spoke specifically about labels and what content you'd want to see in labels, so I wanted to give the other speakers an opportunity to comment on what information you'd want to see in the labeling.

And because this is not a terribly new idea, I'll throw in a follow-up question: Why do you think we're not yet seeing the kinds of changes that experts want to see in labeling, and how can we overcome those challenges? And because that's kind of a bigger picture question, I think after we hear from our speakers, we can see if there are others on the full panel who have comments on that one.

Oh, and Kevin just reminded me, if you would like to comment on this one or you have additional questions, please turn your attend card over and we'll keep track of those who want to speak.

NICK KARTSONIS: So, I think you heard about -- we've had a little bit of a discussion about labeling this morning, and I think if I was to tell you what Merck would have on the label -- obviously, they'd like to be able to reference their resistant

infection studies that have been completed. And I think we'd all like to do that.

But, you know, I'm also not naïve to the fact that the agency is bound by guidance and labels are really there to inform efficacy and safety. And, frankly, none of these studies I think that have been done for resistant infections have actually been anything but descriptive in nature. So, you know, at the end of the day, there is a little bit of a leap of faith in terms of accepting what the data are in particular with regard to those labels.

But on the flip side of it is if you actually look at the five studies that have been done that I think have been completed, four of the five numerically show an advantage for the new drug versus the older drug. Now, the only one where the information is in the label is where the one was inferior to the product, okay? Which, of course, became more of a safety signal as opposed to an efficacy finding.

So, you know, it is -- you're a little bit damned if you do, damned if you don't, right? Because if you do -- if you put it in there -- if you

do the study and it works to your advantage, you can't talk about it, but if it's negative it may end up in the particular label.

So, I mean, I get it. You can't put this information on the label because it doesn't fall within the guidance with regard to that. But if that's the case, then I think fundamentally we should ask ourselves is there another mechanism by which we can do that? And so I offer up the idea of -- you know, the FDA has a guidance on consistent with labeling, you know, that you can actually promote based on information based on what's called CFL. And, fundamentally, I do believe that these studies kind of fall within those particular confines in the sense that they are within -- provided those studies that have been done are within the same indications, they are, in essence, studies where you show that they're susceptible for certain organisms that were tied to the ones that you have within your particular label.

So, that's another something outside the box we could think about -- is there a way we can marry up that information? Because at the end of the day, what the pharmaceutical companies want besides

the guidelines and the labeling, they really want their reps to be able to go out and talk about their studies, right? Irrespective of what we think, there still is a component of the importance of the commercialization of these products and people do have to pound the pavement to some extent to be able to share that particular information.

So, I offer that up as a particular thing to think about, and I'll stop there.

RYAN CIRZ: I guess I'm more interested in introducing some concepts that maybe will get commented on further. Just putting my first principles hat on again -- you know, when I hear we want to see a drug studied in severe infection or resistant infection, I separate those two pretty dramatically in my mind. You know, the severity issue of the pharmacology -- the physiology of a patient undergoing severe disease makes total sense to me. Most of the drugs we work on are water soluble, they'll go where water goes. And as water equilibrium is all messed up in severely ill patients, it makes sense we need to understand that. And a lot of the example failures were largely attributable to not

understanding that.

The harder one for me is sort of that we need to see resistant pathogens. And despite the fact that my entire research team no longer works in this space, they were still willing to answer a text message at 6 a.m. in California for me and do a protein alignment.

So, here's the thing I struggle with as a scientist. I can show you data against a CTXN pathogen pretty readily. Much more common, right? An ESBL. There are four amino acid changes in that enzyme near the active site relative to a KPC enzyme. And so to spend a decade to show you directly that a drug that isn't even a beta lactam will be impacted by these four amino acids that make an ESBL a CRE just seems like it's a huge waste of our time and resources.

So, when I separate, the severe disease makes total sense, and the mechanism goes back to like, what makes sense? Like, if I'm a drug that's affected by that, let's study it. But if I'm not, why do we start with the assumption that some magic change is going to happen and the drug suddenly won't work

anymore when it's really just enzymology? So, those are sort of the two buckets I'm separating and struggling with.

RIENK PYPSTRA: Yes, going back to that question about labeling, part of the reason why these resistant pathogen studies have not been included is because they also -- not only are they not well-controlled but also they don't restrict themselves to the very narrow indication that has been given. The indication was just for UTI and these pathogens have been collected in HAP/VAP, have been collected in bloodstream infections or all kinds of infections.

And so, therefore, my plea would be to -- as that is a legal requirement that whatever information you put is linked to the indication, my plea would be to be a little bit more lenient on the indication and not restrict the indication specifically to just the body site. I know that is what was investigated but that does not necessarily need to be what is indicated.

AMANDA JEZEK: Sumathi?

SUMATHI NAMBIAR: Thanks. I just to make sure I understood your comment. So, the three or

four trials that we've discussed which were really focused on patients with CRA infections were all descriptive studies. They were not necessarily tied to the indication.

So I think there's a disconnect there because we did allow the trial. If you look at the Achaogen trial, it included more than one body site. It was designed for superiority. Had that study been completed and there was a finding of superiority, that would have been a successful trial. So, it didn't have to be tried to UTI. So, I just want to make sure that that's clear to the group.

And even in our unmet need guidance we do allow superiority trials where you can pool across body sites. We just make it clear that there are some uncertainties there because we've seen drugs behave differently at different body sites. And if you really have a deficit in one body site, it may not be very apparent when you do one of these mixed body site studies.

So, I just want to make sure that there is no requirement that this resistant pathogen study, if it is done, should only be in the indication for

which the product is otherwise being studied.

RIENK PYPSTRA: But it is related to getting the information in the label.

SUMATHI NAMBIAR: Right. So, that's a totally different discussion.

RIENK PYPSTRA: Yes.

SUMATHI NAMBIAR: You get it in the label -- what we are looking for is a trial that we can interpret. And as Nick had mentioned, all the trials that have been done recently were descriptive studies. The plazomicin trial, the CARE study was meant to be a study that could have been analyzed. It was designed as a superiority trial. For many reasons that Ryan pointed out, the trial was terminated early. And at the time, there was no plan for any kind of hypothesis testing. So, at the end of the day, it was a descriptive study. So, those are two different issues. So, I think we'd be happy to include... I mean, I know I cannot answer all the questions about labeling but the underlying issue was can we interpret the trial or not? Could there be other mechanisms and ways to put it in labeling is a different question. But I think the basic scientific issue was the fact

that these trials could not be interpreted because there was no hypothesis testing plan.

AARON DANE: Yeah, I think part of it might be, for those resistant pathogen studies, how can we get more out of a small set? Because we can't do bigger studies much of the time so we've got to work out how to interpret that.

But the other thing I wonder from something Ryan said was that -- our design means that as soon as we get resistance, those patients just don't form any part of the evaluation because you can't randomize anymore. So, I'm wondering whether there's something else we should also think about -- is when we have that situation, whether we can start to use external controls, for example.

So, I know there can be problems with external controls, but in that sort of setting where there should be quite a big difference, it feels like that can be more informative and that could inform the label at that point then -- for those patients of most interest.

SUMATHI NAMBIAR: If I can just... Yeah. So, in terms of historic controls, I think you

know better than I all the shortcomings with historic controls and there are some settings where they're appropriate and some where they aren't. I think the antibacterial space where there's so much variability and treatment effect -- and even these so-called pan resistant organisms, you really don't have the kind of treatment effect you would see with some of the other indications. It's not 100 percent yes or no response.

So, I mean, that's been a struggle. There have been some instances where we were allowed to use a historic control where we had a lot more certainty with treatment effect, you know --

AARON DANE: Yeah. I guess for me, it wouldn't be a blanket use of that approach, but just maybe being open to that idea that they could be used in some of these settings where you are -- the patients can receive nothing else so they can't be randomized. So, we must be able to put that result in context in some way if this is the only therapy that they can take.

AMANDA JEZEK: Manos and then Lindsey, and if anyone else wants to speak, please turn over your attend cards so we can identify you.

MANOS PERROS: My comment was going to be on your second question, so if there's more discussion to be had on what should be included in the label I think that should go first.

LINDSEY BADEN: I also had a label comment but -- so I guess my -- I think the label -- I'm not convinced that the label is the most flexible, rapidly changing, informative document, given its structure and its regulatory environment. And sort of Nick's comment -- are there other ways to get credible information into the community and it not be, you know, pinned to the label?

And I guess to the industry colleagues, is that unattractive because the label is the be all end all, or can the label have what meets the statutory requirements and then other venues help expand the dataset which is much more dynamic and changing and, therefore, has to have an environment that can allow for new information of different quality?

AMANDA JEZEK: John?

JOHN REX: That wasn't where I was going to go but that's a great question. Because it's

a variation on this notion of what defines a normative dataset that we all accept? And the reason that the label is viewed as such a strong thing is that a completely independent arbiter has said, this is what we believe.

There's a group that has no conflicts of interest, has no reason to say anything that they don't believe is correct, and they say this is it. Because I was formulating this notion of, you know, maybe there is some sort of another level of data that we begin to accept, but who's going to judge it? And I think, again, that's the thing that -- it's what we pay the FDA to do, is to judge the data that has come in front of them.

And so I was actually sort of (indiscernible) thinking, well, it's adequate and well-controlled when it's enough for Helen to know how to use it.

KEVIN OUTTERSON?: We would have no problem letting Helen be the arbiter.

MAN: You found your arbiter.

JOHN REX: Well, I mean, because, in effect, that's the other end of this -- is ID docs,

you know, I've never had -- I've treated meningitis many times. How many times have I used a drug for which there was an indication for meningitis? None. Ever. Right? So, in that sense I'm also a pediatrician who are never using drugs that are indicated for anything other than something unrelated entirely to what they're doing.

So, I think that is a really good question because I like -- we were discussing over lunch the notion that data change fairly rapidly and the thing -- sort of the downside of the label is it takes a while to get it organized and then to make a change takes more time, right?

Is there a way to approach this question of a version of the information that people are willing to talk about? And I have not heard before this CFL idea, consistent with FDA-required labeling. That's CFL, right? I missed that entirely somewhere along the way.

But the danger with that is that, you know, I'm invested in my compound and I'm going to push my story has hard as I possibly can and I'll do everything I can to pretend that it's consistent with

FDA-required labeling because that's what you do, right? You know? And if I'm selling a new iPhone, that's okay, I can make pretty graphics about how wonderful the new camera is. But if I'm selling a new drug, it's different.

So, you know, but this'd be a great long debate about how do you set this intermediate level of rules in a way that is fair and trustworthy? Dr. Nambiar would like to respond to that.

AMANDA JEZEK: Please go ahead and then we can go to Dennis.

SUMATHI NAMBIAR: It's more a question -- I think on many different occasions we've heard nobody reads the label, but sometimes some people do read the label so obviously there's a disconnect. I've heard both sides of the story. One is we don't read the label. Some others say, we need everything on the label because that's what we read.

I'm just trying to understand is there any utility to the reviews that we post? Because what was studied and what we've reviewed, even though it doesn't get people an indication, it's usually captured in our reviews and it's posted publicly

within a few days -- few weeks of our approval of an NMA. Has that -- does anyone look at it other than other companies, when you're looking to see what my competitor did? I hear that all the time.

Other than that, is it of any utility to clinicians, people who write guidelines? I mean, I'm just curious.

JOHN REX: I didn't. Before I went into industry, I did not know those things existed. I never knew to look. I know do look at them. You know, I even go back and read FDA ad-com transcripts because there's stuff in there -- well, I mean, there's stuff in there that --

MAN: We've got to get you out more.

JOHN REX: Yeah, I know, you've got to get me out more, right. That there is stuff in there that you come to appreciate -- you can get the nuance out of it. But when I was Dr. Busy back at the university, you know, I really kind of wanted to go find one paper online and then get onto the next ten consults, because it was already 4 o'clock.

SUMATHI NAMBIAR: I mean, it might be too much to expect every clinician to read our

Advisory Committee documents and our 2 or 300-page review. Even if you read the summary, it's good, but maybe there is a role for the IDSA or Guideline Writing Committee to look at that. Because there is a lot of valuable information there, and a lot of time has gone into it, and like Rienk mentioned, we spend eight, or nine, or ten months reviewing the data so we do capture this information. And I just wanted to hear from others whether utility or lack thereof (indiscernible).

AMANDA JEZEK: Sure, if it's on the same thread, go ahead. And I know we've got a couple folks who've been waiting patiently.

HELEN BOUCHER: Sorry. So, I think one thing that bears mentioning is that clinicians think differently. And so reading -- understanding how to read an FDA review, you have to really understand how to read it. We're looking -- the clinicians need it in plain English. The reason there's no SERI indication is because there was no statistical test. That's -- it needs to be that plain. And I would venture to guess if you read the review, it's not quite that direct.

And even people who watch the FDA Advisory Committee miss that, even though it was discussed in a public forum on TV. So, I don't know how to say it but I just think that part of it is because we want to hear what we want to hear, right? We want -- they looked pretty good, right? More people lived who didn't get colistin. That's the message we want to hear, but also it needs to be presented in a way that's understandable to the non-regulatory sophisticated audience.

AMANDA JEZEK: Sure. And then, Dennis, I promise we'll get to you.

LINDSEY BADEN: Sure, no, because, Sumathi, I mean, your presupposition is that the moment it goes to the agency for approval, that's the sum total of the data. And what I think is more complex is over the next three years, all sorts of data come out. A case report, a retrospective series, uncontrolled data, renal insufficiency, liver insufficiency. How do those data make it into the label that are even more complex quality but may be very influential clinically, which are not at that a magic moment of formal FDA review, but speak to

practice? And that I think is part of the complexity.

In my view, it's a very dynamic process and I think of agents very differently after two years of clinical use than at the moment they were approved. And how does that get incorporated into the label? How does it get incorporated into communication in normative data, as Dr. Rex says. You know, how do we have those data available to guide practice?

Is it the guideline and is that too clumsy or not? You know, what are the mechanisms to update both unexpected safety or important information about how to use it?

AMANDA JEZEK: Okay, we need to let some other folks weigh in. So, I think the order we have is Dennis, David, Manos, and Amy.

DENNIS DIXON: Thank you. So, first, a comment about the topic here and then my question after that. So, when we did our target at clinical trials we did them under IND but we did not do them with the request or suggestion of a label change. And so some criticized us for that. "Well, what did you even do them for if you didn't do them for a label change?" It's because we felt that providing the data,

the evidence to guide appropriate therapy was all we needed to do. And because these are off-patent drugs, then they're cheap.

And so I think that's different than not getting in the label for a drug an indication that may be 10 or 100 times more expensive than the other drug. So, how can you justify for reimbursement purposes, and how can you even justify for marketing purposes if you don't have that validated claim in the FDA label? The literature alone I don't think would do it. So, that's just my comment.

The question is -- we've seen several drugs that made their registrational approval for what you, John, would call UDR, Usual Drug Resistance. That is not the MDR pathogen. It's for the pathogens normally presenting in UTIs most often. And a hint of maybe some activity for the resistant pathogens but nowhere near enough of them to make reasonable statistical inferences.

So, is there a trial design that's scientifically logical and acceptable to the regulatory agency whereby that trial's historical data could be used as the control for continuing enrollment

post licensure to generate more useful data to increase the numbers to where you can make statistical inferences?

And that does two things: It gives you a chance to generate new data in a new trial, but there is some revenue flow taking place with just the given label change while you're waiting to see if you can add something to the label.

JOHN REX: So, the challenge with that sort of continuously occurring dataset is that we'd be criticized because what you know today influences how you -- the patients you enroll tomorrow. And so I would be very concerned about that impact on the dataset.

And the other thing is that these datasets don't -- we talk about -- we stop the study and we analyze the data. It -- between last patient in to last subject, last visit is, you know, some period of time. And then it's another three or four months before you've got an audited dataset, and then another month or so before you've got the various processing data. You can't -- it doesn't -- it's not on Monday that we go to Tuesday and we have a

decision, then on Wednesday we can change our minds and we'll change our minds again on Friday.

Sort of the chunkiness of time really messes with what you can do with these datasets. And I think unless you've lived through collecting one of these datasets and getting it cleaned up -- I'm looking at David Melnick and thinking about the time I saw him with huge boxes of paper from a skin study, for goodness gracious. You know, weeks, and weeks, and weeks just to get that audited and cleaned up. It's not like an experiment you do at the bench where you did one today, I can do a different one tomorrow, because yesterday is completely done. And I think that's very hard to appreciate in this space, that time thing.

DAVID MELNICK: You know, I wanted to come back to the point that Lindsey made. You know, anyone who's tried to do a trial on the resistant pathogen space has had the same experience -- that it's basically impossible to enroll these patients into a prospective, particularly indication-based or even cross-indication trial in a feasible period of time. And yet, thinking about ceftazidime and

Rubactum, the literature clearly evolved after that staggered approval process.

And, you know, we had studies like the CRACKLE Study. CRACKLE-1 and CRACKLE-2, which clearly demonstrated that there was an advantage of the drug, at least to my way of thinking, clearly demonstrated an advantage of the drug over the polymyxins. And yet, there's not a mechanism -- you know, the data gets published, it gets discussed at meetings, but there's no way that that works its way into the label at this point to allow us to take this to a formulary committee and justify, you know, a price point for a compound. And finding some way to communicate that information would be incredibly useful.

MANOS PERROS: Following on the same theme, I would like to highlight two points. One is the level of complexity or simplicity that we need to have when we communicate our information, and the second is timing. I think Helen and Rienk make the point in different ways, but the point being physicians don't have the time to sit down and put together data from across the board from preclinical all the way to clinical trial results and draw their

own conclusions. The agency has the luxury of time to review the data and what needs to be presented in a way that is relatively easily digestible and adoptable.

That goes for physicians, that also goes for pharmacists. And imagine how much time payers would have when they have to go through the data and understand whether the product is actually worth the premium relative to inexpensive generics. So, the labels -- the customer is not only the physician. For that to make a difference to industry it needs to be across the board. So, that puts one hurdle.

The second one is timing. I love the idea of some way to present the data that will be more rapidly evolving and more adaptive. But the labels as they stand today as a means to launch a new product clearly don't work. To Dennis' point, there isn't any revenue really in the way in which we launch antibiotics today. Companies with lots of money start losing money and the small company can't afford to lose money for three or four quarters before going bankrupt. And we're seeing that time and time again,

and we need to stop seeing that. So, whatever we put together I think needs to be simple and it needs to be available at the time of launch. You don't easily launch a product twice.

So, the last point I'd like to make is, I think, to your question, Amanda, how come we haven't yet adapted? I think the yet is a little bit unfair. Because antibiotics can be used in a certain way forever, and have been used in a certain -- that empiric prospective way very successfully forever. And moving afield from where it has been forever and very successfully so to the place where we are today, which is actually a relatively recent place -- and John Rex, and I had multiple conversations about that less than a decade ago, where we now have to focus on exclusively drug-resistant patients where the medical need is. I think it's great that we're having this conversation and I don't think it's too late, but we need to have it.

AMANDA JEZEK: Amy, followed by John Rex, and John Farley.

AMY LEITMAN: Thanks. So, well, first of all, I just want to say I agree with Dr. Rex about

reading the transcripts. They're not exactly barnburners but they've got a lot of good information in there a lot of times.

So, I wanted to speak also to Dr. Boucher's point about the language that's used in the labels. It is very dense. And one of the things I do hear actually a lot from doctors is that they don't have time to sit down -- because of the constraints of your jobs, you don't have time to sit down and read through the label and, you know, pick through the language, and how do we use the drug and how do we dose the drug, etc.?

I think presenting all of that information in an easier to digest format would be probably really helpful for the doctors. And just speaking to the point of, you know, figuring out the use of the drugs, you know, I know that a lot of times these drugs are approved and they're not tested on NDR pathogens, they're tested on more susceptible pathogens. And it's really hard to figure out how to capture data on using it on an NDR pathogen. It's something that I've sort of wondered about for a long time. And we wondered about it in our disease space

because we've used a particular drug as a salvage therapy for, I think, a couple of decades now and we're finally getting around to a clinical trial to evaluate its efficacy.

I would love to see people put their heads together and figure out ways to capture the data in the real world, because what I hear from doctors a lot of times are, you know, if I'm trying these drugs and, you know, these drugs that are approved for this pathogen aren't working and then I realize this is a multidrug resistant pathogen, I'm going to look at a drug that's approved for a susceptible version of this pathogen, I'm going to throw it at them anyway and see if it works. Kind of like throwing the spaghetti at the wall and see what sticks.

Sometimes when your patient is really sick and your back's to the wall, that's what you're going to do. It would be nice to figure out more creative ways to capture those data in the real world setting and just bring that back in and analyze it, and see if there's a way to either get another indication or at least use that to design some kind of clinical trial that can demonstrate that, yes, this is

another indication we can get for this product.

AMANDA JEZEK: John Rex?

JOHN REX: So, I actually wanted Ryan to share something that he didn't talk about, which is the cost of an antibiotic once it comes to approval and some of you may have been at the meeting in Boston six weeks ago where we had an extraordinary presentation on this. Those of you who weren't really need to hear the comment about "What is it like if a drug comes to you and someone hands you the plazomicin package?" They sign over the lease for the building, they sign over the manufacturing plant, they sign over the patent and they say, "Here, plazomicin is yours." How much money do you need at that point and why do you need that much money? And the place I want you to go with this is what could be done to reduce that number?

RYAN CIRZ: Thanks, John, for the opportunity to plug that workshop. Well, the first thing I'd say is you don't want to assume a lease in San Francisco, so cancel that right away. I mean, I think that workshop was a little bit of a genesis with the struggle I've seen trying to get people past the

endgame. Like, we can make the trials free and it's not going to fix it. We can do all these things for free. I mean, quite honestly, we're getting quite a bit of support anyway -- to blend with investor money, it's still not fixing it.

So, I think the idea there is we tried to break it down to things that were sort of undeniable. And they're the things that you have to do to own a license to a product. I think there's still a lot of doctors and other people that think you can just have it and just let it sit there. It's actually not legal to do that.

And so upon approval there's a minimum set of requirements: Additional clinical trials, pediatric studies, surveillance studies, your AST development and then, of course, the supply chain investments. And I think one of the challenges with the rollup thesis, and I think it's a good one in the long game, but if all of the things you're rolling together are cash flow negative, it amplifies the problem.

And at the end of it, of course, you have one team managing four or five products, seven

products, eight products. But to see that day will require seven or eight years, and so the early stages of that just amplify the problem. And the estimates from my colleagues who did all the speaking, that worked on drugs all the way back to cefepime all the way through to plazomicin and I think almost all of the new agents at some point was in their experience integrating three or four of those experiences as you spend about $400 million before you get to cash flow positive.

And the only way for us to raise that is the public markets because we don't have revenues. And so I think the market cap slide Kevin showed really shows you -- imagine you want to renovate your house and spend $5 million but it appraises for 100,000. You just can't do it. And so we're in this trap right now that's causing an acceleration of the collapse as we realize that the companies can't finance to sustainability -- forget about profit. Just being able to pay your bill for what you have to do.

I don't know how to make it better. My first point I said jokingly last week to someone

that's in tech ops at BARDA -- I said, oh, we'll just reduce quality. That's the easiest way, right? And then one of the greatest challenges -- and I have colleague that works in the rare disease space now, that they're trying to explain -- he's in CMC -- that the CMC package for a drug does not change whether you've got 10 million patients or one. And that's a fixed cost, and we're really trying to understand how to drive that down. But that will become an undeniable denominator.

And then the requirements, everyone agrees we should be studying pediatrics, etc. But we left out any kind of optionality like let's do a Phase IV study and see -- nothing optional, what you have to do, and that was the ultimate thesis was that it's a pretty substantial multi-$100 million loss. And you can even look at drugs that I just heard earlier said were successful and take all of the revenue they've made since approval and they've probably spent it all already on these requirements and have not yet made a single dollar for their investors if you actually put those things together.

AMANDA JEZEK: John Farley?

JOHN FARLEY: Sure. So, just a couple of points of information, which are sort of related and there are follow-ons to a couple of things that have come on. So, Amy, one of the things I wanted to mention, and you brought it up this morning, is that the FDA's website was, unfortunately, not put together by Amazon so it's not particularly usable even to those of us who work there.

But after each drug approval, there's something called a Snapshot written, which is by our staff that focus on communication to people who may not be as sophisticated. And there's even a section for physicians that's a little simpler than the density there. So, I think those are useful in terms of discussing trial results and presenting trial results. I even use them with colleagues in Baltimore who are in primary care, and want sort of the simple version. So, that's something to think about.

I think one of the things that I just wanted to follow up on is in terms of a lot of the labeling, like what you're interpreting as policy and guidance in the agency, is actually based on regulations. So, regulations are written basically to

describe through notice and -- there's a notice and comment rulemaking process, which you would have had the opportunity to participate in. How is the agency going to implement the law?

So, when Sumathi and I are proposing things where we're basically saying to our upper management that the agency should violate its own regulations and do this, that's kind of a heavy lift for us. Just so you know. And those meetings usually don't go well. So, it's something to think about. So, there are some confines to what we can do.

In terms of the updating of labeling with new information, my observation is that that works much better in the HIV and the Hep-C space where there's a lot more industry resources in play. Because the agency -- excuse me, the company actually owns the drug label. So, if they want to update it, they actually have to submit a supplement.

Now, since in the last few years there isn't a charge for those supplements, but as folks in the industry will assure you, there's a lot of work involved. I think one of the things in the Hep-C space that I've also observed is that the guidelines

are living that are online, and how they're used by the field seems to be a little bit different. So, it's just something to think about. Because there will be limitations, A, as to what we can put in labeling for regulatory reasons but also in terms of what's practical and what other information that may be very useful to clinicians can end up in the labeling. It's just a big effort and some may not be what we would call label-worthy information. But they can end up in these living guideline documents. And how those get used, at least in the Hep-C space, they really impact practice.

The other thing that happens, and Sumathi's going to kill me because she doesn't have enough medical officers as it is -- but in the Hep-C space we do have folks who sit on the guideline committees and will actually sort of provide some context for the contents of a review as the guidelines are updated in very real time.

AMY LEITMAN: So, you're in good company. Clinicaltrials.gov is just as hard to use and patients are supposed to go there to find clinical trials.

But with respect to making -- yes, your snapshots are very useful. Sometimes it depends on the audience. You know, if you think about how the label -- to me, a label looks like one of those -- remember those old-fashioned triptychs that you would go to AAA and get? That's what those labels -- those monographs remind me of. It's difficult, I think, for -- especially, like I said, physicians have a limited amount of time with their patient. They need to pick through this information, so they really want to be able to just draw out what do they need to know right away? They can go back and look at the other stuff later. So, yeah, the snapshots are useful.

And then in terms of communicating with patients, which is a different level of communication, we always look at what the information is, how is it being provided, and then what patient population are you talking to. With our patient population it's a little bit different. They experience something that they call brain fog or drug fog. They're on so many medications they don't -- they have cognitive dysfunction.

And actually, as I've talked to more

and more patient advocates about various infectious states, if it's an acute infection in particular they experience that a lot. And that actually lingers after their infection is gone as well. So, those are the kinds of things where, if they look at that monograph, they're either going to cry or throw it in the garbage.

So, yeah, you want to make it as easy as possible in very short bites. So, those are the kinds of things where really breaking it down into those easy soundbites is going to be helpful.

AMANDA JEZEK: And, Vance, did you want to make a comment? I thought I saw your attend card up.

VANCE FOWLER: Yeah, okay, I will. So, I want to get back on this thing about the control -- the use of controls and contemporaneous controls. Because, you know, I think it seems like -- as evidenced by the fact that we're all assembled here, we've got a problem. And guess what? We're not going to get -- we're looking for perfect data. We're not going to get perfect data.

And everyone's like, well, we need this

STAT, we need this data to be able to -- for the clinicians. See, here's the thing. Helen's going to have to go back tomorrow and she's going to make decisions based on what's available at that time. I'm going to go back and I'm going to make decisions based on what is available. And if I don't know, I'll call somebody. And if they don't know, then, you know, you still have to make a decision.

So, I think these events that are being captured with patients that were desperately difficult to find in these drug-resistant trials, they're just sitting out there. I mean, okay, we don't have a P value, it's not adequately powered, but it's informative. Because guess what? I've made decisions in the last week on -- single case reports, one patient. That's not perfect. Okay, I get that but you have to make a decision.

This data is out there. We're sort of obliged, in my biased opinion -- we're kind of a little bit ethically obliged to make this data available so that it's part of the decision-making process. And if there's a means by which those data can be clarified, the meaning of those data can be

clarified using some control group, that's helpful. That advances the overall mission. Whether that is a historical control -- you know, we talked about that and it was no, we can't do historical controls.

Then it was like, okay, what about contemporaneous controls? What about if we had some means by which to simultaneously enroll subjects in an ongoing network -- let's call it, you know, the kind that John Rex described in that 2016 paper, where there's a warm base ongoing and you enroll basis with the same CRF. Use those individuals who have fundamentally the identical CRF and, thus, that's fundamentally the same data that's captured on these subjects of interest, and use those as a comparator.

You know, get an independent third party to oversee the selection of your controls. You know, use a 10:1 propensity match, use something that most reasonable -- you know, that a reasonable third party could look at and say, yeah, okay, that's a reasonable start. Then it makes these data available and helps people who have to make decisions, you know, tomorrow, whether we like it or not. I'll stop there. Thank you.

KEVIN OUTTERSON: So, we have about 15 minutes before I think it'd be time for the public comment, and I wanted to give a little bit of framing just for this last -- I see several people out there with their tents up. They may go right back up. So, thinking about the information -- we can try to increase the quality of the information. And a lot of our discussion was get better information.

The second one is reducing the cost or the time, right? And we haven't talked much about the clinical trial networks. A little bit. So, increase the quality and decrease the cost or the time required.

The third, which has really been the bulk of our discussion, is how do we tell the story better? And, particularly, I'm thinking about John Rex's comment. The FDA is an impartial arbiter of truth and method, or maybe just method, and so people trust what the FDA has made it through their grid in a way that's different than they trust even the peer-reviewed literature.

And so, Lindsey, you know, the New England Journal article, the excellent article by the

Achaogen people, you know, in the world's greatest medical journal, yielded sales of $800,000-and-some-odd worth of plazomicin in the nine months before bankruptcy. If instead there had been some way to take the snapshot or some other material and to put that clinically relevant information in some format that physicians would actually take notice of, I don't think anyone here wants John or somebody or any of our good friends at the FDA to ever violate a rule or regulation. But perhaps with LPAD, perhaps with real world evidence there's a way to come up with something that works for everyone.

So, with that as kind of framing, 10-15 minutes left, have your best shots.

AMANDA JEZEK: I can start with... Sure. John Farley, please.

JOHN FARLEY: It is sort of related to your question and kind of a follow-up. Because one of the things I sort of forgot to mention, and also a follow-up to Vance's point because we had actually talked about this about ten months ago. I think there are a variety of ways that one -- a trial can be adequate and well-controlled, which is defined at 21-

CFR-314.162 for your general information. And Sumathi and I actually spend a lot of time being reminded of that in meetings.

So, I think my observation -- and I've really kind of been observing over the last few years before sitting here -- is sort of wondering why some folks have chosen not to pre-specify a hypothesis. Because what you need to know is that that's one of the definitions, and that's usually the thing we're called upon the most.

The one thing that our leadership does not like is post-hoc analysis. They -- that drives them nuts, and should, I mean, scientifically. It causes all sorts of questions. So -- and there are a variety of ways to do that but sort of toward your idea, there can be more sophisticated hypothesis testing planning. We have Erin here, and Dan, and a number of folks who may have some ideas in that regard. There are ways to combine information from a contemporaneous control with external data, and we're open to discussing that. The devil's in the details. We're not going to work it out today but that is a possibility. The Achilles heel has been not pre-

specifying.

AMANDA JEZEK: John Rex, then Ryan, and then Sue.

JOHN REX: So, let me just say something I think I'm hearing emerge as a concept, which is if you look -- I just pulled up the HCV Guidelines description, how it is that this rapidly updated thing comes to be. And they say, you know, it's a panel of folks who are looking at the best available data and they update it regularly. I mean, that's the short summary of a long page. Fair enough?

And if you think about what we've just been debating -- you look at like, the snapshot -- I pulled up the Zemdri snapshot. Unfortunately, it is limited to UTI. And that's probably the way it's supposed to be written. I'm sure that was the rule. But is there a place here to do what you've pointed out, which is to take the more details -- summary basis of approval, and have a -- have Helen, and Cindy, and Sarah as nominated as my committee chairs here, to look at that for drugs being approved, and then write down the other stuff that an ID doc ought to know and make use of. And maybe that's not in the

label but if the community came together and said, guys, that's what you have to use. You could then say, well, the idea -- this is what you use. You take that to the payers and say, this is what you use, the label and this thing over here, that's the kind of shift that this group could potentially foment.

RYAN CIRZ: Yeah, just going back to sort of trying to optimize for lack -- or minimal waste in terms of our time and resources, since there's a limited -- and touching on kind of what Dennis had brought up before is, you know, a lot of the recent studies we go out -- you know, multi-drug resistance. We just didn't get the CRE, right, or that one step before. We're greasing the 90s, right? We're seeing 20 percent ESPL. We're not quite 20 percent CRE until it jumps to E. coli.

But I struggle scientifically -- you know, from a severe infection versus UCTI, completely understand -- different pharmacology, different physiology. Resistance, though, when people say, we need to see it directly shown to us, that when you change from a CTXM gene to a KPC gene that some magical thing doesn't happen in your drug and it

completely doesn't work anymore doesn't make any sense. And it seems like a huge waste of time and money.

I mean, my limited maybe three years I spent in the biodefense space partnering with BARDA, how do you show something works on gentamicin-resistant plague? You can't. You can show it works on sensitive plague but you can't create a strain of gentamicin-resistant plague to show it. That's illegal, right? It's a violation of international law. But we show everything else in our power to show the things that make gentamicin not work anymore don't affect the new drug. It's super simple and it's very logical and it makes sense. And we're able to do that without a loss in time and efficiency.

So, when I hear like, if we had 20 percent CRE in a UTI trial, some magical new revolution would be revealed when your drug isn't affected by the enzymatic mutations that make a CTX a KPC, as a scientist, that's sort of where I'm like, there's a place we can make some inroads.

AMANDA JEZEK: Sue, then Cindy, then Aaron.

SUE CAMMARATA: I had a couple of comments. One is -- this is around the idea of -- as the FDA has pointed out, a lot of the tools that we have are there. When I was in the rare disease world, the rules are not any different. I keep hearing ID people saying, oh, if we were a rare disease, we'd be able to get approved. That is not true. The rules are the same for all the different therapeutic areas and all the different indications.

Now, how they're implemented and how a trial is designed, that's where you have to talk to the FDA. Whether you look at the statistics, pre-specify, and complete the study, I think if you can do that, that's the challenge -- can you do that? So, I think you have to go in to all of the trials with realistic expectations.

I've been doing this and I still am approached by people saying, you have to do X and enroll these kind of patients. And I will say, probably impossible but I don't want to be the development person that's always saying no, so I'll say, I'll try. The realistic point you have to understand is that it is just hard to enroll some of

these trials.

The other comment I would have is back to this idea bout labeling in general. I'd have to ask, is there any other physician group that asks the FDA how to use a drug to put it in labeling? I would say that that's pretty unusual, because usually the physician groups probably get together. So, I would ask, can the physician group, such as IDSA, in some way implement and help the ID community to understand how to put this information together to give guidance on these new antibiotics?

I just think it's a bit much to be asking to be putting this into the label and asking the FDA how to use a drug that... Because they don't have their own personal experience, they have the data that is out there. It's in the -- it's out there in the public domain. And it's in the reports if you had guidances, and a way to do that, I think that would be very helpful. But I think it is a challenge to say, put it in the label.

AMANDA JEZEK: Cindy?

CYNTHIA SEARS: So, I want to thank John and Sue for their comments, and I hope we return

to this topic in the next discussion round. I turned my thing up because I wanted to respond directly to what John brought up, which, if I understood it correctly, was sort of suggesting transitioning something like the HCV guidance to AMR or, you know, using AMR as a topic.

The one thing I'll point out is the HCV guidance started at a time when trials were appearing very rapidly in the HCV field. And so that was rapidly developed to discuss those rapidly emerging trials. And I know that because I was on the IBSA Executive Committee and we were the review group for the HCV guidance. So, we would get asked do they want to modify it maybe even twice a month, and we would review it within 24-48 hours and get it back to them. It was short and sweet at that point.

As time has gone on, there have been many more HCV trials and the document was just updated for the first time in a year this past August. And, again, the IDSA Executive Committee took that task on. But now the document is 150 pages and is like a bunch of bricks that have been put up and probably needs a sound edit. I had to restrain myself at points from

trying to fix some of the inefficiencies that were there in the language.

So, they're very different situations. You don't have large trials that were powered, so the type of data that you're asking to be assembled for the clinician rapidly is quite different. Now, I think that that's an important point and, again, I hope we return to this later in the afternoon. So, I'll discuss what's going on at IDSA shortly and I'd love to hear your reactions.

AMANDA JEZEK: Erin and Lindsey?

ERIN DUFFY: So, two different things. Ryan, I wanted to clarify this point that you've made now twice about ESBL and CRE. Because I think the intention there -- if you have ten ESBL strains, five of them might just be ESBL, in which case, for instance, an aminoglycoside would work but the other five are going to have friends that have come along that might alter permeability or upregulate efflux.

And so might it not be more about what's the breadth of ESBL coverage when ESBL is ESBL plus friends? And, in that case, demonstrating that is of value?

RYAN CIRZ: Yeah, I mean, the fundamental principle is it's all driven by the microbiology unless otherwise proven. I'm just sort of making the point that we act as if when you elevate from an ESBL to a CRE, some magical thing happens. Equally probable, an ESBL can have some horrible super, you know, RMT-type pan resistant mechanism or CRE could, and that will change every other year. But the fixation on needing to directly prove it in a trial versus relying on the surveillance and the micro, that's kind of where I think there's just a little bit of a loss of efficiency -- as if it's a new disease, the resistance itself. That's where it feel like a lot when it's discussed.

ERIN DUFFY: Yeah, maybe it's just an unfortunate way that we're naming some of these things. The same with MRSA. Why would a quinolone not have activity against methicillin-resistant staph aureus, right? So, it's a similar story, I think.

But then I wanted to address a completely different thing, and this is the support for the concern over post-hoc analysis. So, Sue will laugh I think hard at this but when Sue first came to

Melinta, we had just completed a Phase IIB trial with delafloxacin and ABSSSI, and we showed superiority over vancomycin. It wasn't intended. It was a Phase II trial. And because I'm a theoretician by training, I was asked to analyze the data and there was a single reason for that superiority and that was the performance in obese patients. Not because vancomycin necessarily worked any differently but because, for whatever reason, delafloxacin looked really, really good.

And so we went into Phase III thinking, hey, you know this is -- because this is a big population, no pun intended, but it is. And so, you know, in one Phase III trial we didn't pre-specify, and in the other we did, and wouldn't you know it? In the one trial where we pre-specified is the one trial where we didn't see it.

And so, again, this value of small numbers I think is helpful but often when you do larger studies, I learned painfully it doesn't always work out.

LINDSEY BADEN: So, just to amplify Ryan's point, which I think is a conceptual one we

have to come to terms with. If what we want are effective antimicrobials for very resistant organisms, particularly the ones that don't exist yet or only exist in rare parts of the world as they are in the process of spreading, then how do we develop the dataset or datasets to give us reassurance that we've developed a countermeasure that's effective?

And, obviously, the preclinical models need to be done fully, but how do we think about the clinical models when by the time it's prevalent it's too late, and before it's prevalent it's really hard to study? And how do we find that balance with the clinical dataset?

AMANDA JEZEK: I think we just have three minutes left. I've got John Rex, Aaron, and Sue. I don't think I see anyone else. Okay, great.

JOHN REX: There's only one public speaker, right? Yeah, okay. Okay. So, I want to respond to a couple of things -- to Cindy's comment. What I was thinking of simplistically was not an omnibus rewrite but a one-by-one drug update of the stuff -- the other stuff that's not in the label that you might like to know about that drug. So, PK and

other body sites, the data from a less -- an imperfect trial. It's that secondary information that you might dig around and find somewhere, but at least here you found it and you know that some of your peers have proofed it and that this document then becomes something that actually, by definition, almost meets the rules for -- consistent with FDA-required labeling kind of. I mean, it's the stuff that, if I'm the sponsor, I can happily promote it because I can say it actually has been kind of cleaned up and tested.

So, that to me is sort of the advantage of doing this. It creates an arbiter that's other than me, the sponsor, to summarize the data that when I D-doc I wanted to know, and that's what I was pointing out.

This thing about the MICs, we have spent a lot of time debating this language about MICs and I don't want to give a whole talk on it. But at the end of the day, the antibody can only influence the portion of your disease that's due to the bacteria, and anything else I can't touch. All the information that is relevant to the drug is in the MIC and the PK. And that has been proven over, and over,

and over again by our colleagues, that if the MIC -- "It's the MIC, dummy," as Paul Ambrose would say if he were here in the room. So, the susceptibility to other drugs is interesting but it's actually not relevant to the activity of Ryan's new thing. Zemdri works on Zemdri's susceptible pathogens when the drug gets to the body site. And I think that's sort of the core idea that we need to get at on this.

And my third comment is about orphan drugs. And I think we ought to at least briefly visit the question that sometimes come up: Why aren't antibiotics orphan drugs, and would it help if they were? Would that change things in a way that was useful?

And I'm pretty sure I know the answer to that but it's a question that I do hear from time to time, and I think it would be -- just so that we have sort of collectively toured all the ideas, why isn't suddenly declaring CRE an orphan -- which, numerically, CRE is an orphan -- why does or -- why does that or does that not make a dent in this problem? It's worth saying the answer to that question.

AMANDA JEZEK: Aaron and then Helen.

AARON DANE: Yeah, I just wanted to come back...

SUE CAMMARATA: Sumathi, do you want to respond to the orphan drug question?

SUMATHI NAMBIAR: Yeah, I think the short answer to that is even for orphan products and, as Sue has mentioned, the rules are the same. So, you still need to have adequate and well-controlled trials. Now, how you design the trial, what you control on might be different but in terms of trial -- the requirements for demonstrating substantial evidence of efficacy doesn't change.

AARON DANE: I wanted to come back to the idea of pre-specification. Obviously, as a statistician, I completely agree that we should pre-specify what we're going to do for all the reasons given. I guess what we need to do, though, is be clear on what success looks like.

Because for an orphan -- orphan drug -- for a rare pathogen, we know that there's going to be absolutely no power to actually show a statistically significant effect, which means that no one's going to

run the study. So, we need to think about what the criteria might be for -- what would be good enough for an approval in that specific setting. Or it might be how we use the other data.

As you say, if there are other randomized trials, could we use augmented control designs where you use some of the control arm data from other randomized studies or other external data? You know, maybe just a more open view to looking at all of those things more generally and not using them when they're of poor quality or they're not reliable. But at least being able to look at them more because we need to do something like that because we know we're not going to get it from a randomized trial.

So, I guess we might pick up some of those things tomorrow as well. But it just feels like that's the bit we need to do is, pre-specify yes, but then what is it they're pre-specifying?

HELEN BOUCHER: So, I just wanted to come back to the prior discussion about, you know, if we found a way to communicate this other information not on the label and take it back to Dr. Kartsonis and the other colleagues from industry.

So, if we agree that that happened, so there wouldn't be a labeled indication, so probably it couldn't be promoted in the traditional sense but it might be able to be discussed on a, you know, peer-to-peer with the MCL type thing. And PNT committees and stuff. So, how do you all view that, if that were to occur?

SUE CAMMARATA: I was just going to make a comment that every company does a global value dossier, which is not just label information. So, I think it's really how to make that more useful. But it is the intent of that that includes all this information. Off-label information. So, that exists, I'm not sure it has made a difference but it does exist.

I did have a comment about the -- one comment about -- this is more about conducting clinical trials and this whole idea of rare disease. The one clear challenge for anti-infectives, most of them -- and this is not, for example, for the NTM but for the acute infections. When you're in the rare disease world, you have more chronic diseases. There may be 30 patients that you need to enroll but they

can be found. They can be found ahead of time, and you can fly them across international or continental borders to do trials. You can't do that with the anti-infectives.

So, that is the one challenge for sure for anti-infectives, that you just can't do that. So, that's why to me, some of the appeal of a clinical trial network where you do have sites that are up and running that can be initiated to enroll those patients in real time would be... I understand the appeal of it. Again, I'm not sure how doable it is but it would be very appealing in that respect because we can't fly a HAP/VAP patient across international borders to enroll in a trial.

RYAN CIRZ: All right. I don't have enough experience watching launched products to know if it would make a difference. I know everyone that works in the field tells me it will make a difference. Like, oh, if it was in the label -- if only.

I guess the one behavior -- well, if we started doing it and it doesn't change anything, we'll know the answer. I guess the one thing that I'm interested to watch is if we fix reimbursement -- so

plazomicin had something like a 96-98 percent formulary acceptance with whatever data it had. 90 percent of the use was in the outpatient setting from launch where the economics work. So, it'll be an interesting question: Which is more important, and actually will the data make the difference or is there some other market pressure that's actually creating this incentive to not use these drugs?

KEVIN OUTTERSON: So, I think we're drawing to a close now. I thought that we would have more discussion about the clinical trials network today, and the few discussions we had were actually concerns about making sure it didn't become a bureaucratic machine that made things harder.

Tomorrow morning there'll be two sessions, I believe, that we'll take that topic and maybe additional discussion can happen then. John, are you going to take this next piece? Okay, thank you.

JOHN FARLEY: Thanks, Kevin. So, we'll turn our attention now to formal public comments. Folks were asked to follow the procedure outlined in the Federal Register Notice for this meeting, which

required contacting us in advance. Dr. Luthy has done so and we'll invite her to the podium at this point and ask her to confine her comments to about 5-7 minutes, if that would be okay.

CONNIE LUTHY: Yes. And I have some slides.

JOHN FARLEY: And we have slide up. I always wanted to say that.

ERIN DUFFY: Well done.

CONNIE LUTHY: So, I'll start talking while I wait for the slides to come up. So, I'm Connie Luthy, I'll introduce myself in like, the third or fourth slide. And I want to thank John Farley and Sumathi Nambiar, and our other FDA hosts for creating this brainstorming workshop on how to make the whole clinical trial process more efficient, and useful, and productive. It's all toward what Kevin Outterson brought up, which is increased productivity. So, this left arrow advances the slide? No. Oh, no arrow. Okay, okay.

So, the workshop goals are to better understand the state of antibacterial drug development and consider studies to enhance antibacterial drug

development. And the way of doing that was to assemble a diverse array of subject matter experts in infectious disease.

Like Ryan Cirz brought up, I too am an outsider to this group. I'm a subject matter expert in medical product development, having developed a diverse array of global manufactured medical products, and here are some examples of that.

So, I worked a lot with sterile unpreserved drug products. They have to be pyrogen free, biological products, and Class III medical devices. So, to me, the overarching goal is to consider strategies to enhance the development of antimicrobial drugs that change lives. So, that means being more productive through the whole process.

So, one of my appeals today is would it be possible to assemble a group to brainstorm on the materials that go into these? So, there are two ways that I see to better enhance (indiscernible) drug development. One is to increase the quality of product candidates entering the clinical trials. So, that's what I'm suggesting we might figure out a way to facilitate. And, two, to fund candidates in

development for global distribution. This is a global problem. That's quite clear. And that's the way to do things efficiently, is to address the product in ways that can help everyone.

So, one of the questions -- since leaving Alcon, one of the things I have done is studied innovation and new product development and what makes successful products. You know, nearly nine in ten products fail, generally because they're not solving a customer need. So, it's a very complicated decision that mostly folks in large companies are exposed to in figuring out where to invest the money.

As Rienk pointed out, no one's got unlimited budgets, not even the big companies. So, in order to make funding decisions that result in successful products you need to know where you are in the industry. So, one of the things I'm hoping for this group -- and there are some funders represented here -- is that the programs of CARB-X and others won't suffer the low productivity that the NIH and NSF SBIR programs do.

There's a huge difference in the program -- the SBIR programs operated by DOD and DOE,

and BARDA is apparently the only group represented here that now has this acquisition end. And that difference is the decisions are being made by the folks who are going to use it. So, it's a whole different -- it's a whole different way of assessing things.

So, I'm encouraging the large companies that are represented here to have their employees get more involved in serving on SBIR review committees, serving on CARB-X's review committees, and encouraging those of you who -- those of you -- I assume almost everyone in this room is a scientist or engineer -- who are working in the government entities and the private foundations funding some of this work to seriously try to recruit folks with experience developing products. So, you know, are these decisions being made by scientists or by businesspeople?

I had the fun experience two weeks ago, the day before my homecoming at Rice University, to judge a graduate student presentation competition. And as we were preparing -- being prepared for the presentations, one of the students organizing it asked

me how I decided to become a businessperson. And I was like, really surprised. I mean, I'm a scientist. Every day I'm reading papers, designing experiments, etc. I mean, even after doing an MBA program, which was 19 years after my Ph.D., it didn't change me into a CPA. I'm still a scientist. I'm still doing product development.

I expect that those of you in the room who are product developers feel the same way. That you're still doing scientists maybe more like an engineer, because you're working towards product specifications but it's still doing science.

So, one of the things that I was never -- I never thought about that much until I was in the MBA program, is the difference between science and technology. And science is really a method that those of us trained in that method used for obtaining laws -- knowledge about the laws of nature. Whereas the technology as the result of a design process begins and ends with a solution is the product of human thought. The scientific method is used in testing the designs. So, the purpose of science is to gain knowledge, and the purpose of technology is to change

the material environment.

So, during your career, have you developed a product, a technology, or discovered the laws of nature? I think all of us have been involved in discovering the laws of nature and I would even include Ph.D. economists who -- that's a science and they're discovering different laws of a different kind, but still laws of nature. And basically go by what are you selling. Your activities. If you're doing scientific research, you're selling information. Technology development, you're selling a component or a tool. Product development, a finished product.

Now, this one also is a little different perspective from perhaps most of you. So, in a medical product development team you've got lots of different functions represented. As Sue pointed out, with a small company you also have to outsource some of those functions to consultants.

But as we go through the process, as things flow kind of from left to right, there are the makers, and the testers, and the documenters, and communicators, and, yes, trialists. Those of us on the maker side think of you as testers. So, I am

trying to help figure out ways that we can make better materials to be tested and how that process might be made more efficiently.

So, my request for those representing big pharma and big biotech is get your folks out into the community more, more involved helping startups, more involved serving on these volunteer -- basically, volunteer committees reviewing the grants to small business and the grants from the private foundations.

Some advice to small companies is new product development is not taught in school. And the place it's most efficiently and effectively taught is inside profitable companies in the same industry. So, if you're not able to attract employees with appropriate experience, outsource.

So, for new product development -- and this is not just medical product development; all of new product development -- it's really a combination of the product strategy, registration strategy, and the management team that will lead to the efficient use of money, and the well-defined products are funded, developed, approved, and change lives. Thank you.

JOHN FARLEY: Thanks very much. All right. So I think we are ready for a break. And so we'll take a break at this point and reconvene at 3:15 for Session 2A. Thanks.

SUMATHI NAMBIAR: All right. So, welcome, everybody, back to the next session. It's Session 2A on Antibacterial Clinical Trial Innovation: What Are the Realistic Options for Enhancing the Antibacterial Clinical Trial Enterprise. The first speaker in the session is Dr. Baden, who is associate professor at Harvard Medical School, and who you've already heard is the Deputy Editor at the New England Journal of Medicine. And we've had the distinct pleasure of working very closely with Dr. Baden in his role as the chairperson of the Antimicrobial Drugs Advisory Committee, where he has done a phenomenal job discussing some very challenging topics.

LINDSEY BADEN: Thank you. We shall see if I can master the technology.

So, I'm going to tell you nothing new. What has been discussed this morning I will amplify, I will frame a little bit differently through my lens. But the group that has been assembled has tremendous

depth in this set of issues that we are struggling with. And hopefully through discussion, we can find a better path forward for us as a community.

So, what is it depends on who wants to know about it. And since I'm brought here as a journal editor, alliteration has resonated in my head. So the six Ps, which have no real meaning other than I kind of liked it. The practitioner, the producer-developer, the purveyor, the investor, the permission grantor, the patient, and then asked to talk as the publisher, although I also am a practitioner, investigator, patient, and care provider.

But the question that all groups care about is new findings; what does it mean to me? What does it mean to me? And what has been discussed earlier is how do I know about it and how do I know about it in a credible, informative, balanced way?

So it depends on your frame of reference when new data emerge and it depends where you sit, what you're looking for, what your metronome is, what you want to do with the data. And all of these different perspectives are true, but they're different and they may approach data with a different

goal. And one can look at an image, and you can look at it in all sorts of ways. I need to get from here back to Boston, I want to build one of these, I'm an engineer. All of these are true representations of the data, but, boy, are they different representations, and they're different for the different communities of relevance. Ultimately what everybody is after is truth. What is truth and what does truth mean for how these data are to be used? And so there are major challenges in identifying what truth is.

Human biology is complex. Clinical trials are really, really, really hard to do. They really are. And I think all of us has struggled with them from the different vantagepoints where we sit. And we must do the trials that answer the question so we answer the question, but we will never answer all the questions. In fact, we have to highly-constrain the question to get an answer that is valid, but then limited generalizability, which we then lament. But at least we can answer the question.

This is colored, as discussed earlier by Dr. Boucher and others, our patients are sick. The

need is urgent. We don't have time. I need to make a decision tonight when I get back and round. How do we manage that? How do we manage bias? And the bias is not a straightforward bias. I've spent ten years of my life working on this. You know, the financial is the easiest to manage. But to all other sort of bias, including hope to cure my illness. And this has to be managed so we continue to approach truth. And then my favorite is the P of 0.05 is the altar we worship at. I don't know what it means, I don't believe it's truth. With all of my hats that I wear, I do not believe it's truth, yet it is our altar. And we need an altar to minimize the play of chance. Because that is such a tricky parameter to manage.

So mission of journals, I don't need to say, we want to find the best work, we want to report it dispassionately, as Dr. Rex advocates. We want to help advance science, we want to improve patient care. In fact, we all want to improve patient care. I think we are unified in our mission and our interest in this room no matter where we sit. But then how do we do that and how do we do that efficiently and how do we do that in an ecosystem that is self-sustaining? And

so at a journal we bring rigorous peer review. At our journal we have multiple, multiple layers of review, including multiple content experts, statistical, editorial board. Multiple, collateral experts will comment to make sure we can identify the best work and what it means. If it is favorably viewed at our shop -- and I can't speak for all journals, but I think most journals sort of feel the same way, of how do we get it right and how do we get it into the hands of the people who need to know. But at our shop, post-acceptance also not a trivial issue is how do you communicate it. And this was alluded to before with the gray box.

And what I put -- and this is from the SHINGRIX study showing how to -- a new vaccine against shingles. And what's beautiful about this is this figure has both zero-to-one access, it's twenty-fold amplified to see the real difference. You have the number of people at risk, the number of events. In a short box there is a lot of information if you want to understand the finding and the strength of the finding. But this gets to the issue of how do you communicate the data so people can understand it

efficiently from their vantagepoint.

And there are intrinsic tensions when we publish, from author sponsors, people who are promoting a viewpoint. How do we as arbiters weigh, balance, and then share? And so this is a simple slide, which is we all want something to be right, and that is our guiding principle. The question is how do you know it's right with all of the other pieces that need to go with it? So there are issues and implications of what we publish.

And this is just highlighting a little bit, which is was the study designed well, did they analyze it as they designed it. But then which outcome do we care about? Do we care about the day five, the day 10, the day 14, the one year, the microbiologic, the symptomatic, the integration, the efficacy, the side effects? Is it the IT, the MIT, the micro TT, the PP? Is it inferiority design, a superiority design? Does that influence which of these parameters we favor? Does it matter if it's the resistant bug or not? Yet why don't we just take every data available and slap it on the label?

I just think that that gets to the

complexity of the data. And I find whenever we talk about let's just report the data, I sit here and struggle with what are the data. Because I would like it to be transparent, but I don't find it so straightforward to know what the data are that everyone needs to know in the context that gives it meaning to how they want to use it.

So, some clarity about publishers and publications. We're not a regulatory agency. We don't make regulatory decisions. We may look at the same data or not even the same data. They have statutory authority over all the data; we don't. But we have community input. We have a different review process. We look at the protocol and the analyses, because sometimes studies may be designed to have a high likelihood of making the product look good whether or not that really represents what the product can do. That doesn't mean it doesn't work, but how do you then present that in a way which is a little fairer as to what is found?

Publications allow community awareness, debate discussion, as we are doing here, independent expert review to bring in more perspectives on what

the data may mean. We help with the data interpretation presentation. And the graphic that I showed you from the SHINGRIX study was just an example of how you can communicate a whole lot of data I believe efficiently. But that's just one way of presenting the data. And I didn't even tell you if it was the ITT, MITT, PP, you know, which analyses we even presented there. And should all of them have been presented and then have you work your way through the data? And we don't make corporate decisions as to what go forward or not, as the plazomicin discussion pointed out, although hopefully we helped with it getting on to formularies because we helped show what the activity of the agent was.

So I like real examples of things that happened. Theoretical is great, but practical, real -- these are what happened and these are examples of three compounds that came before the agency in the last 18 months. So whatever about them is antiquated, these are the data of things that we as a community evaluated in the last 18 months. For whatever reason, these are current in my view.

So I'm not going to go over the

specifics of the data. I want to just point out certain things about the data. One is this is a CUTI, not something we need plazomicin for. However, it is a scenario where you can demonstrate efficacy and safety. They studied about 300 active 300 comparator, and they showed efficacy. You know, terrific, we know it works.

They also were able to look at key subgroups and show that in subgroups. It works in bacteremia, it works in the few non-susceptibles that were there. When we publish the data, we can publish it with these kinds of figures, we can publish it with these figures, which is impossible to read. But doesn't it matter which bug, which resistance determinant, which resistance determinant for the active versus the comparator? And these are the simple data to present, let alone all the other data we're talking about everybody wants.

And then we do side effects, and it behaves like aminoglycoside with renal dysfunction. My point here is if you enroll 300 people, a one in a hundred side effect you might be able to see. So they might be able to see one in a hundred side effects.

But if you see one in a hundred side effect and it's serious and not really expected, you may then call it noise, which it might be. So how do we actually declare safety?

And one of the things we do in the supplement, for particularly new compounds, is list the safety data more expansively, because you don't know which safety data are noise and which safety data when the next thousand people experience this compound actually turn out to be a pattern. And it gets very hard to know which data we care about, because there are a lot of noise in sick patients with resistant bugs.

Then the HABP/VABP BSI, which failed to complete because of futility, but yet we all are aware that there was a mortality signal. So what do you do with these signals? And the agency is under different obligation to interpret data that are post-hoc, redesigned, shrunken, halted study than we are when we can present the data for what they are; is this true, is this noise? But there is a signal that looks very encouraging, and it's important for the community to be aware and to debate. And so there looks like there

is a mortality benefit in the plazomicin compared to the colistin-treated group in this type of post-hoc redesigned study because of practicality issues.

So when we publish the data, we publish the research, we can publish letters with additional research, we can publish commentary that helps put the research into context given the complexity. And this gets to the tempo. These were the data available at a certain time. As a year or two go by and more data can be generated, and then it supplements how we think about a compound and how do we as a community of a dynamic nature to be able to absorb new data that emerge that may not be as well-pedigreed or created, but still may be informative.

Cefiderocol, which is another agent for resistant REM-negative organisms, three different trials. CUTI study is done, published about a year ago in Lancet ID, showed that in green on the right there is a non-inferiority to imipenem and maybe even superiority with a substantially better outcome by composite response, microbiologic response, clinical response. And then in the publication, they showed different body sites, different organisms. The

farthest plots are different ways to try and slice these data to understand them. But for the most part a fairly consistent finding that it works against these kinds of organisms.

But then you have the credible data. And this is an early look. But now in red -- green being good, red being bad -- you see a mortality signal. But these are immature data. They're not complete. It's not the way the study was designed. They're doing a look because they see a signal. So we have the plazomicin where you see efficacy. I want to believe that. And now the credible where I see mortality, well, that has to be noise. I don't know what's true in either case. I don't. But the data are the data. And we as a community should be discussing them and we as publisher should be publishing them to allow discussion to know what they mean to help inform the next round of studies, and also so the community is aware of the uncertainty. And then as the data gets stronger or filled in or the study is completed, then the data can be updated, and maybe this finding doesn't hold when the complete data are available.

Three days ago this was approved and Dr. Farley made some comments. I think the issue of limited and no-alternative treatment option is something we as a community need to think more about, is how do we position, just like oncology drugs, that maybe it shouldn't be a yes/no light switch, but there really are ways for us to caveat antibiotics of last resort or antibiotics for very special pathogens that live in a bucket that is both different from an agency standpoint, but different from a use standpoint so that they are used in a way that is commensurate with where the need is and where the benefit potentially is.

With inhaled amikacin, I think want's important about these findings -- and it was interesting to see how this compound is a success in the marketplace, but when this went to the committee, to the agency, to AMDAC, it was striking that it cleared the cultures but had no measurable health benefit. Oxygenation, walk test, mortality, anything with a clinical benefit, we couldn't see. Or at least not in the data they had. But it did clear the cultures. So there is a benefit. I don't quite know

what that benefit means.

And this gets for Dr. Fowler and others, what are the surrogate endpoints that we design for studies that inform us? I believe clearing cultures is a good thing. But that does have to be linked to some kind of benefit that has even greater meaning. But it is an important element. We know with TB and other bacteria that clearing cultures and ultimate outcome may not be correlated as well as we would like it to be.

So as a publisher, we have to balance the data needed for regulatory approval, how do we optimize patient benefit, how do we protect the community benefit. And then the elephant the room is how do we have the incentives to really allow the antibiotic development to grow in the way we need it to. So we have to manage information flow. As journals, trust is the most important thing. And as Dr. Rex said, who is the arbiter of new information. And that trust is really important. With new agents, it's a different complexity than an agent we understand the safety profile. And with new agents and new data, the uncertainty is really high because

we don't know what to look for. And that becomes very tricky in how we then deploy those new agents and report on them. And then we need to understand what do we know, when do we know it, who curates it, how do we share it, and then how do we update it.

So in conclusion, I think the role of a publisher is to facilitate, air, provoke discussion from all perspectives. We need to provide factual, interpretable, and relevant information. The data means different things depending where you sit. By publishing data, hopefully we more completely inform the risk/benefit balance. We need to deal with the data we have; not the data I want. We can push the community to develop the data we want, but the data we have have to guide us. And all of this has to be wrapped up in a format that allows a virtuous cycle with antimicrobial development.

So our goal is to find the best work, publish it dispassionately, help advance science, improve patient care. And I would argue that's the goal of everyone in this room. Thank you.

(Applause)

HELEN BOUCHER: Thank you very much,

Dr. Baden.

Now it's my pleasure to introduce Dr. Cynthia Sears, who is Professor of Medicine and Oncology at Johns Hopkins, as well as Professor of Molecular Microbiology and Immunology at the Bloomberg School of Public Health. Dr. Sears is an ID expert who is focused on GI infections and is the recent past president of IDSA. Thank you.

CYNTHIA SEARS: Thank you, Helen. I want to thank the FDA and the other co-conveners for the opportunity to come and talk to you a little bit in general about guidelines, as well as what's going on at IDSA in guidelines. We've already heard guidelines come up in many capacities today. And I think this will reinforce some of the ideas that have been floated. These are my disclosures.

So I'm going to start off with this slide from the Magic Foundation, whose goal is to increase value and decrease waste in the healthcare system based on evidence ecosystems. And the reason I'm showing you this is that what we're discussing, the production, dissemination of guidance or guidelines, is really only one component of a much

more complex ecosystem of information needed to actually do excellence in guidelines. I think this is all well-known to you, but just to review what the purpose and promise of clinical guidelines is. The purpose is to provide evidence-based, trustworthy -- a word we've heard quite a bit today -- recommendations to support patient care and to develop a framework for determining acceptable clinical care.

The action is systematically synthesizing typically complex data into a format that can be used by physicians and other healthcare providers to inform patient care decisions. And the promise or hope of guidelines is that this will support more uniform care for patient, yielding better patient outcomes and diminishing health disparities.

However, they are not dictums. And so physicians and healthcare providers must be able to judge the quality of the evidence and assure themselves that the recommendations apply to their patient or populations in care.

Now, the next two slides just show some of the ups and downs of what we know about how guidelines may affect outcomes. this is a paper from

2009 from the U.K. where they were trying to assess whether the publication of the U.K. National MRSA Treatment Guidelines impacted 28-day all-cause mortality. And as you can see in the table pre and after the guidelines were published, there was no change in 28-day survival. However, this is a very weak study because it actually didn't look at some of the critical features that are important to assessing that result.

This paper and others, and as the discussion has highlighted today, have questioned the clinical acceptance of guidelines, the impact of guidelines on care, and the voracity of guideline processes. And there is no question that over the last 20 years there has been many formats for guidelines that have differed a lot.

This slide you already saw by Dr. Outterson. Alan Carr and Helen Boucher shared this with me. Recently presented at ASM and ESCMID just this year.

And these data suggest that publication of C. diff guidelines by IDSA modified use of fidaxomicin and vancomycin. But again, this lacks a

lot of nuance that we would like to know about the impact of guidelines. And in general I would say that our data on the impact of guidelines remains pretty weak or limited.

So the standard today for guidelines really stems from the seminal report from the Institute of Medicine in 2011 titled Clinical Practice Guidelines We Can Trust. And the IOM set seven standards for trustworthy guidelines. These are establishing transparency, management of conflict of interest, systematic review, establishing evidence foundations, and rating strength of recommendations, articulation of the recommendations, external review, and updating.

And I would say that in stages, IDSA has sought to implement these IOM standards to its guideline process.

So IDSA guidelines within our society are the highest-rated IDSA member product, critical to member satisfaction. In parallel, our members, others outside the society, and our guideline panel members in fact have all expressed dissatisfaction with the long timelines for development and update.

That said, the production of guidelines by IDSA has been pretty stable. Over the last 20 years since 2016, 19 guidelines produced.

So what really constitutes the guidelines process, attempting to meet IOM standards? There is a lot of argument about this. But in a recent review looking at various approaches, they really all led to what's called GRADE, which stands for Grading of Recommendation, Assessment, Development, and Evaluation. This is a complex process. Pre-development phase, development phase, post-development phase. And I'm just going to run through this so everyone understands the challenges in the room.

So in the pre-development phase, you're composing your panel, you're finding a methodology, you're figuring out the COI, and you're setting up agreements, usually with multiple societies since most guidelines have collaborating groups.

There are three phases to the development phase. The first is to define the scope of the topic; frame typical questions that typically should apply to a large proportion of patients, and

select patient-important outcomes. The second phase is the systematic literature search. Requires a librarian. They are hard to find. Literature screen, assessing risk of bias. Then evidence synthesis and grading. And lastly, the development and grading of the recommendations by the panel and writing the manuscript.

Post-development it's reviewing the process, reviewing the manuscript and approval, and then the guideline dissemination and implementation. We've heard about all of these steps during the course of the day.

The estimated and optimal process to do this is one-and-a-half to two years. But there is no question there are issues. Most of the people doing guidelines are busy physicians and their time is at a premium and sometimes can't be fully devoted to this process. There is a paucity of methodologists and librarians available to do this work and in general the process has been poorly understood. But I have to say since IDSA has invested in educating the panels and in workshops, panels are enthusiastic about this. Once they understand it, they actually find it to be a

good way to try to put the data together.

So the next three slides are just giving you an idea of the scope of the work. We have three types of guidelines, IDSA-led guidelines. And the ones marked in red are those that involved antibacterial therapy. Most of the IDSA-led guidelines currently do. We have jointly-developed guidelines. These are led by a different society, but we have a formal role. All of these are linked to antibacterial therapy. And then we have IDSA-endorsed guidelines. These are led by another society. We may or may not have a representative, and a subset of these are linked to antibacterial therapy.

However, there has been a lot of discussion about what are the other options for conveying science-derived, actionable bedside advice to clinicians. And as has already come up, there's probably two marquee examples we would all discuss. One is the HCV guidance, which was a collaboration or is a collaboration between AASLD and IDSA and has been very successful for the community. And a second actually would be AIDSinfo which is a DHH-NIH HIV guidelines, but they are not great.

Other names are applied to these types of documents; clinical consensus statements, practice guidance, provisional clinical opinions. And these are generally thought to be most applicable when the evidence base is considered to be insufficient for a clinical practice guidelines. But there are significant practice variations going on and there's many opportunities for quality improvement.

Now, I will tell you if you talk to the people who are experts in GRADE, they disagree with this statement quite a bit. In general, these recommendations are not done with a formal process like GRADE. But there are in the literature potential hazards when some of these processes are reviewed, including accuracy, completeness, conflict of interest, and transparency. All topics that Dr. Baden brought up as well.

So the overall key challenge is upholding methodologic rigor while meeting a reduced development timeframe. Recently there has been a discussion of rapid guidelines meant to meet certain conditions. And similar documents have been put out by the CDC, U.K. National Institute for Health and

Care Excellence, and WHO, all given different names. However, a key limitation is it requires a high concentration of skilled resources to be rigorous and rapid. And each of these documents has been subject to the types of criticisms I brought up on the previous slide, including transparency and process.

So I'm going to tell you a little bit about an activity at IDSA this last year. And you'll see why in a moment. We went through a strategic planning process. This involved data collection, tons of conversations, and a lot of debate. We applied a business model to our discussions called the Run-Grow-Transform model. And I'll just say a Run initiative is one in which you have a base, but you intend to invest to improve it. And Transform is an effort to have long-term, high-impact effect.

I bring that up because we've recently published the 2019 IDSA Strategic Plan and CID. There are four initiatives for the next five years. And two are quite relevant to discussion today. One is to optimize guidelines, and the other is to invest in and lead efforts to decrease AMR with our partners.

We fully acknowledge there is a gap.

Trustworthy, real-time, focused guidelines guidance on treatment of antimicrobial-resistant infections is a gap in our repertoire. So this is a moment of opportunity. A completion of the 2019 strategic plans means we're gearing up to invest significant staff and financial resources beginning in 2020.

So what's under discussion? So we intend to expand IDSA's guidelines program to meet the needs of the clinical ID community. There are a lot of things on this slide, but I'll just point out our intent is to expand the portfolio of guidance products and to provide interim recommendations and rapid updates to supplement standard clinical guidelines.

So I'm floating a proposal under discussion in which your feedback would be welcome. So using a title of Antimicrobial Treatment Alert and Clinical Commentary from IDSA. And components that we might envision in this is the rapid dissemination of emerging trial and drug data on antimicrobials put into context by clinical experts. Considering developing comparison charts of new versus current therapies for bacteria involved. And I was fortunate enough to be able to modify this slide. But listening

to what was going on this morning, I put in there inclusion of in-progress antibiotics, listening to Helen's patient and trying to figure out what in the world you're going to do with a patient for which you don't have a drug. It would be nice if there was a resource that would help you know who to call quickly. And also inclusion of delineation of questions that need further research.

So as I've tried to say a couple of times today, this is a moment of opportunity. We really would love your suggestions and input. Some of the questions I would like to hear discussed later is what should be the format and components of real-time AMR treatment advice, who is the clinical audience, what will be the requirements and standards for data inclusion, and perhaps even more importantly, what will be the criteria for changing that advice. How would we best disseminate this, and what are your concerns about such a process and approach?

So, thank you very much, and I look forward to the discussion.

(Applause)

SUMATHI NAMBIAR: Thank you, Dr. Sears.

If we can maybe spend five minutes and see if there are any clarifying questions for either Dr. Sears or Dr. Baden. Then we can go into the panel. Also wanted to mention that as this is a workshop, members of the audience are welcome to participate as well. So if you have any questions, feel free to -- there isn't a microphone. Oh, there is one right there. So please feel free to come to the microphone and introduce yourself and ask questions.

Any clarifying questions for Dr. Baden or Dr. Sears? No? Okay. Seeing none, we can go into our moderated panel discussion. So we have three questions. We'll start with the first, and then depending on how much time we have, whether or not we can get to the second and third question.

So the first one is -- yeah, thanks. Thank you, Cindy. So the first question is what are some serious infections -- and you've just listed a couple of examples here, staph aureus bacteremia, prosthetic joint infections, diabetic foot infections -- for which there is a clinical need for new therapies. What are some feasible approaches to obtaining clinical trial data in patients with these

types of infection?

So the reason for bringing this question up is, you know, as we have heard today and we've heard in other prior discussions as well, that there doesn't seem to be a need for new therapy for say a UTI or intraabdominal infection. And those are not the kinds of infections clinicians are actually treating their patients for these days. So we would like to hear from everybody here what might be some serious infections for which there is a need for new therapies and how do we go about putting together such a list. And I think also very importantly is how do we work to design trials. You know, we at the agency don't have the experience of having design trials for some of these indications. So what would be the next steps to build up on the list of indications we come up with? How do we design trials and what might be some feasible approaches to obtaining these data?

So I'll see if there's anyone who wants to volunteer and have any thoughts. Vance?

VANCE FOWLER: I'll volunteer. I note you have staph aureus bacteremia on there. We can talk about that one all the livelong.

You know, I think that practical steps -- I would say that's one of the few trials in this space for which there actually was a successful model, and there no longer is. And what I mean by that is that I think some of the restrictions that I have personally seen -- and I've been involved. And as a matter of fact, Dr. Cosgrove and Dr. Boucher were involved with essentially all of the Phase IIIs that have come through on bacteremia. And the general trend has been sort of a gradual, inexorable tightening of the noose to ultimately futility. And I would demonstrate or provide as exhibit A the (indiscernible) study in the same space that the (indiscernible) study was done.

Some specific examples in that space which I feel like would sort of resurrect that approach, an incredibly clinically-needed indication, would be revisiting the current approach towards PENS, specifically the potentially effective non-study antibiotics. And for those in the audience, that means in trials complicated trials. You know, patients in real life, people get a lot of antibiotics. Right? And sometimes a person will get

an antibiotic for some period of time that's not a part of the study. And then the question is what do you do about it and to what level can you attribute the ultimate outcome of the trial to the investigational agent of choice versus the compound in place.

And I feel like -- and granted I'm biased because I was part of the adjudication committee for the dapto trial. But I feel like the dapto trial had it pretty close to right because there was the ability for clinical interpretation of those data by an objective third party. And I personally have seen from my own involvement in several of these subsequent trials the gradual erosion of that clinical ability for interpretation. And I think to the detriment of the trial and, frankly, the detriment of the compound.

And I've probably caused enough trouble, so maybe I'll stop there for right now. But that's a good place to get things going.

HELEN BADER: And I'll just ask a follow-up. So who can help think about doing these trials? Are there any particular groups that we

should be including in this discussion?

WOMAN: I think the point Vance is making is that there was an incredible value of having infectious disease physicians review the cases of PENS. Because in contrast to most other infections that we treat now, where we've seen five days, seven days, and so forth is fine. That's not the case still for staph aureus bacteremia. And so specifically when you're at the tail end of a four-week course of therapy, there is a good chance that someone sent a urine culture and they get three days of Bactrim. And clinically three days of Bactrim has no relevance to whether the 28 days of whatever the drug being studied is was effective for staph aureus bacteremia. The problem in staph aureus bacteremia is we can't clear the blood cultures in staph aureus bacteremia. So if three days of Bactrim at the end of the course of therapy was going to solve all the problems, we would have figured that magic bullet out already.

And yet those patients become failures. And then you have such an enormous bias in these studies towards failure, that you don't end up with useful information about the drug. So I think the

people that can help are people who take care of patients with staph aureus bacteremia, you know, to make these distinctions amongst different infectious disease syndromes.

SUMATHI NAMBIAR: Yes. So it's certainly -- any other comments?

SARA COSGROVE: Well, the only other comment I wanted to add was just understanding from a pharma point of view is how you bring in other -- the challenge of doing some of these trials is bringing the viewpoint from other regions. So here is a roomful of U.S. focused people. And the problem is that I need to design a trial that can go to China, Latin America, Europe. And so not only is it the challenge of the agencies talking together -- which we know they talk. Obviously they do talk. But it's trying to get consensus there. But also the medical communities, because the standard of care or the opinion or the approach to disease could be very different in different regions. So that would be the other thing to make sure from a pharma point of view that everybody remembers; they have to be global trials typically.

JOHN REX: So is there another way to frame this question? And I am wondering whether we could be doing some sort of a systematic approach with one or two drugs to help us know whether or not site-specific PK is a useful tool. And I guess I'm trying to come at it from a more generalizable approach to interpreting the kind of data that we live with. And I guess I've always assumed that the concentration of the drug in in the CSF meant something, and whether I should choose it from meningitis or not, is there a -- I don't have any clinical data on that. And if I even had that once, that might actually improve my comfort with using that sort of information. And I realize I'm just posing another question without an answer, yet I think that you will -- what's driving this if I take every drug that comes along the way, I'm never going to have data on sites A, B, C, D, and E that are off the short list. And I would like to have a way to generalize to sites A, B, C, and D.

SUMATHI NAMBIAR: So your comment is in general terms, right? Not specifically with regard to staph aureus bacteremia? You're just saying for a drug should we be collecting PK at a variety of all

these sites.

JOHN REX: Right. And it's an ill form of the question. But let's take prosthetic joint infections. That's one that I'd like to know how better to manage those. But it's a combination of surgery and drug therapy. And is there a way to, short of studying a series of drugs -- am I going to compare a oxazolidinone with a beta-lactam with something else for PJI? No, none of that's every going to happen. But maybe there -- but is there a way to get at something from a PK-PD standpoint that would be helpful here? And maybe I just answered my own question. I think the answer to that question is no.

I was really just spinning off of is there a way to provide information that is more generalizable than one-off studies with individual agents. And I don't know the answer.

HELEN BADER: Well, just to be a little more provocative, what about getting more pragmatic? What about getting to a much more pragmatic trial in staph aureus bloodstream infection, right? It's really common in my hospital right now. It's really

common because of the opioid epidemic. What about something where you don't even get to the minutiae that Vance was talking about with the composite endpoint with the 22 parts. What about we're going to give Drug A, Drug B to real people with staph aureus bloodstream infection. Maybe not with left-side endocarditis, but everybody else, and follow them for 42 days. Count the bodies, see what happens to the blood cultures.

VANCE FOWLER: So I really see -- and I guess I'm probably going to address this to some degree tomorrow. I really see there's sort of two silos of work here with fairness. I think there's the registrational element, which is absolutely critical, necessary. But I would respectfully submit insufficient to fully inform clinical practice. And I think parallel and also by itself insufficient is the need to answer clinical questions. And I feel like ultimately the trial designs of those two inextricably important needs are going to be different.

And so as an example of which, to carry on staph aureus bacteremia, you know, when you're a hammer, everything's a nail, right? But we've

published earlier this year in CID that the average screen to enroll rate for staph aureus bloodstream infection, in complicated in particular, is at least 30 to 1. Okay? And that's from three different studies, including the telavancin experience with their Assure study, of which I was a small part, and two others.

Now, compare that -- and the cost of course was prohibitive. And the data was ultimately truncated by the fact that they had stopped the study. So compare that for example from the perspective of strategy trial to what's going on now in Australia where they are really taking the play of borrowing from the playbook of the cardiologist and sort of taking simple questions, randomizing adequately-powered samples, and then letting this -- it's not going to meet the level of stringency that of course needs to be in place for an FDA trial. But they're two different purposes I would submit.

So what's my point? I guess my point is that I really see there is sort of two needs here. There is the need to get drugs to market, and then there's the need to know how to use the drugs once we

get them to market. And I think the trials are going to have to reflect that reality. And I'll stop there. Thank you.

SARA COSGROVE: I'm just going to respond to what Vance said, because I can't remember what I was going to say originally. But -- I actually do remember, but...

So, I think that it's important to note that the study that Vance is referring to, the big one, was called the MERINO Trial. And it looked at whether we should be treating ESBL bacteremia with meropenem versus pip/tazo. And there were no U.S. sites. And that is because it really was too difficult for U.S. sites to become involved. And we must fix that. Because not only are we not taking advantage of all of our patients and their experiences in the United States, we're also not getting any information from the United States.

And so I really think that we need to figure out how to make it so that these kinds of approaches can be operationalized in the United States, whether we're participating with the global group or doing it ourselves in the United States.

SUMATHI NAMBIAR: Aaron, you had a comment. And then we'll come to you, Pam.

AARON DANE: I was just going to pick up on the idea of a pragmatic trial. So I guess even from a regulatory perspective, a pragmatic trial and an inferiority trial would be problematic because of all the different elements of noise. But I guess if it's a superiority study and you're aiming to show that something new is better, then -- I mean, I'm just checking. But wouldn't that be more acceptable because come of those concerns in non-inferiority are less prominent in a superiority study?

SUMATHI NAMBIAR: That's true. I mean, if you look at the KARE study -- I don't remember all the specifics -- but we didn't have all these concerns because it was designed as a superiority trial. So maybe 96 hours. But fair amount of prior therapy was allowed. So yes, and that was the problem with the KARE trial. After it was completed, one couldn't even try to interpret it as an NI trial because it had all these other issues which confounded an NI assessment. But in a superiority trial, if you get a lot of prior therapy, other concomitant therapy is going to be just

harder to demonstrate superiority. But if you can still do so, I think that's much easier to handle.

AARON DANE: Yeah, that's what I'm thinking. So when we talk about some of these areas, it's not going to be universal. But in some of them it might be that a pragmatic trial could be possible if we are in a situation where something new is going to likely be better.

PAMELA TENAERTS: And I think I'll continue a little bit on the pragmatic trial, because I think -- first of all, people have discussions about what is a pragmatic trial. But the truth of the matter is every trial could be more pragmatic than what it is right now. I mean, it might not be total pragmatic with a three-page CRF and everything, but -- and the way to get there is really changing the approach that you design your protocol. And Vance has heard this before, is a quality by design approach where you bring everybody around the table, including the physicians, the clinicians, the coordinators, the patients. In a drug development program, the statisticians, the operational people. Everyone together and walk through a series of things that you

need -- how you set up your trial so that you can make it as simple as possible and focus on the things that matter and not focus energy on in the end things that don't matter.

And by the way, ICH E8 has gone through a draft guidance, so it's E8(R1). And they are proposing exactly that approach; that for registrational trials in the ICH communities, which is basically everyone at this point, you should use a quality by design approach. And I think that is very different than whoever is sitting in their offices dreaming up the trial, and then the clinicians go, oh, this doesn't work. Well, then talk to the people and see what will work and what will work for everyone, and create those trials. And then they should be streamlined, only collect the data you need, and all those good things.

VANCE FOWLER: So, Pam, just -- part of that -- your point is totally valid. Part of the concern arises from -- well, my understanding, not being in industry, but my impression, is that part of that arises from industry's very legitimate concern to be able to respond to questions that are posed in

public forum, which is an ad board meeting or -- you know what I mean?

And so I would be interested in getting the perspectives of some of our industry colleagues on that point and what could assuage that perspective.

PAMELA TENAERTS: That's exactly right. And we did a project a couple of years ago when pragmatic trials were still called large simple trials, if somebody remembers that. And so we did a project then that was actually asked us to -- that the FDA asked us to do, because they wanted to see -- and I say sort of generalizable. But some people wanted to see more large simple trials.

And what we found is exactly that; the resistance of industry saying, but what if I didn't answer a question you're not going to ask me. And the same resistance was actually at the FDA when we did the surveys, that, well, what if I ask a question and they don't have the answer. And it goes back to -- and I think the publication was published in JAMA. Mike Lauer was one of the -- and then (indiscernible), that maybe it's not the ideal pragmatic trial, but just make your trials more pragmatic, like make them

more real world. It doesn't have to be that you don't collect any data. You can still collect what you need. But yeah, your point is well taken.

JOHN REX: And that's something that we've all been picking at; the question of smaller amounts of data. Whether it's a small amount of data on a large number of patients or a larger amount of data on a small number of patients. And we've not yet seen that actually done. I remain fascinated by the fact that the EMA says in their guidance, just bring us some randomized data. And we understand if it can't be fully powered, just bring us some randomized data. All right? And, Ryan, you brought them some randomized data. You know, that is randomized. The critical CS or the little study that only got 40, 50, 60 people in it, right? That's randomized data. And the problem is the heterogeneity that's implicit in anything where the N is less than a hundred. And even when you get up to 200, the heterogeneity. Every person is -- it doesn't take much to move it.

Remember, for noninferiority, the central point estimates of the two usually can't be more than three or four percent apart. If it's more

than that, then the -- even 10 or 15 percent confidence, balance will be out of whack. You know? But the point estimates have to be really close, and you can't be off by very far. So I'm going to take that idea and say the theme here is that this is the community that understands that it wants the drugs. It understands that it wants the data. And we as a community have to say out loud we get it that this is all there is. It's not going to get better. And we have to quit whining about it. And there's that word normative. We have to say to ourselves and to our peers that put up or shut up. You know? This is it. And you can't have it both ways.

So somebody earlier said -- the comment about qualities of data. And I'm sorry, I can't quote it right now. But we're blowing hot and cold out of both sides of our mouth. We can't have it both ways. We have to declare that this is all there is, and there isn't some hidden trial. Industry's not keeping some secret in the corner and not telling people that they'll do it that way. Rant over. Sorry.

SUMATHI NAMBIAR: Vance, I have a follow-up question to your earlier comment, that there

are registrational trials and then there may be need for additional trials.

So say if a new gram-positive agent came along. And the traditional way has been, you know, do skin trials first and then think of follow-on indications later. But that's exactly the criticism we are hearing; we don't want another skin trial. But if you didn't do that and you didn't get the product available, how would you do your pragmatic trials? So I just wanted to know what your thoughts what might be and what other indications we could think of if skin is not the way to go.

VANCE FOWLER: That's a fair question. I guess my response to that would be largely being the one who says we don't need another skin trial. And my response to that largely is we don't want only another skin trial. I actually understand why the skin trials are done and the complicated UTI trials are done. It makes sense. These are entities that are clearly well-described. There's airtight guidance that's in place. You know how to do the trials. They're affordable, the patients are there. And it gives you data on performance and it gives you data on safety.

So I actually understand that. The question is what next. Because realistically if there were a viable next step for these compounds, for tedizolid and dalbavancin and all these drugs that are staking up, delaflox, and just stacking up like cord wood out there. They've all got ABSSSI indications. And then what? Nobody's using them because they're too expensive. Right? So you get stacked.

So let's say they did their skin study and then there was some other thing, that for the purposes of discussion, may not be quite to the level of rigor as the skin studies. Get them through the gate, but then you do some other trial whereby there's some flexibility on both sides in an indicator that, with respect, clinicians actually care about. Like osteomyelitis. Okay?

If you talk about gram-positive, okay, you can treat skin and that's fine. But the truth is, you know, one of the leading indications folks with, you know, NID you're dealing with now is osteo. And we don't have the first idea, or at least I don't, about how to do it. The studies that have come out have been studies from Europe. There was that one

paper in the Lancet about the six weeks versus three months for vertebral osteo. There's fundamentally no real strong guidance in those spaces. And so, okay, could there be some means by which you get it out there, you get your baseline safety and all that kind of stuff. Do the PK, do whatever is felt to be rigorous and responsible and appropriate. And then there's some flexibility on more of a strategy trial kind of approach in clinical questions that are relevant to clinicians. And I use osteo just as one example. If you put it in the gram-negative space, then maybe it's bloodstream infection. But that's the concept that I think is probably worth thinking about a little bit.

MAN: So, in listening to this discussion, I think we're trapped a little bit into thinking of different infection sites as being exactly the same or completely different. And neither one of those mental models serve us very well.

Clinically, we often share information across diseases that have various degrees of heterogeneity. Osteo in one bone we pretty much treat like osteo in another bone. But if it's not the bone

and it's the cartilage or not the bone and it's the muscle, then those are more different.

And I think there are statistical methods that are used in other areas of medicine for quantifying the degree of similarity and learning about the degree of similarity of treatment effect across infection types or disease types that are similar, but not completely similar, and different, but not completely different.

And so one of the thing I hope to do tomorrow, in a shameless plug for my talk at the end of the day, is to actually give some specifics about the statistical modeling that can be used to directly address this question of how do you leverage the data you can get -- for example, in skin and soft tissue infections -- to indirectly address and supplement the harder-to-get information on these other diseases. And I feel that throughout the day, we've had the lumpers and the splitters. And the lumpers will be challenged by evidence of heterogeneity of treatment effect. The splitters will be challenged by never having enough data in any particular group into which they've split the patients. And as long as we are of

those two different philosophies and we don't quantitatively and rigorously and in a prespecified method have a plan for falling in between, we're going to be hopelessly hogtied. And I think that one of the things that I think is interesting as both a statistician and a practicing clinician is that clinically we do this all the time. The patient I'm going to see tomorrow night at midnight in the ER -- I'm a little bitter about that -- is not going to look like any other patient that I see. But I am going to borrow information that I can recall at that time of night to try to make a treatment decision.

So I think we need to bring the thought process that we use clinically, combine it with rigorous statistical modeling, and come up with ways of learning the same way from our trials that we do in clinical practice.

HELEN BADER: That's really great, thank you. Can we do -- Lindsey Baden had a comment. Lindsey, go ahead. Sorry.

LINDSEY BADEN: That's the problem with being tucked in the corner. The conversation, Sumathi, that you and Vance were having, I'm having a

little bit of trouble in that the cUTI study is, as Vance sort of said, there's a way to do a study for regulatory approval that has parameters we all understand and therefore can measure efficacy and safety. And then there's the complexity of all of the other conditions that we treat in real life.

And I guess, Vance, are you proposing that the only studies you can do have to be registration studies, or can't there be studies which are designed for registration and then studies which are designed to inform practice, realizing they may have different metronomes?

VANCE FOWLER: I thought that was exactly what I said, the latter scenario. Essentially there's the registrational trials, and there's strategy trials. Tomorrow I have two columns. It says strategy trial, registrational trial. And it will be more clear. But yeah, I think that's precisely what I'm saying. I'm saying that both have objectives and responsibilities that they need to address. But neither in and of themselves is sufficient to address all that needs to be done.

In other words, for a new compound,

it's important in my view to pursue a pathway along the lines of what's being done with registrational trials. Because there's a great deal that's not known. The safety is not known, the efficacy isn't fully known. And so you really want to test the drug and not the test. By which I mean put it in -- evaluate it in a situation whereby most of the other potential area for variation is minimized. That is skin study, complicated UTI study. Having done that and gotten a base -- let's call it a baseline of understanding in terms of the performance, the relative areas of weakness or strengths of a compound, that you then focus that subsequent effort in an area that actually addresses more of the clinical need. Because the unmet sort of clinical need that the drugs have the potential to address. So that's exactly what I'm saying --

LINDSEY BADEN: So for osteo, it would be terrific to have agency guidance on here is the right way to do an osteo study. Prothesis, yes/no. Bug, yes/no. You know, which bone.

However, that doesn't stop you from designing such a study and determining if drug X works

for osteo.

VANCE FOWLER: That's correct.

LINDSEY BADEN: Because the study can be done. It's a matter of can we design it in a way that the community thinks is meaningful and achievable.

VANCE FOWLER: Yeah. Basically what I mean there is that if these are the studies that the community needs, then the community may need to be ultimately responsible for designing, implementing them, and funding them.

AARON DANE: And it remains off-label.

JOHN REX: Philosophically I'm very sympathetic. So that's my warning that I'm now going to disagree with you a little bit.

And something that I often think about is FDA -- you're to assume between a trial that's good enough for the FDA and a trial that's not good enough for the FDA. FDA is not really any different than any of the rest of us. They are docs who are asking the questions that you will ask when you get the data. And if the trial wasn't good enough to be interpreted by Sumathi and John, when Helen gets it, she's going

to say I don't know what to do, either. And so are you.

And so I want to flip it around and say have we seen examples of we'll call it lower-quality pragmatic trials that people actually believed? And what was the characteristics of those studies and how do we get at those?

VANCE FOWLER: ARREST Trial, Lancet.

JOHN REX: Which one?

VANCE FOWLER: 2018. It was a Guy Thwaites study, randomized. Rifampicin or placebo to patients with staph aureus bacteremia. You know, I guess I'd say there are different needs for different things. I've got a pickup truck that I drive since 1993. It's very effective for -- you know, down on our farm, we've got our family farm. It's great down there. I don't drive it to Washington DC because, you know, because I've had it, well, since 1993.

So I'm saying these are fit-for-purpose trials. You don't need a $250 million study or a study where -- whatever it was in the dapto study for instance, a hundred thousand dollars per patient enrolled? Do you really need that to answer every

single question about staph aureus? Of course not.

So I would say yes there are trials that have different purposes, and that there are fit-for-purpose studies that if we actually want to get some answers to these questions, we're going to have to look at how folks are doing it and the rest of the world.

I'll give you another example. CAMERA2 study. Steve Tong and Josh Davis down there comparing vancomycin or -- with or without an antistaphylococcal penicillin to confuse the issue with facts with regards to whether this combination therapy in terms of staph aureus bacteremia makes a difference or not. That study was done for less than $2 million, and it provided an answer that will fundamentally change clinical practice. Was it done to the level that absolutely has to be done in this context of answering the questions that the FDA needs answered? No, probably not. Was it good enough to help me know that combination therapy is probably not in the best interest of patients with MRSA bacteremia? Yes, it was. And I'll stop there.

JOHN REX: But it's noninferiority, so

you don't know whether the test was valid or not.

HELEN BADER: Well, it was superiority, right? But it's a little different than the focus of our question, which is about new drugs. Right? So I think what we're getting at is the notion of whether we the community need an indication for some of these, quote, more meaningful or more serious infections, or are we happy to get -- and again, I'm the simplistic simplistic person. But are we happy to get a skin indication and some PK/PD data in bone and other things to help us bridge to the right does and those things? And then ARLG or some other network or somebody else does the trial, and it gets published in New England Journal because it's such a great study and it informs practice.

So, Dr. Cosgrove?

SARA COSGROVE: Well, I kind of wondered if there was appetite for further discussion -- and this is directed at industry colleagues and FDA -- figuring out if there is any interest -- I mean, if the federal government has to fund these studies, that's a separate issue than if we thought that somehow you could tie these pragmatic clinical trials

to the label, or to something that would be beneficial in terms of marketing the drug. And I'm just curious what people think about that.

MANOS PERROS: If I can take a stab -- oh, sorry. Go ahead.

RIENK PYPSTRA: I just wanted to comment on the previous question. If it is indeed enough to just have the skin indication or the cUTI indication and practice be guided by some other information that is not reflected in the label, then we may not need an indication at all in the label anymore. It would just say this antibiotic is approved, full stop.

HELEN BADER: It was a purposely-provocative statement, but I think that to circle back to where we started at the beginning of the day, that is where a lot of us are in our day jobs, right? We have these product, right? We have these products that were approved, one of which is maybe not available, but that have a spectrum of activity against the more resistant pathogens. They're approved for a less-serious illness. And I've got a patient with a bloodstream infection or pneumonia.

So I was being provocative. Of course that's not what I'm suggesting. But I wanted to generate the dialogue.

RIENK PYPSTRA: Yeah, but to be clear, we want just a bit more in the labels, not less.

MANOS PERROS: If I may build on that why, this idea of an approvable trial followed by an additional trial that could get you additional data for indication. If you want to see new drugs developed for osteomyelitis or for multidrug-resistant pseudomonas, this is not a single trial; this is a 15-year R&D investment. And if you wanted to see a drug that's already approved for something else being used for osteomyelitis, that may be enough. You might be able to just put the data out there. The investment in the study is relatively small. The cost of developing and commercializing the product have been amortized. Maybe someone will put it on the market. But if you want a company or companies to invest in R&D project who will get you a new osteomyelitis drug, I suspect you need to have something on the label that will get approval, and you'll be able to go out there and promote the product.

RYAN CIRZ: Just listening here, sort of --

JOHN REX: Or in something you can use in a similar, Good Housekeeping Seal of Approval way.

RYAN CIRZ: It just seems like as an early-stage scientist, that's predominantly where my passion is; new things. It seems like there is an opportunity to help a little bit, especially the physicians and pharmacists, with explaining that to their peers, that this is a way we get drugs approved. Because it is hard to hear, like, oh, another drug for UTI. That's not how we do discovery. That's not how it works in the lab. We do chemistry and we test against resistant pathogens and look for spectrum gaps. And when we find them, we say ah, this works on something that nothing else works on. And then we say how do we find those pathogens in an easy way so we can show the new drug works just like the old one when the old drug works. But it will work when the old drug doesn't work based on the micro. And just to work for a decade and then have everybody sort of shrug and say oh, another UTI drug. And that's not actually the intent. Everyone here knows that. But

actually we could use your help explaining that. Because they're not going to believe it from us, honestly.

PAMELA TENAERTS: And I think the other reason why you're probably not happy with just UTI studies is that how are you going to get the approval for all the -- when you're using it off-label, so to speak. We've heard this morning about issues with hospitals not really jumping at the bit to provide drugs that are not approved in an indication and give those as part of DRG. So I think there is other things that need to fall in place, too, and other reasons why you may want more studies.

NICK KARTSONIS: And if I could just add one other thing. That's part of the reason why we did all those HABP/VABP studies, was not because we were masochistic, but because we really wanted those additional indications to help support us. And, frankly, outside the U.S., those are critical for reimbursement purposes and help drive value.

Now, studies like the osteomyelitis. If we were to pursue a path like that, we probably would say we won't do that as an -- I'm speaking for

big pharma right now, right? But we wouldn't do that for an indication, but we probably would try to support those through investor-initiated programs and what have you. And we've used those kind of programs before to try to fill these in when we know ultimately we're probably not going to pursue an indication, but are valuable from a strategy standpoint, to the extent we can do that, right? But those are subject to receiving proposals that pass some sort of muster as well.

SUMATHI NAMBIAR: So, Nick, as a follow-up -- Nick? Sorry. As a follow-up, when you said you wouldn't want to do such a study to seek an indication, what is the main reason? Is it the risk or is it the cost? Oh, sorry, I didn't --

NICK KARTSONIS: Yeah. I mean, I think at the end of the day it's going to come down to a business case. Right? I mean, I hate to be commercial about it. But at that point the company is going to say, okay, Nick, give me the financial return of doing -- if the study is going to cost $30 million, I want to see an MPV that's going to say that it will be positive. And you showed the (indiscernible) and

daptomycin slide earlier. By the way, I will never show that to my senior management.

But at the end of the day that's basically how it comes down to. I mean, because they could invest that money in oncology study and try to make those tough decisions in that particular way.

SUE CAMMARATA: And it's not only the money; it's just trying to get consensus on how to do those trials. I mean, you think about all the clinicians in the room. Do you all approach these diseases in the same way? The patients are somewhat individual and the problems you might have, the bugs you may have. So it's the challenge of cost, time, money. And then for these difficult indications, just getting a consensus around -- again, I'm going to emphasize around the world, because we have to think about it in that respect.

DAVID MELNICK: You know, we're struggling to expand our value dossier to support reimbursement at the same time we're trying to do the $300 million worth of post-marketing requirements and commercialization costs. I mean, what we're talking about comes very close to the pragmatic approach that

the companies take. We use a core indication to get to market, and then we do, to the extent that's possible, these small value expansion studies to try to demonstrate the value of the antibiotic. But we're in a position where we can't really discuss that in the marketplace to the clinical community.

ROGER LEWIS: It strikes me that we're stuck with a common dilemma of having to make choices between options that are actually available to us. There's on option, which is to -- and in the setting -- and I think the comment about us talking about new drugs, not pragmatic use of older drugs is really important for context.

One choice is to get very good data that meets the traditional regulatory standard and defines labeling on the easier-to-study indications for which we have drugs, because they were easier to study. And then to allow the clinicians to fly relatively blind in terms of their use of those drugs for other indications. Not absolutely blind, but they're trained clinicians. They recognize how these diseases work. But relatively, because there's both a relative lack of well-collected data that has been

interpreted by the regulatory agency. The regulatory agency is not in a position to write language of any sort of guidance such as might be contained into a label. Therefore the marketing can't reflect the agency's input. And there are things like investigator-initiated studies which are another form of marketing. And we just have to ask, is that really the right situation for us to be in?

I also suspect that the comments and the perceptions on antibiotic stewardship reflected in this room come from a highly-selected set of institutions that don't reflect the level of antibiotic stewardship that exists in most of those 80-bed hospitals in the U.S. And in those hospitals, if a brand-new antibiotic comes out and its indication is UTI, it seems like fair game to treat a UTI. And that is a real problem in terms of the development of new resistant organisms or multiply-resistant organisms.

So I think that we really need to look for opportunities that allow us to both study the diseases that we can study because they're practical to study, and also collect objective, randomized data

on those harder-to-study indications and have the regulatory agency or agencies, if it's a multinational situation, show a little more flexibility in how they use that data that is of lesser quantity, but not quality, in order to inform clinicians and therefore marketing and how those agents should be appropriately used, and in a way that really does support stewardship.

What I'm really concerned about the one more drug for complicated UTI is the degree with which that approval with that language and only that disease systematically undermines the public health imperative for stewardship at the hospitals that don't have the stewardship programs that are reflected in this room.

AARON DANE: I think I was going to echo some of that, which was something Roger said earlier actually. Because we moved back towards saying, well, you do a skin study or an osteomyelitis study. But I wonder whether that is an area where you do a study with both and you have the core of the skin, but then you do borrow information or do something like that so you don't need to do the fully-powered osteomyelitis study, but you can draw on what

you've got there. Obviously that would involve more detail looking into the design, but it's just the idea that rather than just saying, well, it's two completely separate studies of a similar size, you actually -- that other aspect could mean that it's a lot smaller if we can draw heavily on the skin data that we've got. So there's a number of areas we could do something like that and maybe consider that as a way of getting it both within the same study.

VANCE FOWLER: So, I mean, there are things that we can do and we can't do. It seems like one of the things that would be at our disposal if the intent is, again, focusing solely on new compounds and stand on that line, okay. So the trials that need to be done aren't being -- look at the question of why are the trials that need to be done not being done. And, you know, at least from my experience with working with sponsors on staph aureus bloodstream infection in osteo in particular, a lot of it probably has to do with what they're encountering in terms of the regulatory pieces. The PENS example is one. The timing of follow-up for osteo patients would be another.

In fact, there was a beautiful idea, I think Barry Eisenstein proposed it maybe ten years ago. Still one of the coolest ideas I've ever heard in terms of trial design about using surrogate marker for osteo at the time of a two-step revision whereby if you found culture or acute inflammation, which would be actionable items clinically, that you could use that as your endpoint.

So, you know, finding means whereby this would be, again, get your skin, get your complicated UTI. But then for that second study, you find some means of flexibility whereby some of these restraints are revisited in a way that still achieves the goals of the FDA, but at the same time makes -- the study is doable. And I'll stop there.

HELEN BADER: All right. I think we'll move on to question two in the interest of time.

DAVID MELNICK: Could I just add one thing?

HELEN BADER: Sure.

DAVID MELNICK: You know, this is a perfect segue to the idea of networks and platform trials. You know, if we used a core indicator, you

know, sort of a market entry indication to establish safety and demonstrate the performance of a drug, if there were standing networks dealing with skeletal infections or bloodstream infections or HABP/VABP or resistant pathogens, one could then feed the new agents into those master protocols. And in fact you find that in a HABP/VABP study, somebody's got Acinetobacter, they go in one direction. They have CRE, they go in another direction. They have (indiscernible), they go in another direction.

So to me that's one way where we could amortize the cost of developing this downstream data across a number of products and hopefully have some central support to do it.

HELEN BADER: Okay. So question two. As there are some approved therapies to treat CRE infections and others in development, future noninferiority trials could enrich such organisms. For a future new agent targeting gram-negative pathogens that retains activity in the presence of certain resistance mechanisms, what should the design of clinical trials look like to get interpretable data? Please comment on the choice of comparator, the

patient population, and enrichment strategies, something that some of us have talked about before.

JOHN REX: Reading this again, I'm thinking here about the notion that now that -- we now actually have drugs that treat CRE. It's not every one of them, but at least some of the time we do. And so if I now did a randomized study of new drug versus Zemdri, new drug versus (indiscernible), I could reasonably go to a place that has a lot of CRE and say rock on. You know? Sign them up. And if we happen to get 10 or 15 percent CRE, then great. That would be a wonderful thing.

I think I had not processed this question fully until I was just reading this slide again just now. So is that really what you guys were thinking as you wrote that question down?

SUMATHI NAMBIAR: So I think the lookback may be four or five years ago when we didn't have these products that were CRE active agents. We had to do the kinds of trials that were done just enriching -- just in CRE with CRE patients. But now you have two or three therapies, there's more in the pipeline. So hopefully they will be available as

well.

Then it really is like the MRSA paradigm. Now in skin trials or bacteremia trials, you can enroll in MSSA and MRSA because you have an appropriate comparator. So then that really raises the question, do we need one of these standalone CRE studies which we've heard are difficult to do and then difficult to interpret and really cannot get into label? Are you then better off doing a noninferiority trial for your standard indication, use the appropriate comparator such that these trials can actually have patients with CRE infections and they will be described in labeling? That would make our lives a lot easier. So I just wanted to bring that up for discussion. Because things have changed, right? The discussion we had five, six years ago was not -- is not where we are today. And so I just wanted to get everybody's thoughts on that.

I mean, we've had some of these discussions with some of you individually when you have come to meet with us, at least some of the practical challenges we've heard is these comparators are certainly a lot more expensive, so it adds cost.

It's probably not available in a lot of the counties that are enrolling. But I think a lot of those could potentially try to overcome if the net gain is that then you don't have to do the CRE study, which costs a lot of money and really doesn't seem to be very helpful. So that's the background for this question.

HELEN BADER: Okay. So it looks like we have Nick, Ryan, and then Roger. So, Ryan.

RYAN CIRZ: I think this question was sort of the genesis of the earlier comments that I made. And Aaron rightfully corrected -- you know, sort of trying to simplify. When we went to Phase I with plazomicin, I think we looked and said, oh, it would be hard to get enough VSPLs in a trial. But it took us a long time, and it's actually really easy. And I think we'll get there with CRE, unfortunately. That's why we're still working in the space. Maybe it will be 10 or 20 percent. But it's still this interesting logic trap.

And so again, just to use an example because they're different, and to use it on an equal playing field, let's just say complicated UTI (indiscernible) and Zemdri. Right? If both agents

are active, you could potentially show that they're both noninferior to one another. If the CRE has a (indiscernible), it won't work in (indiscernible), and you won't be able to show that because you can't enroll. And if you have a Class B metallo, (indiscernible) won't work and plaso might. But you can't show that because you can't enroll.

And so the idea of showing plaso as NI to (indiscernible) isn't any different to me than showing plaso is NI to meropenem on ESBL. It's just a genetic change. So we could do it, and I think it will happen by mass action, but I don't understand the scientific point of worrying about doing it.

AARON DANE: I guess my question was on that. It does sound like a good idea. But what you would be able to say about CRE after a study like that. So are you in a better position than now with the situation of a study where you can say anything on the label, would you actually be able to make some statement about CRE in a noninferiority study?

SUMATHI NAMBIAR: So why -- I mean, we could say something about CRE, right? They were part of the study. It would be like how we describe

microbiology data currently in the label.

AARON DANE: Yeah. I suppose it's this disconnect between do a properly compatible study and can't say anything about it whereas if you do it as part of a noninferiority study, you can. But I guess if that's possible, it feels like it an option.

SUMATHI NAMBIAR: Right. As long as your comparator is -- I mean, if you're going after NDMs, certainly you cannot have (indiscernible) or any of the currently-available as your appropriate comparator. But if you've chosen an appropriate comparator, could you not enrich and include patients with CRE in the trial?

AARON DANE: I think so, yeah. I think it wasn't so much the design; it was more what you're going to be able to say about CRE afterwards given you're only going to have the same number of patients as they had at the moment. That was all.

SUMATHI NAMBIAR: They will be part of the overall population, and that's all you can describe.

HELEN BADER: It would be like MRSA in a skin study or pseudomonas in a HABP/VABP study.

ROGER LEWIS: So this is actually -- I'm stealing the microphone from you, because this is exactly what I was going to address. I think your answer is actually potentially a bit concerning.

So when we enroll patients with a variety of pathogens, and we simply list all the pathogens that were included in the study, what we are implying is that we think they are all exchangeable. We have no reason to believe that one pathogen is more or less likely to respond to either the comparator, the test, or at least the delta is expected to be the same. And that may be true in many cases. It's probably not true if you've specifically enriched for CRE. Just the way you folks talk about CRE -- I'm not an ID person. The way your body changes when you talk about CRE, okay? You clearly think that organism is different than the other organisms. Okay? So that violates the assumption that you should just think about them the same.

So I think the prior question was really good in the sense that the amount of enrichment for CRE and the fact that you get some representation -- and I don't know in your mind if you're thinking 20

percent or 30 percent. It's not -- that doesn't mean you can just assume they're all the same suddenly because you had enough of them. There has to be some sort of quantification of whether you have enough information to justify lumping them all together, or you have to have enough that you can separate out and make some sort of estimate of whether there is evidence of heterogeneity of treatment effect with a confidence bound around that estimate of the heterogeneity.

And so the way the question is worded, it sort of implies that, well, if we have some magic, enough fraction of CRE, because it's like the other things we throw in, isn't that good enough? It may fit tradition, I'm not sure it fits inferential rigor.

HELEN BADER: Good point. Rienk?

RIENK PYPSTRA: I would like to respond to that. You're absolutely right if you can only look at clinical results. But we have the advantage of being in infectious diseases. We have the pathogens separate, we have the pathogens in animal models. We have a whole body of evidence. And what I hear from Ryan, and I fully agree with you, is we need to look

at the whole science, at the whole data package. And there is no reason to believe that a CRE is going to behave differently than the completely sensitive E.coli if you are confronted with a drug that acts through a different mechanism of action. And that is the crux. And so why would you have to go through all the effort in demonstrating it if you can make the argument very logically?

RYAN LEWIS: Right. And I certainly didn't want to debate the relative validity or assuredness that is available from preclinical and ancillary studies or laboratory evaluations of clinical isolates. But if we believe we need new randomized clinical data that includes CRE, we can't at the same time say we don't. If you do need it, you should know why you're collecting it and what threshold of evidence you need from it. If you don't need it because, sorry, Ryan is correct and he can predict these things, that's great, too. But we shouldn't be internally inconsistent in our logic.

HELEN BADER: Ryan?

RYAN CIRZ: Maybe a useful study or a publication from the community would be something --

you know, it's not that I'm not openminded that a change in a genetic sequence of an enzyme that degrades a beta lactam could completely change the pathology of the organism. I just wouldn't start there as the first principle. But if there was a study that suggested that, it would be really interesting, and maybe it could be true. But why start with that as the base case, which overcomplicates everything for everybody. And I've been struggling with sort of my history of why do we think it's different. And then you all are much better at figuring out co-variants, things like, well, if you have CRE, maybe you've been on six rounds of antibiotics because you're immunosuppressed, or all these other things that scare us more that are just co-associations. But one that strikes me a lot is kind of the traumatic experience in the narrow nears before the new agents.

And one of the tragedies of the KARE study as sort of an arcadian historian was when we showed up in Greece -- remember, this was seven years ago -- people told us colistin isn't that bad and these patients are just sicker. You know? The

colistin is fine; it's these patients that have CRE, they're just sicker than everyone else. And I think that impacted the potential of the treatment effect. And honestly if we had known the number of patients that it might have taken to show that, we probably would have kept the study going, but we didn't. We thought it was going to take another 300 patients I think was the estimate.

And so part of my bias goes back to that fear from maybe a poor-performing drug for a period of time, putting this idea in our head that this organism is somehow different. Completely open-minded that it is. I just haven't seen any evidence that it is.

HELEN BADER: Manos?

MANOS PERROS: I'm delighted to hear so much support for taking in the totality of the scientific evidence. I'd like to make a slightly different point, which, apologies, might be obvious. But by the time you have a pathogen or indication for which there are a number of adequate treatments, the medical need is lower. So though that question is important, it's not as important as the question of

can you do that for drug-resistant pathogens.

HELEN BADER: Sara?

SARA COSGROVE: I think there are a bunch -- I mean, CRE means carbapenem-resistant Enterobacteriaceae. So obviously there are not all the same. They have different resistance mechanisms. So some are enzyme producers and some have other non-enzymatic mechanisms. So I do think you actually have to think a little bit about what mechanisms you're interested in when you think about that question.

But I do think that something that keeps nagging at me is that there is no patient that I have treated with any of the new agents that is anything like the patients that were in the clinical studies. And that's really the problem for me right now.

So can I feel confident that these drugs are safe in the patients that I am using them in who have -- I mean, I can't even succinctly explain the problems of the patients that I have been using them in. And that does worry me a little bit. So we can enrich for CRE, but if it's still for complicated UTI, it's still not going to have the patients I'm

using the drugs in in the study.

NICK KARTSONIS: If I could make a comment to that. I bet you the resistant infection studies are more like the patients that you treat, right? You know, the KARE studies and the Restoria studies, they are very heterogeneous and they're very difficult to interpret from a statistical standpoint, but they probably are more real-life in that regard.

RYAN CIRZ: And that's the exact genesis of why earlier I was trying to separate the resistance piece. It's just biochemistry. I get it. The severe physiology condition is a whole different ballgame. Although it is something that if you separate the two suddenly and say it's not the CRE I care about, it's the severity of the condition, then you can start to think about different ways to get evidence to give you information on performance in those settings. Putting them together is what gets us into the we have to run this $50 million, ten-year trial.

SUMATHI NAMBIAR: So should the approach then really be trying to enroll patients with comorbidities and these sicker patients in the trials

that we are currently doing? Should that be the focus moving forward? And that's something we've always encouraged, but I think there are practical difficulties in enrolling them in these trials. So that's the tension here.

Certainly the resistance phenotype comes usually with the host, right? It's really the host that matters at the end of the day. And whether or not it works against a resistant phenotype XYZ really is not that important. Because if it's susceptible to the test drug, a point that you made earlier, that's what we really need. It doesn't matter what else it's resistant to or not resistant to.

But if you're really looking for the most sick patients, because those are the kind of patients who are being treated, then maybe that's what we need to focus on. And how can we get those kinds of patients and what are the limitations in being able to enroll such patients? I mean, it's not just studying the pharmacokinetics and renal-hepatic impairment; they're only one part of it. But what else do we think we should focus on moving forward?

JOHN REX: Isn't that in effect what we've now seen two or three drugs do? They have run a -- pick an indication trial. And then they have in parallel typically at the same study sites -- it could almost have been one study. Okay? Here's Study X, here's your study. It's got two arms. Arm A, cUTI, kind of ordinary cUTI. Arm B, whatever. And you're randomizing and it's a stratum. Arm A has one randomization and Arm B has another randomization. And two-and-a-half years later you -- actually, 18 months later, your cUTI study is done, 400 patients there. And you've got 82 patients in Arm B, and you analyze it. And that's what you've got. And I don't know how to do better. I mean, honest to Pete. What do we do that is consistently and predictably better than that? And I can't really run it for five years. I need to get to done. I need to have made a certain -- you know, think about it. All the CMC stuff. How much drug product do I have to have had available to run this study and to be at these sites? And then there's the plant I've got to -- I can only have so much stuff available at the time I do the Phase III study. It's not an infinite universe. And I'm going

to run out of money because I've just now spent $70 million, and that's the last I'm going to get out of anybody, ever.

So to me, I'm really -- you know, Roger has brought in this notion of why aren't we more willing to borrow data across body sites and indications? And we would like better data and we would like a pony, too. You know, I'd really like to -- but a pair of sandals is better than walking barefoot. And I think that's the theme that we're getting at here, is that the pair of sandals is better than walking barefoot. And yes, I'd prefer to ride, but I'll walk if I have to; just give me the sandals.

HELEN BADER: So is there any inferential question we can ask?

JOHN REX: No. It is -- and it's going to -- we're thinking here about what -- because the confidence (indiscernible) are going to be too broad. Dan's head is going to explode. And as it should. We're not saying that it is of the quality that we would like, but it's the quality we're stuck with unless we want nothing. I mean, your choice is sort of between a sin of omission and a sin of commission,

if you will. I mean, is there another choice?

AARON DANE: Well, I think the reason it's worth thinking about that is because this question, which is specific to CRE, may work. But that relies on there being three therapies available. So when you get to the next pathogen that hasn't got that, you're stuck again. And so it feels like we need a way of knowing how we're going to do this for both situations, both when there is a comparator there and when there isn't. Otherwise, we're going to keep going round the same cycle every few years.

HELEN BADER: Point. Nick? Left over? Okay. Lindsey? Sorry.

LINDSEY BADEN: No, I just think John's decoupling too many issues at once. Because I think Ryan's point about decoupling the microbial resistance determinant, because there is a strong logic, one could imagine really pushing that logic to make sure it makes sense. I'm still not convinced that the same antibiotic is going to work the same in CNS and in lung and in prostate without more evidence that it behaves that way. But I could imagine a study that looks at pneumonia and doesn't only target the

incredibly resistant organism. Because that's the decoupling that might make these trials more approachable. And then one has to believe that whether or not the genetic, not the phenotypic resistance determinant being present or absent is not the critical element.

So I think that decoupling has the potential to reframe some of these trials. It's a bridge that is even further if we no longer need to look at the different body sites for in vivo activity and just assume in vitro activity.

JOHN REX: So I think that the preclinical community has convincingly proven that if you have two isolates with the same MIC to drug X but different MICs for drug Y, drug X will work the same way on both of them. The drug on the bug in a plastic dish or in a mouse will work the same way. So you have two isolates. They have identical MICs for drug X and wildly different for drug Y. Drug X's effect will not be impaired by the presence or absence of activity for drug Y in the test tube. And just provided the drug concentration is adequate -- I mean, Paul Ambrose has done that over and over and over

again. The MIC tells you -- but the two patients who are infected -- that's where you're going. The two patients that have those two isolates, they might have different clinical responses because the patients themselves, as Ryan said, having the wildly resistant organism is a marker of your comorbidities or your other illnesses.

LINDSEY BADEN: No, not necessarily. I was agreeing that it's worth really thinking about the decoupling for presence or absence of genetic resistant X. Decouple that and say maybe that isn't the in vivo element that is critical to the study. The in vivo element that's critical to study is new drug works in pneumonia in critically ill patients the same as standard drug for the isolate that isn't necessarily the resistant genotype.

And because I do worry that critically ill folks have different physiology and I do worry that drugs and sites don't always behave the we predict. But the genotypic issue the data are -- there's a strong rationale to be able to overcome the genotypic concern, which is I think what Ryan was getting at as the two parameters that make it

impossible. You need critically ill plus you need genotypic proof in order to study it. And that becomes undoable. But if you only need critically ill syndrome and the right organism, then you might be able to study it using the other data to bridge the genotypic issue.

And part of the reason I think that's so important is that ultimately we want countermeasures for bugs that are rare, because those are the ones I'm most concerned about. I'm most concerned -- you know, 1990 we didn't care about VRE because it didn't exist. I'm worried about the bug that doesn't exist or does exist in a limited place that is about to be amplified and expand globally. And in order for us to have data on how to treat that, by definition we can't study it in vivo because it doesn't exist in large enough numbers.

So these other data are able to be strong enough for us to say we think it should work. And then it would need to be confirmed when one can. But is there a regulatory path to allow that? And I think that's part of what Ryan is suggesting. And, you know, there's strong rationale for that.

HELEN BADER: Okay, thanks. So we'll do David, Roger, Ryan.

DAVID MELNICK: It seems to me we're cycling back to the current starting point, which is that sponsors have struggled mightily to deliver these resistant pathogen studies unsuccessfully. We've tried to enrich our trials for resistant pathogens, we've tried to deliver cross-indication RP studies, and we've failed. Maybe the one exception was the CAZ-AVI resistant pathogen study, which worked only because the resistant pathogens had become very, very prevalent.

So, you know, I think this idea that somehow we can drive our current trial designs to deliver data that's going to be adequate for inferential testing, not going to happen. And it's certainly not going to happen in this commercial environment.

So we need -- I think we need to look at alternatives, whether they're pragmatic trials or making use of some other data source that comes in after the fact to provide evidence to support the utility of these new compounds outside of their core

entry indication. Otherwise, we're never going to win.

ROGER LEWIS: So I think we're challenged when we have a single threshold for what an inferential criteria is. Oh, sorry. I think we're challenged when we have a single threshold for inferential success. And the conversations have been illuminated by lots of examples of ancillary information or augmenting information that should appropriately change that threshold.

So it appears that there are situations in which folks might reasonably think you don't need new data because you know so much about the organism and the site and the penetration, the MIC and the PK that you just -- you can put all the organisms together and write that on the label.

There are settings in which the diseases are different enough that you wouldn't want to simply assume they behave all the same; meningitis, osteomyelitis, settings of foreign bodies. But if you started to have some supporting information and the information supported the idea that the treatment effect was homogeneous across multiple diseases, that

would meet a reasonable inferential threshold. And there's a different setting when the disease is so different or the organism is so poorly understood or new or we can't even pronounce it as a panel, that you really need standalone information.

And I think the thing that we need to struggle with is how to have informed, multidisciplinary conversations about how to adjust the threshold for considering the inference strong enough to support recommendations to clinicians that's good enough for the right situation. And again, I think that if we stick into sort of an all-or-none where it's either the standard threshold which we can never meet, so we're going to throw up our hands and give people no guidance and collect no data, that seems like a really sad conclusion from a group with the intent of improving public health and the information that guides medical care.

RYAN CIRZ: And just to go I guess one step deeper on kind of demystifying logically why would a drug work in one site and not another, I think there's plenty of reasons. But we never quite sit down and list them and then say how do we start

knocking these out, that that's not true. We just sort of say you have to show it directly. But, you know, the lung lining fluid is like the number-one example, right? And I can only think of one where there was a really unique situation where the drug was inactive in that compartment. In almost every other case, it's just a matter of, especially in the gram-negative drugs, they're all incredibly water soluble. They have to pass through interstitial barriers, it takes time, and the drug's clearing out of the kidney while it's dialyzing. It's all the same principles affecting every polar drug. And there are ways to study this and get our head around it without a complete trial and try to prove it. So two potential cases. There's less drug there than there is in other sites, or the drug works differently when it gets there than in other sites. And I never see a real logical sort of walking through that. Just sort of, like, show me, because I can't believe it unless I see it. But I think there's some ground to begin. They're just leveraging other reference points showing that honestly most of the gram-negative drugs -- I'm guessing if you do a study internally controlled,

because some of the methodology is so dicey for measuring pulmonary levels, you'll find out they're kind of all the same because it's physics; it's just how the body operates. And if we can show that, then we can show the physiology for one drug predicts the other. Because these patients that are crashing, it's fluid volume, it -- you know, obviously we're pushing extra water in. The drug dissolves in water. We could probably translate a lot of results from different drugs to each other as long as they share similar physical properties.

So the one thing I see lacking as a scientist is even if in the end we still have to do the exact same trial, it would be really refreshing to hear us talk about here's the exact physiological thing we're concerned about and why we need to go show it just to make it feel more real.

HELEN BADER: Aaron?

AARON DANE: I was just going to echo what Roger was saying. So what I'm going to try and talk about tomorrow is this idea of these magical criteria we have for inferential statistics. If we know we can only get 50 or 100 patients, we know the

setting. Can we shift some of those? Can we do that in an informed way so we don't just blindly do that? But it feels like that's a way of rather than saying, well, if we can't do 200 or 300 patients, then there's no point in doing anything, which seems to be where we are at the moment.

And so understand the risks, understand the consequences of that, but certainly look at it in that way and try and have a bit more of a broader view on what we might be able to do with the numbers we can get to.

HELEN BADER: Okay, we'll have a quite note for question number three, which is some feasible approaches to updating treatment guidelines more frequently. Anybody want to have a stab at that? I'm between everyone's dinner time. Dr. Sears, you've been nominated.

CYNTHIA SEARS: Well, I tried to present a structure in which we're considering -- and I don't know if silence is, you know, okay, give that a try or if there's other comments.

It is a complicated business and it is definitely hard to rally all the forces needed to do

something like this. You can all think about it. My email is readily available. And just send me any thoughts. Because we are there. So if you want to have some input, now is the moment.

HELEN BADER: Great. Kevin?

KEVIN OUTTERSON: So I was just wondering, what do you think it costs? What is the budget for IDSA? And then the second piece of that is, you know, if you had a larger budget and you could have a full-time person, a post-doc that, you know, was on the budget for -- is there a way to increase the quality and speed?

CYNTHIA SEARS: You know, I don't know what it costs. I know that budgets are under development. The IDSA budget is approved by the Executive Committee and the Board in December. That's flexible. You know, we're not static at all.

As just a comparison, the HCV guidance was a $400,000 project. And yes, more money always -- you know, to do this at the pace that I think I sense the group would like, you know, takes really a big investment. And then to keep it going, to keep people -- we need a group of really engaged people who are

ready to move quickly. And, you know, that's complicated, trying to figure out exactly how to put that together to draw on those resources at the moment you need them. But, you know, money always helps.

KEVIN OUTTERSON: So just to put the question back. So you said $400,000 for the hep C. So would it be fair to say that a million dollars a year for the next five years, you know, if that money came from someplace else, that that would really just transform your ability to do guidance?

CYNTHIA SEARS: I think the short answer is yes.

KEVIN OUTTERSON: And Amanda had a little proviso.

AMANDA JEZEK: I was just doing to add it depends on if that money comes with any strings.

KEVIN OUTTERSON: It could not come from any company at all.

AMANDA JEZEK: Right. Well, or if it came from a federal agency, what would be the requirements around that. If we wound up having to invest the majority of those funds and simply reporting back to a federal agency and not actually

developing a guideline. Just as an example, not that that would ever happen.

KEVIN OUTTERSON: That's never happened in the history of...

HELEN BADER: Okay. Aaron, did you want -- okay.

MANOS PERROS: Thank you. It's also a question more than a comment. Guidelines are important, but well-informed infectious disease physicians can put two and two together and from the published data and molecular data they can often make the right choice as infectious disease pharmacists as well.

From a company perspective, the constituency that we do influence goes well beyond that. Guidelines, for instance, influence hospital administrators, so payors (indiscernible) as an example.

HELEN BADER: Great. All right, well, I'm very aware of the hour and just want to say thank you to everybody. I think the talks today were outstanding, as was the discussion. Really appreciate everyone's really respectful, engaged, spirited

dialogue.

I just want to remind everyone to take all of their things. Just leave your tent cards if you would, panelists, but take all your paperwork and everything. Because I think we may even be in a different room in the morning. Same time tomorrow. Registration starts at 7:30. The meeting starts promptly at 8:30. And we will see you soon. Thank you.

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