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FOOD AND DRUG ADMINISTRATION (FDA)  
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)  
  
PUBLIC WORKSHOP:  
  
FACILITATING ANTIBACTERIAL DRUG DEVELOPMENT FOR  
PATIENTS WITH UNMET NEED  
AND DEVELOPING ANTIBACTERIAL DRUGS THAT TARGET A  
SINGLE SPECIES

Monday, July 18, 2016

FDA White Oak Campus  
10903 New Hampshire Avenue  
Bldg. 31, Room 1503A (Great Room)  
Silver Spring, MD 20993

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

8:30 a.m.

## WELCOME AND INTRODUCTIONS

DR. COX: Good morning. Good, the microphone's on. Welcome, everybody. I'm Ed Cox. I'm director of the Office of Antimicrobial Products. And can folks here me? We're good? Okay. I just want to start out by welcoming everyone. I'm still getting myself oriented here at the podium a little bit -- to our public workshop on facilitating antibacterial drug development for patients with unmet need. And just so that folks, you know, understand, I mean, this is a workshop. It's not an advisory committee. So it really is an opportunity for discussion. It's not really an exercise in achieving consensus.

We do provide conflict of interest information, which I think is available at a table out front, if folks are interested in seeing that. And we'll also, later on in the day, have an open time for comments for anyone who wishes to provide their viewpoints. And I thought what we'd do first is just



1 go around the panel and have folks introduce  
2 themselves this morning so that folks know who is on  
3 the panel. And maybe we'll start on my left with  
4 Kert. And please just introduce yourself and use the  
5 microphones so that folks, both on the webcast and in  
6 the room, can hear you.

7 DR. VIELE: Hi. I'm Kert Viele, from Berry  
8 Consultants. I'm a statistician.

9 DR. RUBIN: Good morning. I'm Dan Rubin, a  
10 statistical reviewer at FDA.

11 DR. AMBROSE: Hi. I'm Paul Ambrose, from  
12 the Institute of Clinical Pharmacodynamics, a PK/PD  
13 guy.

14 DR. FRIEDLAND: Ian Friedland. I'm the  
15 chief medical officer at Achaogen.

16 DR. REX: John Rex. I'm an internist and ID  
17 specialist at AstraZeneca Pharmaceuticals.

18 DR. KARTSONIS: Nick Kartsonis. I'm an  
19 infectious disease clinician and I work at Merck.

20 DR. CAVALERI: Marco Cavaleri, head of anti-  
21 infectives and vaccines, European Medicines Agency.

22 DR. MARKS: Lynn Marks, infectious disease

1 specialist at GlaxoSmithKline.

2 DR. NAMBIAR: Sumathi Nambiar, director of  
3 the Division of Anti-Infective Products, CDER, FDA.

4 DR. BORIO: Lu Borio, ID clinician and an  
5 acting chief scientist.

6 DR. DUDLEY: Mike Dudley, from The Medicines  
7 Company and head of research and development.

8 DR. LARSEN: Joe Larsen, acting deputy  
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10 DR. LOUIS: Tom Louis, Johns Hopkins,  
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12 DR. DIXON: Dennis Dixon, NIH, NIAID.

13 MR. DANE: Aaron Dane, statistical  
14 consultant.

15 SESSION 1: GENERAL CONSIDERATIONS FOR UNMET NEED  
16 PROGRAMS

17 EFFECTIVENESS STANDARDS INCLUDING ORPHAN  
18 PRODUCTS

19 DR. COX: Great. Thanks, everybody. And we  
20 appreciate all that have come to join today and all  
21 the panelists that have also traveled far and wide to  
22 come and join us. And let me just -- I'll just

1 briefly walk through -- I think folks have the agenda,  
2 so I'll briefly walk through some nuts and bolts.  
3 This morning, we'll talk about general considerations  
4 for unmet medical need development programs. We'll  
5 have a series of talks, you know, describing different  
6 pathways. And then, as we move on in the day, we'll  
7 actually hear from a couple of folks that have, you  
8 know, tried to venture into this area. They'll share  
9 with us their experiences to date, what's worked, what  
10 they've run into as far as the challenges in doing  
11 such programs. So we appreciate their willingness to  
12 provide us with those details. I think that'll be  
13 very helpful.

14           And then, later in the afternoon, we'll have  
15 some discussion about statistical considerations for  
16 developing antibacterial drugs using an unmet need  
17 paradigm. So I just want to provide a little bit of  
18 background and some context. You know, we typically  
19 find that as we're preparing for a workshop,  
20 oftentimes there's a lot of very rich discussions  
21 during the course of the preparations for a workshop.

22           So what I'm going to try and do -- my talk

1 is a little bit disjointed. But I'm going to try and  
2 touch on a number of the issues that came up as we  
3 prepared for today's meeting because I think that may  
4 be helpful. You know, folks know that the  
5 antibacterial drug development area is particularly  
6 challenging. Scientific reasons make it difficult.  
7 You're not exactly sure what the patient's diagnosis  
8 is. The patient may need other overlapping therapy  
9 that can obscure the assessment of the drug that's  
10 being tested. There's a lot of drugs out there, but  
11 there are still patients who -- for whom those drugs  
12 are not good options because of the development of  
13 resistance.

14 Economically, it's also challenging, not  
15 within the scope of what we'll be talking about today,  
16 but there has been a lot of important work looking at  
17 the economic issues for antibacterial drug  
18 development. And also though it's not really parsed  
19 into these two poles, but more of a continuum, we do  
20 see antibacterial drug development in terms of  
21 standard development programs. These are the more  
22 traditional development programs where there are

1 molecules that are being developed using sort of  
2 traditional NI margins, traditional study approaches.  
3 And then, on the other end of the pole is the area of  
4 unmet need development programs. So these are  
5 development programs that are characterized typically  
6 by a greater degree of uncertainty and it's not a  
7 decision per se to go one way or the other based on  
8 the absence of information about the drug. Actually,  
9 the drug and its characteristics are very important in  
10 determining which pathway one might choose.

11 For a molecule that is pursuing an unmet  
12 need development program, there really has to be a  
13 particular characteristic that make it a reasonable  
14 choice, such as it's a molecule that operates via a  
15 new mechanism of action. It's otherwise stable to  
16 resistance mechanisms that would otherwise chew up a  
17 molecule or it's paired with a resistance inhibitor or  
18 something of that nature. So we know the current  
19 antibacterial pipeline is quite fragile.

20 There have been some changes that have  
21 happened over the last several years that have helped  
22 some, with passage of GAIN, the qualifying infectious

1 disease product legislation that came in place, which  
2 provides for fast-track designation, priority review  
3 and an additional five years of exclusivity for drugs  
4 that qualify. And the QIDP designations so far are up  
5 to 63 different unique molecules, probably the more  
6 important number. The 107 is sort of a factor of how  
7 you split up -- if you look for different formulations  
8 or different indications. So 63 is probably the  
9 number to index off of here. And then, we have to  
10 keep in mind that, in general, most drugs that enter  
11 into Phase I are not ultimately shown to be safe and  
12 effective. So although these numbers sound quite  
13 large, you know, some of them may -- some of them  
14 won't make it we know just based on experience.

15           And it's also important to keep in mind too  
16 that when we think about bacterial diseases and  
17 antibacterial drugs, that the response that a patient  
18 experiences is not just the antibacterial drug, but  
19 there's also the immune system, tissue repair and  
20 other events going on that happen as the patient moves  
21 from being ill to being better. I won't spend much  
22 time on this slide. But folks are aware of some of

1 the recent approvals for antibacterial drugs and I've  
2 included in here also a drug for TB. And unmet need,  
3 so if we think about unmet need, how do you get there.  
4 Well, if you have a less than robust antibacterial  
5 drug development pipeline, it provides an opportunity  
6 for resistance to essentially get a little bit ahead.  
7 And so, a situation where you have unmet need is  
8 actually something that you prefer to avoid. You  
9 don't want to end up in a situation where you have  
10 bacteria that are resistant to multiple drugs such  
11 that you have patients who lack good therapeutic  
12 options.

13 So ideally, if you have ongoing development  
14 that's robust, you can have agents already available  
15 that have already been shown to be safe and effective  
16 prior to the point in time that you need them. And we  
17 know already that it's difficult to react in a timely  
18 fashion once an unmet need has arrived -- has arisen.  
19 You know, it may take 5 to 10 years to develop a new  
20 antibacterial drug. So a resistance mechanism that  
21 pops up today, to embark upon a program at that point  
22 in time is really not a timely way to respond.

1 Sumathi will go into a little more detail on  
2 trial design options for unmet need. But here's some  
3 of the different options that you might think about, a  
4 non-inferiority trial design. You can do it in a body  
5 site of infection. Superiority trial in one body site  
6 or you could do something pooled across multiple body  
7 sites. And Kert will talk some about some of the work  
8 that his group has been doing on this a little bit  
9 later today. Nested NI superiority trial designs  
10 based upon the patient's baseline isolate. And we've  
11 also seen development in the area of .-lactams that  
12 have been previously approved paired with new .-  
13 lactamase inhibitors. In this situation, you can rely  
14 upon the previous finding of safety and efficacy for  
15 the previously approved .-lactam drug. Another area  
16 too where there's some activity is that of showing  
17 superiority of an adjunctive therapy with standard of  
18 care over standard of care.

19 And let me talk some about non-inferiority  
20 trial designs. You know, this is an issue that comes  
21 up. It's a topic of which there's really much  
22 discussion. And Sumathi and I and some others wrote



1 on this even a couple of years back. I think it was  
2 in 2014, in the summertime. If you think about it and  
3 what the circumstances that you need to have in order  
4 to be able to show superiority, it's likely time-  
5 limited. It really is dependent upon enrolling  
6 patients with, you know, resistant phenotypes for  
7 which you have inadequate options. And this could be  
8 really challenging, particularly if, you know,  
9 patients who have, you know, few options are -- you  
10 know, if the frequency is not that high.

11 And if you think about it, if this is a very  
12 difficult paradigm to follow, you could take a good  
13 drug, an effective drug and run into challenges and  
14 difficulties in conducting the clinical trial. So  
15 you're not really just testing the drug. You may also  
16 be testing the test. And if the test is one that  
17 really is not achievable, the drug may fail because  
18 the test can't be performed, not because the drug  
19 wouldn't have otherwise been shown to be effective.  
20 And we really don't want to wait for the incidence of  
21 highly-resistant organisms to be high enough to make  
22 superiority trials easy enough to perform.

1 I mean, some would argue if that's the  
2 circumstance that you've gotten yourself into, you've  
3 not done well. And we have to keep in mind too that  
4 when you're studying best available therapy and trying  
5 to show superiority over best available therapy, best  
6 available therapy may actually have some effect.  
7 Resistance is not a binary, you know, hundred percent  
8 or zero percent. It's a continuum. So you may have a  
9 lesser likelihood of response. But it's not going to  
10 be zero. So best available therapy may have some  
11 effect which may make showing superiority somewhat  
12 challenging. What I mean by that is it's not that the  
13 new drug isn't better. But the effect size may be not  
14 so -- not as large as you might expect initially  
15 without sort of putting more thought into this.

16 So the trial may be one of considerable  
17 size. And if you think about a trial that's designed  
18 to show superiority and the reason that you can show  
19 superiority is that the options currently available  
20 are not that good, once a new standard of care has  
21 been demonstrated, the ongoing trials would, from an  
22 ethical standpoint, need to include that standard of

1 care. So there may be a certain degree of  
2 unpredictableness/uncertainty that may accompany doing  
3 a superiority trial.

4 So just thinking about, you know, if you  
5 take a non-inferiority approach, the drug that you  
6 study, you may not actually elicit all of the  
7 attributes of the drug in a non-inferiority trial.  
8 There may be mechanistic reasons that the drug will  
9 have utility and preserve its activity; again, certain  
10 resistant isolates that may not be enrolled in the  
11 non-inferiority trial because patients in that trial  
12 would generally be ones in whom you would want the  
13 comparator drug to be effective. We can talk more  
14 about the nested superiority/non-inferiority.

15 And then, just one last final point and that  
16 is as we think about where the drugs that we use today  
17 came from, including the drugs that we use to treat  
18 patients who have resistant organisms, they were --  
19 many were studied at a time when the resistant  
20 phenotypes of concern didn't even exist. So, and  
21 superiority trials, you know, I'm trying to get to  
22 sort of the practical issues here. There's no

1 question superiority trials provide clear evidence of  
2 efficacy and that they are easy to interpret and that  
3 they don't have some of the trappings of a non-  
4 inferiority trial.

5 But they can be challenging to conduct, as  
6 I've just discussed. And through the course of the  
7 presentations today, I think you'll hear some more  
8 details on this. We understand that some folks are  
9 interested in such claims. You know, and we're more  
10 than happy to work with folks that are wanting to do,  
11 you know, superiorly trials. But we think it's  
12 important that folks think about this and, you know,  
13 balance some of the issues with achievability, you  
14 know, so that the drug can be studied if you run into  
15 particular challenges if you're trying to pursue  
16 something in the area of superiority. And some have  
17 raised too issues with regard to generalizability  
18 using a non-inferiority approach. And that's  
19 something we can talk about a little bit more today  
20 too.

21 And so, here I'm jumping around a little  
22 bit. But you know, just thinking about some of the

1 challenges that we face in antibacterial drug  
2 development, if you contrast serious acute bacterial  
3 diseases with oncologic conditions, HIV, hepatitis C,  
4 rare metabolic disorders, and go through sort of a  
5 couple of different characteristics -- and I'll just  
6 do this informally. I don't know that it's engraved  
7 in stone or that I've got it completely correct. But  
8 I'd welcome your thoughts on this too.

9           But if you think about it, identifying  
10 patients -- well, for serious acute bacterial  
11 diseases, it can be really any of a number of  
12 different folks across the globe who may show up with,  
13 you know, an acute infectious disease caused by  
14 bacteria. And they'll show up, you know, quickly,  
15 whether they're already in the ICU or they present to  
16 the emergency room. You know, and for an oncologic  
17 condition, usually you're going to have a tissue  
18 diagnosis. You're going to know who these patients  
19 are; likewise, for HIV and hepatitis C. For rare  
20 metabolic disorders, the patients may be in a registry  
21 of care at a referral institution. So it's a much  
22 more defined population.

1           So that's one issue that can make studying a  
2 drug for an acute bacterial disease quite challenging.  
3 The disease course over time for most serious acute  
4 bacterial disease, it starts, you know, quickly and it  
5 ends fairly quickly. So the period of time to either  
6 enroll a patient in a trial or, you know, study an  
7 intervention is very limited. It makes it, again,  
8 very challenging. And that's not quite the case -- I  
9 mean, the other disease -- you know, you may want to  
10 intervene within a relatively short period of time.  
11 But the time pressure is much different, in my  
12 opinion.

13           Diagnostic certainty -- for the patient with  
14 a serious acute bacterial disease, is it pneumonia, is  
15 it heart failure, is there something else going on  
16 here. You know, just think about the patient in the  
17 ICU with HAP/VAP and the challenges of making that  
18 diagnosis. And you know, again, for these other  
19 conditions, typically you have a fair degree of  
20 diagnostic certainty. We've already talked about the  
21 urgency of the situation. For acute infectious  
22 diseases too, there may be considerable variability in

1 outcomes. You know, when I talk with my colleagues in  
2 the oncology group, they oftentimes will tell me, you  
3 know, that the tumor won't shrink. It simply doesn't  
4 happen.

5 So if you have a lights-on/lights-off  
6 phenomenon, you know, an ammonia level that's going to  
7 stay up here absent an effective therapy -- things  
8 could be quite different in an acute bacterial disease  
9 and it could make things fairly challenging. Also the  
10 opportunities for rescue for serious acute bacterial  
11 disease, the opportunities for rescue may be really  
12 quite limited. You know, you may jump in there. But  
13 given the serious nature of the disease, the rapidity  
14 with which it can progress -- and for some of the  
15 other conditions, there are opportunities to jump in  
16 there and come in with another therapy.

17 So you know, a credit to all the folks that  
18 are, you know, here today working on what is an  
19 important but also a very challenging area of  
20 antibacterial drug development. Clinical trials  
21 continue to teach us new things, many of which we  
22 didn't necessarily expect and that we would have hoped

1 to have avoided. So I think it's important -- and I  
2 won't go through these, but I thought it would be  
3 helpful just to have them out there, all based on  
4 information that's out there in the public. You know,  
5 we see that some drugs didn't pan out in certain  
6 conditions. Some drugs didn't appear to work as well  
7 as their comparator.

8           And some of these things are surprising to  
9 us. We see some that work in some indications and  
10 then some that have troubles in others. So you know,  
11 it may be intrinsic characteristics of the drug. It  
12 may be the dosing of the drug. There may be other  
13 things going on here that weren't necessarily  
14 expected. And again, I'm jumping around a little bit.  
15 But one of the things we hear sometimes is that there  
16 isn't much going on in HAP/VAP and HAP/VAP is really  
17 challenging to study. There's no question about that.  
18 I don't think there's any debate.

19           But if you go to [clinicaltrials.gov](http://clinicaltrials.gov), you can  
20 actually see there are a handful of studies going on  
21 in HAP/VAP and that's good news. So and typically  
22 what we're seeing is that folks are doing, you know,



1 complicated intra-abdominal, complicated UTI  
2 indications and then subsequently moving on to the  
3 more challenging indication of HAP/VAP. So if we  
4 think about antibacterial drug development too, it's  
5 important that we continue to advance the science.  
6 This is a challenging area. You can tell we're  
7 dealing with a fair degree of uncertainty in some  
8 situations in order to, you know, have drugs that can  
9 be studied, that can be available for patients.

10 But it's also important too that we continue  
11 to tend to the science. And the folks at the FNIH  
12 have been working on developing and evaluating  
13 endpoints. The folks at CTTI are doing important work  
14 looking at trial efficiency and design. They have a  
15 very important project, in my opinion, in HAP/VAP,  
16 trying to figure out how they can make HAP/VAP trials  
17 more efficient and they're progressing well on that.  
18 And the Duke-Margolis Center has been looking at  
19 overarching issues in antibacterial drug development  
20 and, you know, has a conference following this on  
21 economic development. We work at our colleagues at  
22 EMA -- and we're very glad that Marco came over to

1 join us -- you know, through our confidentiality  
2 agreements. And we've found those interactions to be  
3 very helpful. It gives us a chance to share opinions  
4 on development programs and on approaches to  
5 development. And I think really an important theme  
6 here is that curating the science supporting clinical  
7 trial design and endpoints is key both here in the  
8 United States and for harmonizing available approaches  
9 internationally. And there's no reason, if the  
10 science is there, that we shouldn't be able to do  
11 similar things.

12 You know, whenever somebody holds a  
13 workshop, it's an opportunity to talk about all the  
14 issues that we face. And I think it's important to  
15 recognize right from the start that it's important  
16 that, you know, we recognize the multifaceted nature  
17 of the challenges that we face. And FDA plays an  
18 important part here. But I think there's also a lot  
19 of other groups that are involved. And you know, I've  
20 listed a variety of the different areas and I think  
21 folks will recognize, you know, resistance  
22 surveillance for the prevention of infection, a lot of

1 work of colleagues in stewardship, a lot of colleagues  
2 at the CDC research and development. We're glad that  
3 Dennis could join us here from NIAID.

4 And there's an important role of academia,  
5 industry and government, hospitals, patients, society  
6 in general because of the issues around antibacterial  
7 drug use. Professional societies publish treatment  
8 guidelines and provide, you know, other advice to  
9 practicing physicians. Public-private partnerships  
10 and payers all play a role here. And I think it's  
11 important that we keep that in mind as we work through  
12 the day. So to overcome these challenges, we'll need  
13 a variety of different solutions to deal with the  
14 multiple different factors that we're facing and the  
15 challenges of antibacterial drug development, the use  
16 of these drugs, antimicrobial resistance.

17 It's important that basic science, R&D  
18 continue to feed and develop new lead molecules for  
19 early development that then progresses through  
20 advanced development. Again, colleagues from NIAID,  
21 Joe Larsen from BARDA is also here with us today. And  
22 I think too, you know, the value of new antibacterial

1 drugs, you know, if we look at some of the economic  
2 reports -- and I've cited the RG report here -- you  
3 know, the societal value of having a new antibacterial  
4 drug exceeds its private value. So there's a little  
5 bit of an imbalance here that suggests the need for,  
6 you know, continued work on incentives to try and be  
7 able to get things in balance with regard to the value  
8 of these drugs to society.

9 Another very important area I think that  
10 could help advance the science in this area is that of  
11 a clinical trial network. And our colleagues from  
12 BARDA recently put out a request for information to  
13 understand a little bit more about what might be  
14 involved in developing a clinical trial network. And  
15 when we talk about a clinical trial network, at least  
16 in my mind we're talking about infrastructure so you  
17 avoid having to start up each time. So you know, you  
18 do a HAP/VAP trial, you're not just starting from  
19 square one and the last group that did one just sort  
20 of deflated all their infrastructure.

21 This should allow for the development of  
22 expertise, the lab support being in place and ideally

1 there'd be a common protocol that would be used for  
2 each of the several drugs. It could also allow for  
3 the concurrent study of a couple of drugs at the same  
4 time. And it also may serve important roles too for  
5 developing diagnostic tests, another important area.  
6 I mean, if diagnostic tests can be developed, that  
7 could transform the way that antibacterial drugs are  
8 utilized out there and used more prudently and could  
9 also help some with clinical trials too.

10 And just if folks are unfamiliar with sort  
11 of a common protocol or master protocol idea, here's a  
12 schematic of what one might look like. You have a  
13 control group on top and the control group is shared  
14 between the drugs that are enrolled during the same  
15 time period and you can see drug A in blue is the  
16 first experimental drug. So during that initial  
17 period, it's drug A and the control, to which patients  
18 are randomized. Drug B is introduced in that second  
19 segment and there control patients are shared between  
20 drug A and drug B. And then, subsequently drug C pops  
21 in and all three share the control group. So you have  
22 three drugs being studied concurrently. Drug C is

1 monitored and stopped early for futility and drug B  
2 continues on to be studied throughout the duration  
3 there. Drug A finishes a little bit early and is  
4 analyzed.

5           So there are certain efficiencies here,  
6 certain development of degrees of expertise that could  
7 be gained with a master protocol. There's no question  
8 there's fixed costs. There's a lot involved in  
9 setting up such an infrastructure. But it seems like  
10 there's an area where such approaches might help. So  
11 I want to stop there. I know it was a little bit  
12 disjointed. But I wanted to cover sort of a variety  
13 of different topics that have come up, done so in sort  
14 of a whirlwind fashion.

15           And now, I want to introduce Sumathi  
16 Nambiar. Sumathi is the director of the Division of  
17 Anti-Infective Products and also a very good  
18 colleague. And she will be providing us a talk on --  
19 let me make sure I get my classes on here -- trial  
20 considerations for unmet medical need. So she'll be  
21 walking us through some of the nuts and bolts of unmet  
22 medical need development. So Sumathi, it's all yours.

## 1 TRIAL CONSIDERATIONS FOR UNMET NEED

2 DR. NAMBIAR: Thank you, Ed. Good morning,  
3 everybody, and welcome you to this two-day workshop.  
4 Can you hear me okay? All right. Okay. I'm going to  
5 try and build upon some of the principles that Ed has  
6 laid out in his talk. So here are some criteria that  
7 typically drugs have to be met -- can you hear me?  
8 Sorry. This is better? This is right in my face.  
9 All right. Okay. It sounds like you can hear me.  
10 All right.

11 So these are some of examples of types of  
12 antibacterial drugs that might be suitable for an  
13 unmet need development pathway. This is not an all-  
14 exhaustive list. But if you have a product that acts  
15 via a new mechanism of action or has an added  
16 inhibitor that can neutralize a mechanism of  
17 resistance or the activities preserved in setting of  
18 resistance to other antibacterial drugs would appear  
19 to meet an unmet need. I just want to emphasize this  
20 point because more recently we are seeing proposals  
21 for bridge [ph] programs without a real good  
22 justification for why one thinks the product actually

1 meets an unmet need. So one needs to spend a little  
2 bit of time and effort to really justify and make it  
3 clear as to why a proposed product has the potential  
4 to meet an unmet need.

5           So in general, for unmet need programs,  
6 smaller data packages are acceptable and hence such  
7 programs, there will be greater uncertainty about  
8 risks and benefits. Single, adequate and well-  
9 controlled trial may be adequate. We need good  
10 support of evidence to support that single trial. And  
11 it's very important that this thorough evaluation of  
12 the activity of the drug in vitro and in animal models  
13 of infection to support the smaller clinical data  
14 package. Healthcare communities should be aware of  
15 the uncertainty, both around risks and benefits, and  
16 these risks and benefits and the shortcomings will be  
17 communicated appropriately and labeling. And labeling  
18 from such programs will include a limited use  
19 statement.

20           We expect adequate in vitro data and  
21 activity in relevant animal models of infection,  
22 adequate evaluation of PK/PD relationships from animal



1 models of infection. It's very important, and I  
2 cannot emphasize this enough, that understanding the  
3 PK in patients with renal or hepatic impairment early  
4 in development is very important because this will  
5 facilitate enrollment of such patients, as they often  
6 have important comorbidities. And you'll see this  
7 theme come up in subsequent presentations. I think it  
8 comes up in Dr. Friedland and Dr. Dudley's talk, where  
9 how patients with unmet medical need are in fact a  
10 little different from patients who typically enroll in  
11 some of these trials. So I think this is very  
12 important. And also it's important to collect PK data  
13 in clinical trials.

14 I just want to remind everybody that drugs  
15 being developed to address unmet medical need must  
16 meet the statutory standard for effectiveness where  
17 substantial evidence is defined as evidence consisting  
18 of adequate and well-controlled investigations. And  
19 an adequate and well-controlled study is described in  
20 21 CFR 314.126. Since the passage of FDAMA, you know,  
21 we are allowed to -- I think they sort of clarified  
22 that we could consider data from one adequate and

1 well-controlled clinical investigation confirmatory  
2 evidence to constitute substantial evidence. And  
3 every often in discussions that come up that the  
4 standards might be different for products which are  
5 designated as orphan and orphan drug products do still  
6 need to meet these statutory requirements.

7           So we go through some trial design options.  
8 I think as Ed has already mentioned, we are of the  
9 opinion that well-conducted non-inferiority trials are  
10 important to maintain a robust pipeline of  
11 antibacterial drugs to meet patient needs. Treatment  
12 options should be available before new mechanisms of  
13 resistance emerge, and if we are in a situation where  
14 these trials are in fact easy to do because levels of  
15 resistance are so high, then antibacterial drug  
16 development has not kept pace with emergence of  
17 resistance.

18           A well-conducted non-inferiority trial will  
19 provide evidence of a drug's efficacy in a given body  
20 site of infection and in general these trials will be  
21 limited to situations where the baseline organisms are  
22 susceptible to both the test and comparator drug. So

1 these trials often enroll few or no patients infected  
2 with multidrug-resistant phenotype organisms. But  
3 the evidence for this activity against those  
4 particular phenotypes comes from the drug's activity  
5 in vitro and in animal models of infection.

6 So what might be some options if one wants  
7 to conduct a non-inferiority trial? A single trial at  
8 any one body site would be acceptable. As I mentioned  
9 earlier, it's important to enroll patients with  
10 severity of illness or comorbidities which might be  
11 similar to those seen in patients with unmet need. We  
12 are willing to accept a wider non-inferiority margin  
13 than one would accept for a traditional development  
14 program. Data from such a trial could be supplemented  
15 with data from a study in patients with infection due  
16 to the specific phenotype of interest. From such a  
17 study, one can obtain PK data and in a sicker  
18 population or patient population that has  
19 comorbidities. And it also provides some clinical  
20 experience in patients with infections due to these  
21 specific organisms, which we've heard from our  
22 clinical colleagues is very valuable to them.

1           We've certainly had a lot of discussion  
2 amongst ourselves whether it's possible to do a non-  
3 inferiority trial pooled across body sites. We do  
4 think that poses additional challenges, but we'd  
5 certainly be interested from thoughts from attendees  
6 at the workshop. I think some of our main concerns  
7 have been that the magnitude of treatment effect can  
8 vary across the infection types that one is attempting  
9 to pool. The endpoints are highly variable. And I  
10 think, very importantly, such a trial may not  
11 demonstrate if there's a potential deficit in  
12 treatment effect across the different infection types  
13 that are pooled. And we've seen examples of drugs  
14 that have worked in one or more body sites and not  
15 worked in other body sites. And Ed had shown us a  
16 slide which sort of gave examples of recent  
17 experiences.

18           One can certainly do superiority trials. It  
19 provides a clear finding of efficacy. But we do think  
20 it poses -- it is extremely challenging to do one of  
21 these trials. And again, this will come up in  
22 discussions and presentations during the course of the

1 day. We think the ability to rely on superiority is  
2 likely time-limited because once a new therapy becomes  
3 available, an ongoing trial which is designed to  
4 demonstrate superiority of a standard of care would  
5 likely become unethical because now you have other  
6 options available. And subsequent trials would need  
7 to be non-inferiority trials. Superiority trials  
8 could be at a single body site or one can pool across  
9 certain body sites, as long as you have a  
10 representative sample from each type of infection.

11 In a superiority trial, you can attempt to  
12 demonstrate superiority over active comparator. And  
13 I've said earlier, it's usually dependent on the  
14 comparator of the trial representing suboptimal  
15 treatment. In other words, it's very hard with the  
16 currently available therapies to demonstrate  
17 superiority. It does happen, but not very frequently,  
18 where an antibacterial drug is actually able to  
19 provide additional benefit over active standard of  
20 care. One recent example was a trial in complicated  
21 UTI with ceftolozane/tazobactam where superiority of  
22 ceftolozane/tazobactam over levofloxacin was

1 demonstrated. It's important to note that just over  
2 quarter of the baseline isolates in the comparator arm  
3 were levofloxacin non-susceptible. So this raises  
4 questions about whether one can in fact repeat such a  
5 trial, going back to the same study sites where the  
6 prevalence of levofloxacin non-susceptible isolates is  
7 that high.

8           There has been a lot of discussion and some  
9 interest in potentially using external controls in  
10 demonstrating superiority of external controls. And  
11 the challenges in using external control data are  
12 well-described in ICH E10. There's always a question  
13 of comparability between the treatment and control  
14 groups because they can differ not only in what we  
15 know -- so the known risk factors, but also in  
16 unrecognized or inadequately measured risk factors.  
17 And it's very well-documented that untreated historic  
18 controls tend to have worse outcomes than an  
19 apparently similarly chosen control group in a  
20 randomized trial, possibly reflecting a selection  
21 bias. As a third option for superiority trial would  
22 be a product that is being administered in addition to

1 standard of care, some kind of an adjunctive therapy  
2 within the test drug plus standard of care is compared  
3 to standard of care versus placebo.

4           So again, I mentioned this earlier in  
5 superiority trials. We're willing to consider pooling  
6 across body sites. So for a Gram-negative drug,  
7 pooling, you know -- pooling across cIAI, cUTI and  
8 HABP/VABP is acceptable. We do recommend that at  
9 least half the patients have HABP/VABP because this is  
10 one indication where we've seen deficits in  
11 performance of antibacterial drugs. There's been more  
12 than one example. In such a trial, patients with  
13 document infections due to a certain resistant  
14 phenotype would be enrolled; for example,  
15 carbapenemase production. Best available therapy  
16 would be used as a comparator. All-cause mortality or  
17 disease-specific definition of clinical success is  
18 acceptable. And we've considered allowing the use of  
19 one-sided alpha of 0.05, given that the comparator  
20 regimen will have some treatment effect. And again,  
21 you'll see this in an example later in the day.

22           One other option, which I know we've all

1 discussed a fair bit, but we've really not seen a  
2 proposal come forth is a nested non-  
3 inferiority/superiority trial design where in a  
4 subgroup of patients that have the -- of a resistant  
5 phenotype, one can attempt to demonstrate superiority.  
6 So you demonstrate non-inferiority in the population  
7 susceptible to comparator and superiority in the  
8 subset of patients that have baseline organisms  
9 resistant to comparator. Here if a superiority is not  
10 demonstrated, it does not in fact impact the  
11 conclusion of non-inferiority.

12 So I thought what I would do next is just  
13 walk you through maybe three or four potential  
14 scenarios of what development programs can look like.  
15 Again, I think it's very important to note that it's  
16 really not a one-size-fits-all and these are general  
17 approaches. But we do have to make adjustments  
18 depending on the specific drug and the specific  
19 program. so in this example, if a drug has a -- it's  
20 a Gram-negative drug and it has a spectrum of activity  
21 that includes Enterobacteriaceae and P. aeruginosa.  
22 We have activity that demonstrates that this drug



1 works against ESBL-producing organism including serine  
2 carbapenemases.

3 So your potential options could be a single  
4 non-inferiority trial at any one body site. You could  
5 choose cUTI. You could choose cIAI. The benefit  
6 there is you could test the drug as monotherapy.

7 Should you be interested in developing the drug for  
8 HABP/VABP, I think one really needs to address how the  
9 concomitant therapy that's used to treat *P. aeruginosa*  
10 and its impact on assessing treatment benefit will be  
11 addressed. And again, I think this is a topic that's  
12 going to come up hopefully today, but certainly in  
13 tomorrow's discussion. Again, superiority trials are  
14 an option. This could be done at a body site, any of  
15 the body sites that I have listed above or a  
16 superiority trial where one pools across body sites.  
17 And a third option would be a nested non-  
18 inferiority/superiority trial.

19 A second example is if you have an  
20 antibacterial drug that only is active against a  
21 single species; for example, *P. Aeruginosa*, *A.*  
22 *baumannii*. We understand there is interest in

1 developing such drugs and we will spend a whole day  
2 tomorrow talking about this. So I'm not going to go  
3 into further details.

4 A third example, and we do see a fair bit of  
5 this particular option, is a new  $\beta$ -lactamase inhibitor  
6 which has been combined with an approved  $\beta$ -lactam  
7 antibacterial drug. And under section 505(b)(2) of  
8 the Food, Drug and Cosmetic Act, we can rely in part  
9 on our previous finding of safety and effectiveness  
10 for the corresponding approved indications for the  $\beta$ -  
11 lactam drug. And this can provide part of the  
12 evidence needed for the BL-BLI combination.

13 Again, as I said early on, it's very  
14 important that if you are using this sort of an  
15 approach, that you provide adequate justification that  
16 the addition of the  $\beta$ -lactamase inhibitor addresses an  
17 unmet need. We need robust evidence of the  
18 contribution of the  $\beta$ -lactamase inhibitor in restoring  
19 the activity of the  $\beta$ -lactam and this can come from in  
20 vitro studies and from animal models of infection. We  
21 need adequate dose rationale, including the  
22 appropriate ratio of the  $\beta$ -lactam and the  $\beta$ -lactamase

1 inhibitor. And importantly, we need -- even though we  
2 can rely to a great extent on what we know about the  
3  $\beta$ -lactam from previous approval, we need adequate  
4 safety data for the  $\beta$ -lactamase inhibitor and the  
5 combination product.

6           The clinical data package for such a drug  
7 could vary. It really depends on the approved  
8 indication for the  $\beta$ -lactam. So it depends on which  
9  $\beta$ -lactam you are choosing, what that is approved for  
10 and the indications in which the BL-BLI have been  
11 studied. So you could consider doing a single,  
12 adequate and well-controlled non-inferiority trial in  
13 a body site of infection and such a trial does not  
14 need to be enriched for organisms that are non-  
15 susceptible to the chosen  $\beta$ -lactam. We've also  
16 considered smaller trials in indications for which the  
17  $\beta$ -lactam is approved, as in the example of  
18 ceftazidime-avibactam that was approved last year.  
19 And such a trial ideally should include some patients  
20 with infections due to the  $\beta$ -lactamase-producing  
21 organisms.

22           Lastly, if one is looking to develop a

1 product that will be administered as adjunctive  
2 therapy to standard of care, some examples would  
3 include inhaled antibacterial drugs being developed  
4 for ventilator-associated bacterial pneumonia, immune  
5 modulators, monoclonal antibodies targeting a specific  
6 organism. The trial design would need to be a  
7 superiority trial where the test drug plus the  
8 standard of care is compared to the standard of care.

9 So in summary, we've laid out some potential  
10 development pathways for a drug that has a potential  
11 to address an unmet need. One could do a non-  
12 inferiority trial at a single body site. We're  
13 willing to accept a wider non-inferiority margin. And  
14 one could include a nested superiority option, if  
15 desired. If one wants to pursue a superiority trial,  
16 such a trial could be done at one body site or you  
17 could pool across relevant body sites. And the drug -  
18 - the test drug is compared to the best available  
19 therapy.

20 If the drug is being used as an adjunctive  
21 therapy, then you add it to the standard of care and  
22 compare it to standard of care plus placebo. And if

1 it's a new  $\beta$ -lactamase inhibitor being developed  
2 that's being combined with an approved  $\beta$ -lactam  
3 antibacterial drug, one could rely in part on Agency's  
4 previous finding of safety and effectiveness of the  
5 approved  $\beta$ -lactam. Thank you.

6 [Applause.]

7 DR. MARKS: Thank you, Ed and Sumathi. What  
8 a great start in terms of the clarity with which the  
9 regulatory environment in the U.S. has evolved, where  
10 I think many of us see the Agency as being part of a  
11 solution clearly as we try to deal with this difficult  
12 issue. And now, similarly on the other side of the  
13 ocean, we have Marco Cavaleri, head of anti-infectives  
14 and vaccines at the European Medicines Agency talking  
15 about the regulatory pathways and approaches to unmet  
16 need. And I would give a similar comment about Europe  
17 as well in terms of being part of the solution. Thank  
18 you.

19 REGULATORY PATHWAYS AND APPROACHES TO UNMET  
20 NEED

21 DR. CAVALERI: Thank you very much, and good  
22 morning. I would like to really thank Ed and Sumathi

1 for the invite. It's a great pleasure for me to be  
2 here and to present the perspective of the EMA. And  
3 as Ed said, I think it's important to stress also the  
4 fact that the EMA and FDA has been continuously  
5 discussing over the last years about options for  
6 developing of new antibacterial agents and  
7 particularly for those that might address unmet  
8 medical needs related to multidrug resistance. So  
9 again, it's a great pleasure for me to be here and  
10 presenting the European perspective and discuss with  
11 you options.

12 I was asked to start with to describe to you  
13 very briefly what is -- what are currently the  
14 approval pathways according to European legislation  
15 for medicinal products that could also apply to  
16 medicinal products that address unmet medical needs.  
17 So one option is a full marketing authorization and  
18 maybe it's important here to also add that recently in  
19 Europe Union there has been approved a  
20 pharmacovigilance legislation which would allow the  
21 EMA also to pause study also in the context of a full  
22 marketing authorization as post-authorization safety

1 study or post-authorization efficacy studies,  
2 particularly in order to address uncertainties that  
3 are considered key to the benefit-risk of the  
4 medicinal products.

5 And then, I will talk more about conditional  
6 marketing approval and approval under exceptional  
7 circumstances which are the regulatory tools that we  
8 have in those circumstances where we feel they might  
9 be needed or would be expected that an approval based  
10 on less than normal level of evidence could be done.  
11 Then, the last option is the Article 58 scientific  
12 opinion for use only outside of the EU, which will not  
13 apply in this setting and therefore I will not bring  
14 you any further details on this.

15 So as said, one option that we have in order  
16 to come to, as we called it earlier, approval is the  
17 conditional marketing authorization. This will be  
18 based on a less comprehensive data package and subject  
19 to specific obligation in the post-approval phase.

20 The scope -- so the products that will be in  
21 scope for this pathway will be products that address  
22 serious debilitating diseases or life-threatening

1 diseases or products that are to be used in emergency  
2 situations, like pandemic influenza, or for orphan  
3 medicine or products. And the criteria which all have  
4 to be met is that the risk-benefit balance is positive  
5 for the product and is likely that the applicant will  
6 be in a position to apply comprehensive clinical data  
7 after approval and also that the unmet medical need  
8 will be at least in part fulfilled and here of course  
9 the wording is a bit strong. But of course it will  
10 have at least a clear impact on addressing an unmet  
11 medical need and also importantly that the benefit to  
12 public health for the immediate availability on the  
13 market of the medicinal product concerned outweighs  
14 the risk inherent in the fact that additional data are  
15 still required.

16           The other option that we have is called  
17 under exceptional circumstances. And as the European  
18 law says, in exceptional circumstances and following  
19 consultation with the applicant, the marketing  
20 authorization may be granted subject to certain  
21 conditions, in particular relating to the safety of  
22 the medicinal product. And also, it goes on saying



1 that the marketing authorization may be granted only  
2 when the applicant can show that he is unable to  
3 provide comprehensive data on the efficacy and safety  
4 of the medicinal product under normal conditions of  
5 use.

6 And the grounds are set out in Annex I in  
7 which situations this might be applicable. In any  
8 case, it will be linked to an annual reassessment of  
9 the conditions. So and here are the grounds as per  
10 Annex I of the directive. So it has to be an  
11 indication for which the product in question is  
12 intended -- is rare, so that the applicant cannot be  
13 reasonably expected to provide comprehensive evidence  
14 or in the present state of scientific knowledge,  
15 comprehensive information cannot be provided or it  
16 would be contrary to generally acceptable principles  
17 of medical ethics to collect such information.

18 So to summarize the differences between  
19 conditional MA and MA under exceptional circumstances,  
20 in this slide I will try to summarize. So the  
21 conditional MA, full conditional MA comprehensive data  
22 are expected after authorization with the idea to

1 later switch to a full marketing authorization, while  
2 for MA under exceptional circumstances, comprehensive  
3 data are deemed not possible to gather and therefore  
4 is supposed to remain such indefinitely. The  
5 conditional MA is valid for one year only with annual  
6 renewals that have to take place, while the MA under  
7 exceptional circumstances has the normal validity of  
8 any other marketing authorization and goes through an  
9 annual reassessment procedure. The conditional MA  
10 applies only to centralized procedures while the under  
11 exceptional circumstances MA is possible in all  
12 registration procedures.

13 Now, a few words on the PRIME scheme, which  
14 is something brand new the EMA brought forward. And  
15 this is a scheme that is aimed to foster the  
16 development of medicines with major public health  
17 interest, so building on the existing framework and  
18 with an eligibility program that is according to the  
19 existing accelerated assessment criteria. And the  
20 idea here is to reinforce scientific and regulatory  
21 advice to developer in order to foster and facilitate  
22 earlier interaction, optimize development for robust

1 data generation, indeed try to work together with the  
2 developer in order to have an efficient development  
3 plan, and also enable accelerated assessment at the  
4 level of the CHMP.

5 So from this principle, this boils down  
6 essentially to first of all having a written  
7 confirmation of PRIME eligibility from the EMA  
8 following a submission of a request and the potential  
9 for accelerated assessment, an early CHMP rapporteur  
10 appointment during development, kickoff meeting with  
11 multidisciplinary expertise from EU network and  
12 enhanced scientific advice at key development  
13 milestone/decision points, including also the option  
14 to discuss with technology assessment bodies. There  
15 will be an EMA-dedicated contact point and fee  
16 incentive for small and medium enterprises and  
17 academics will be provided for their scientific advice  
18 procedures.

19 So now I give you a bit of an overview of  
20 the entire regulatory framework in Europe. And now,  
21 we will move more directly into the area that is  
22 discussed today and tomorrow, which is around the

1 development specifically for MDR pathogens in area of  
2 unmet need. And the position of the EMA is summarized  
3 in the Addendum to the Guideline On the Development of  
4 Agents to Treat Bacterial Infection and I would say  
5 that the position of the EMA has not changed since the  
6 issue of that document in 2013, even if of course we  
7 are having a lot of interaction with developers and we  
8 may amend or fine-tune some of the options that were  
9 provided in there.

10 So I will start describing you very briefly  
11 what is in that document and what are the main points  
12 that we would consider for developing new  
13 antibacterial agents in area of unmet medical need.  
14 Well, first of all, these products have to be eligible  
15 for the acceptance of limited clinical development and  
16 that might not be straightforward in all cases. First  
17 of all, there has to be demonstration that the  
18 investigational product has the potential for treating  
19 infection for which there are few remaining  
20 therapeutic options. There also there is a need of a  
21 good understanding of the impact of all possible  
22 resistance mechanisms on activity and not just

1 focusing on a few of the main ones as that is not  
2 telling you the entirety of the story.

3 So it's important that the microbiology and  
4 the PK/PD is already there to address the fact that  
5 this agent has the ability to address an unmet medical  
6 need. And if the product is active only on single  
7 genus or species, there should be justification that  
8 indeed the organism is problematic. So the possible  
9 scenarios will be from the rather easy one of a new  
10 drug in a new class or let's say new mechanism of  
11 action. That should be fairly straightforward. Or it  
12 could also be new drug of an existing class with a  
13 novel spectrum. Of course, the data, the micro data  
14 and the PK/PD data will be important here, or could be  
15 a new or known drug of an existing class which is  
16 coupled with a new protective agent. And the example  
17 of a  $\beta$ -lactam with a  $\beta$ -lactamase inhibitor is an  
18 obvious one, but might not be the only one.

19 Now, there is a range of possible clinical  
20 programs that could be considered here, depending on  
21 the properties of the agent assessed or whether it's  
22 limited or broader spectrum and also, importantly,

1 what is the aim of the developers in terms of level of  
2 claims and SmPC. And an example would be whether a  
3 specific indication for a certain type of infection is  
4 looked at plus an unmet medical need indication or  
5 only a claim for using circumstances of unmet need.  
6 It's important to stress, as I said before, that  
7 further evidence of safety and efficacy post-approval  
8 will be expected.

9 In the future, we might be more and more in  
10 the situation in which requirement for post-approval  
11 commitment will take place. This may come from  
12 pivotal studies that are already planned for  
13 additional site-specific indications by the developers  
14 or that also could be a rather easy one or could be  
15 prospective uncontrolled studies that might be needed  
16 depending on what are the uncertainties in the  
17 benefit-risk evaluation or observational data from  
18 registries. And again, also here to stress that at  
19 the EMA there are a lot of efforts to try to  
20 understand how much can be gathered from observational  
21 data, how much can be gathered from real-life data and  
22 to what extent such data could have an impact on

1 regulatory decision, which I think we are just at the  
2 beginning of that journey. But it's important not to  
3 forget about these aspects.

4           So one of the pillars in the development  
5 specific for MDR pathogens will be to conduct an  
6 extensive microbiology and PK/PD program to fully  
7 document expectations for the products in order to  
8 support the dose regimen to be tested, support plans  
9 for regimen adjustment in patient subject, to support  
10 the anticipated efficacy against the target multidrug  
11 resistant pathogens and to identify any type of  
12 infection in which it should not be used or may need a  
13 different regimen -- as an example, could be  
14 penetration in the ELF or binding with the surfactant,  
15 but there could be many other examples -- and then,  
16 confirm the regimen using PK data from patients and  
17 conducting exposure-response analyses during the  
18 clinical trials. So this is an important area where  
19 it might be difficult to gather conclusive evidence,  
20 but still efforts are expected to be put in place.

21           So I think it's important for me to stress  
22 that in the addendum and in the EMA guidelines, we are

1 not demanding for a single specific approach to be  
2 followed. But we are highlighting the potential  
3 option for clinical development. So in a way, we are  
4 kind of framing what are the possibilities that will  
5 be acceptable for the EMA in terms of development in  
6 the area of unmet need. And indeed, the goal has been  
7 to enlarge the portfolio of acceptable clinical  
8 development options besides the standard approaches in  
9 light of the unmet medical needs.

10 So the addendum illustrates circumstances  
11 which would allow either an indication for unmet need  
12 or both an indication for unmet need and a standard  
13 type of indication and also stress the importance to  
14 put efforts to collect data with target pathogens.  
15 Clearly there is an expectation from the CHMP that  
16 efforts are put there, particularly for the target in  
17 an unmet need indication. But of course we have to be  
18 realistic and pragmatic and the prevalence will drive  
19 the ability to collect such data at the end of the  
20 day. So we should not forget that. And also, last  
21 but not least, it's important of discussing with  
22 European regulators the specificities of the proposed



1 program. And as I said, we are putting effort of  
2 discussing this whenever there is an application that  
3 goes both to the EMA and the FDA also with colleagues  
4 at the FDA to see what could be the potential way  
5 forward.

6 So in the addendum, essentially we are  
7 giving some examples of what could be way forward in  
8 the context of unmet need related to MDR. And the  
9 scenario one that we are bringing forward is not far  
10 from what Sumathi was describing before. So a single  
11 randomized non-inferiority study in one indication,  
12 that for Gram-negative targets should be studying  
13 HAP/VAP or intra-abdominal with standard alpha and  
14 non-inferiority margin expected or alternatively a  
15 study in UTI provided the PK extrapolation to other  
16 body sites possible. And the data with the MDR  
17 pathogens may derive from a limited controlled or  
18 uncontrolled studies. And in this sense, if the  
19 results are supportive and the evidence sufficient to  
20 draw conclusions on the benefit-risk, it will be  
21 possible then to grant an indication for both the  
22 unmet need and the selected type of infection that was

1 studied.

2 A second scenario would be in case the  
3 target is really the unmet need indication only. So  
4 it would be a randomized study in mixed infection  
5 types with a target organism, excluding infections  
6 likely to need different regimen or where PK is  
7 lacking, like meningitis, osteomyelitis as an example.  
8 Superiority, we don't believe it will be feasible, at  
9 least if we look at endpoint that will be the standard  
10 endpoint that we would require for type of infection.  
11 And the non-inferiority is also not possible as it  
12 will be impossible to define a non-inferiority margin  
13 in such context and with this mixed type of infection  
14 study. So what we would recommend in this case is not  
15 powered for formal inferential testing. At the same  
16 time, we would recommend that some comparison to look  
17 into superiority on secondary clinical endpoints could  
18 be explored nevertheless. Control therapy might need  
19 to be flexible, so best available therapy and this can  
20 be discussed and also tomorrow we will have a chance  
21 to discuss a specific case. And the use of  
22 experimental rapid diagnostic testing to enrich

1 enrollment would be fully supported. In this case,  
2 the indication would be for the unmet need.

3 A third scenario would be just to conduct an  
4 uncontrolled study confined to target organisms using  
5 historical and external controls. The justification  
6 would be based on the rarity of the target pathogens.  
7 The use of rapid diagnostic testing to enrich  
8 enrollment here would seem rather necessary. This  
9 would be the least preferred option and the data would  
10 need to be convincing. But of course we are not  
11 ruling out this and it could be well-justified that  
12 this is the only way forward. And in this case, the  
13 indication would be for the unmet need.

14 So at the end of the day, in terms of what  
15 the label will look like, what we are saying in our  
16 guidance document is that the indication in section  
17 4.1 of the CMPC will read something like for the  
18 treatment of infection due to the specific pathogen --  
19 let's say to the example before, Gram-negative aerobes  
20 -- in patients with limited treatment options. We  
21 referenced to section 4.4 and 5.1, which is the  
22 warning section and the section of pharmacodynamics

1 data.

2 Consideration should be given to official  
3 guidance on the appropriate use of antibacterial  
4 agents. And also, in section 4.2, we would state that  
5 it is recommended that the new agent should be used to  
6 treat patients that have limited treatment options  
7 only after consultation with a physician with  
8 appropriate experience in the management of infectious  
9 diseases, which would also lead to in the opinion to a  
10 status of restricted prescription medicinal product.  
11 And I think this is all. Thank you.

12 [Applause.]

13 DR. COX: Great. Thanks, Marco. And now,  
14 our next speaker is John Rex, from AstraZeneca. And  
15 as many folks know, John's been a thought leader in  
16 the area and done a lot of work and we're grateful for  
17 his willingness to join us today and all of his  
18 contributions to preparing for the workshop too. So  
19 thank you, John. The podium is yours.

20 DEVELOPING ANTIBACTERIAL DRUGS FOR UNMET

21 NEED AND SO THAT WE STAY AHEAD OF THE

22 EPIDEMIC: POINTS TO CONSIDER FOR DEVELOPERS

1 DR. REX: Thanks, Ed. And thanks to the  
2 organizers for the chance to be here. Am I loud  
3 enough in the back? It sounds okay to me. So these  
4 are my affiliations and my disclosures. If you know  
5 me at all, you know that I'm an internist who went  
6 into industry a little over a decade ago because I was  
7 seeing bacteria that I didn't know how to treat. And  
8 so, that's what I work on now. I'm going to cover  
9 several topics. They're somewhat orthogonal to each  
10 other and to the presentation's we've had today. But  
11 it will all come together into a clear message at the  
12 end: pathways for registration, economics, some  
13 common mistakes and some conclusions.

14 So pathways to registration -- there are  
15 five ideas that I'd like to be sure that you walk away  
16 understanding. I'm going to cover the first four in  
17 detail in my talk. Joe Larsen will pick up on the  
18 fifth one in his. Let me just now just start walking  
19 through them. The first topic has to do with  
20 language. And we've struggled for a long time with  
21 the problem that a year ago we finally sort of tumbled  
22 into a partial solution to, which is the problem that

1 we understand how to talk about MDR and XDR. We also  
2 understand the idea of wild type. But there's  
3 something in between wild type and MDR that's really  
4 important and that's the proposal is for a label  
5 called UDR -- usual drug resistance.

6 And what UDR means is that it's what you  
7 expect. It doesn't mean susceptible. It doesn't mean  
8 that it's susceptible to everything. So if I'm using  
9 a carbapenem as my comparator in a clinical trial,  
10 then UDR is anything that a carbapenem would cover.  
11 You know, and so it means I can study every kind of  
12 resistance but a carbapenem in a UDR's group. But are  
13 they really MDR? Well, it depends on your  
14 perspective. Okay, so that's the idea of UDR. UDR --  
15 and the real implication is that in a clinical trial,  
16 I can pick a single blinded comparator that I can use  
17 globally comfortably.

18 When you get into MDR and XDR, the  
19 comparator just gets harder and it could be that XDR,  
20 there's no such thing as a single standard comparator.  
21 Every patient may need a different comparator. UDR  
22 and MDR and XDR are a sliding scale. So in 1940, when

1 penicillin was invented and active against *S. aureus*,  
2 *S. aureus* was UDR to penicillin. But then, MRSA  
3 emerged and then it was the DMR nightmare bug. In the  
4 1960s, we found a lot of papers about the horror of  
5 MRSA and then vancomycin appears. And so, now it goes  
6 back to being UDR.

7           The other message is that if an organism is  
8 susceptible to the novel test agent, it's susceptible  
9 to the novel test agent. The response is independent  
10 of whether it is UDR, MDR, XDR to other drugs. Here's  
11 another way to see that. In theory, UDR is relatively  
12 common and XDR is relatively rare, if we're doing a  
13 good job. And the notion is that when it's UDR, I can  
14 pick a global comparator relatively easily and that  
15 the activity of the drug is independent of the other -  
16 - of its status relative to other drugs.

17           So with adequate PK, data in a UDR setting,  
18 which remember doesn't mean wildly susceptible, it  
19 could be resistant to lots of other things. But data  
20 in a UDR setting tells you a lot about how it's going  
21 to work even when it's susceptible to almost nothing  
22 else. But it only tells you how it's going to work on

1 the infection and that's an important thing to  
2 remember as well. People who have XDR or super XDR  
3 killer bugs often have had a lot of health care  
4 exposure for some reason. The antibiotic will not  
5 cure their cancer, motor vehicle accident-related  
6 trauma and whatever else they've got, their underlying  
7 immune deficiency. It can only cure an infection.

8 This matters because, as you're going to  
9 hear, it is much, much harder to do prospective,  
10 randomized registration quality studies in patients  
11 with infections due to MDR or XDR isolates than UDR.  
12 Our internal data is that it's at least twice as slow  
13 and twice as costly, if you can do it at all. A  
14 number of reasons -- you'll hear some of them today --  
15 but I'm going to only mention some of the ones that  
16 I've seen most commonly. First, patients have to  
17 present at a study site, as referral is hard.  
18 Infections move rapidly. Therapy has to start now.  
19 And if you say -- if you call up your hospital  
20 administrator and say, I want to transfer somebody  
21 into my hospital that has the most resistant  
22 *Klebsiella* that anyone has ever seen in the world,



1 they're going to say, really?

2           And actually, sites work really hard to make  
3 those isolates rare, which is why your administrator  
4 is going to think you've gone daft. No site wants to  
5 be a center of MDR, XDR excellence. Think about that  
6 billboard in front of your hospital. So chasing  
7 MDR/XDR is really an exercise in Lasagna's law. For  
8 those of you who don't know him, Louis Lasagna was a  
9 pharmacologist who noted some years ago that the  
10 incidence of patient availability sharply decreases  
11 with a trial begins and returns to its original level  
12 as soon as that trial is completed. So the bottom  
13 line is we want MDR/XDR rates to be low. If it's easy  
14 to do a study in this space, we as a community have  
15 done something terribly wrong.

16           Number two, superiority versus non-  
17 inferiority. New antibiotics are going to be, and  
18 indeed must be mainly developed in a non-inferiority  
19 setting for comparison versus an existing agent in the  
20 setting of UDR pathways. But I say again, UDR doesn't  
21 mean susceptible to everything. It can be resistant  
22 to lots of things. It's just susceptible to the

1 comparator. The reason for this is that as a  
2 designer, I have to design my trial to actually avoid  
3 superiority. I cannot, should not and I will publicly  
4 shame anyone who seeks to enroll patients where we  
5 know that resistance is likely to the test or the  
6 comparator. That's not fair to the patient.

7           It's very unlikely to -- you're just not --  
8 it's really rare to see superior efficacy over a fully  
9 dosed modern comparator when the pathway is  
10 susceptible to same. I mean, when the carbapenems  
11 work and you fully dose them, they're good drugs.  
12 It's very hard to be superior on toxicity. We're only  
13 treating for 10 to 14 days. You know, most tox  
14 signals take longer than that to develop. And again,  
15 MDR/XDR is rare, we hope. Superiority is a high  
16 stakes gamble for a novel agent. As Ed has said,  
17 you're testing the drug and the test. You could lose  
18 a drug because you gamble on this. If your primary  
19 aim is superiority and the study fails, that's it.  
20 You're done. The study result says failed. You  
21 cannot go forward. But if you see superiority by  
22 accident in a non-inferiority study or in a subset,

1 you can claim that result.

2           Simpler pathways, LPAD and tier B/C. We  
3 spend a lot of time discussing simpler ideas and  
4 there's a consensus and it makes sense that PK/PD-  
5 based dose selection should make it possible to  
6 register in somewhat smaller data sets. But actually  
7 doing this has turned out to be very hard. LPAD is an  
8 idea that was created for in the U.S. some legislation  
9 to kind of help with this about approval based on  
10 combinations of data plus some safeguards. But the  
11 bottom line is that LPAD really seems to be unlikely  
12 in the U.S. and it actually would have been only for  
13 the U.S. anyway.

14           And in fact, what we have now is a very  
15 practical implementation, as you have been hearing,  
16 about what -- of the tier B and tier C ideas that  
17 appeared a couple of years ago. And I'll say that the  
18 tier A, B, C, D nomenclature is not something that you  
19 will ever see in a guidance document. It's not needed  
20 but it is useful in presentations to have a feel for  
21 it along this pathway. It basically corresponds to  
22 example one and example two that you heard Marco and

1 Sumathi present.

2           So tier A is the classic setting where you  
3 can do two big trials. That's what we've always done.  
4 It's nice and easy. Tier D corresponds to this idea  
5 called the animal rule -- more discussion about that.  
6 But basically it's a setting where you can't do  
7 efficacy studies in man, like anthrax. I hope I can  
8 never do that trial. And then, in between, there are  
9 some stair steps. And the easiest way to explain B  
10 and C is to see some examples.

11           So here are hypothetical tier B and tier C  
12 drugs. Tier B is a drug that has a spectrum that  
13 covers an entire syndrome. You'd be happy using it as  
14 monotherapy for complicated intra-ab. So what you  
15 should do is one standard Phase III study of drug B  
16 versus a standard comparator at a standard body site.  
17 This will be focused on UDR pathogens, no super, super  
18 MDR/XDR. But if you choose your comparator well, you  
19 can cover a lot of resistance ground. This study will  
20 provide a crystal clear view on safety and efficacy of  
21 drug B. And then, you put with that a little study  
22 that's not pivotal. It gets as much as it gets. It's

1 an open label salvage study, might be randomized,  
2 might not, where you play go-fish for really, really  
3 hard pathogens and you acquire some data.

4 Tier C, this is a drug that is -- one  
5 version of this is a drug that's narrow spectrum,  
6 perhaps only one organism, perhaps only P. aeruginosa.  
7 What are you going to do here? Well, the problem is  
8 that P. aeruginosa, as we're going to discuss in great  
9 detail tomorrow, is a relatively uncommon pathogen.

10 So here, because of that difficulty, the idea is  
11 you're going to do something prospective and  
12 randomized, the best you can, and you're going to be  
13 doing it versus whatever is the best available therapy  
14 for that drug which means it's almost certainly going  
15 to have to be open label. You may have to go to open  
16 body sites to get enough numbers. So you may end up  
17 with sort of this really small data set where no part  
18 of it individually is satisfactory. You might also  
19 run an open label salvage study where there's no best  
20 available therapy. And you might even do an  
21 observational study of inadvertent, ineffective  
22 therapy for the target pathogen that might estimate

1 placebo response if it's a pathogen that is so  
2 resistant that you do that. It might apply to  
3 Acinetobacter.

4 Forward -- am I doing something wrong?  
5 There we go. The good news is that tier B works. The  
6 guidance from the FDA and EMA, as you've clearly  
7 heard, both describe a tier B-like idea as entirely  
8 acceptable. The candidate must address unmet need and  
9 the label will include language in the form of  
10 patients with limited treatment options. It makes  
11 perfectly good sense. We're not yet there with tier C  
12 and that's the purpose from my chair of today and  
13 tomorrow is to sort of wrangle with this notion. And  
14 it's the problem of limited statistical testing. And  
15 you know, I can say that for the FDA it's a sticky  
16 point because there's a statutory requirement for  
17 substantial evidence based on adequate and well-  
18 controlled investigations. We heard from Marco that  
19 the EMA is willing to consider it. It's not entirely  
20 clear to me yet if it could be the only indication  
21 you've got, but maybe so.

22 But clearly they're using a language in the

1 form of treatment of infections due to x in situations  
2 where you can't gather much data. But let me say  
3 that, you know, if you phrase it as a regulatory  
4 issue, you're making a mistake. It isn't a regulatory  
5 issue. Actually it's an all of us issue. What do you  
6 as a doc want to know? Well, I want to see something  
7 that shows me that it gets to the site of action. I  
8 want to see something that shows me that it at least  
9 cures a few people. I want something. So in many  
10 ways, what you're seeing here is sort of an advanced  
11 declaration of what you as a doc are going to say  
12 about it when it hits your doorstep. So don't phrase  
13 this as a regulatory hurdle. I think that is a wrong  
14 way to look at it. Really what we have to come up  
15 with as a community is what's acceptable. You know,  
16 what's workable and don't make the perfect the enemy  
17 of the merely good.

18           So my practical transaction is that for a  
19 single pathogen, tier C drug, it's going to have to be  
20 non-inferiority. But you're going to have to make  
21 some -- do some wiggling around, and tomorrow you'll  
22 see some examples of that kind of wiggling around.

1 Build the largest data set you can at plausible body  
2 sites. Adjust some wide margins. Maybe do more than  
3 one experiment. Maybe triangulate on this thing.  
4 Look, superiority is always acceptable, but see above.  
5 I just think that's a very high risk gamble.

6 Pressing button, but nothing is happening.  
7 I have to wave my hands. Let's see. There must be  
8 another button. No? Yes? Would someone advance the  
9 slides for me? I'm going to retreat to that. Thank  
10 you. A little disambiguation, pathogen-focused. The  
11 phrase is tier C and pathogen-focused pathways can be  
12 confusing. I want to make it clear at least what I'm  
13 talking about. Here are the three ways you could read  
14 this language. Truly narrow, Acinetobacter only.  
15 Broad-spectrum, but includes a rare pathogen; or any  
16 spectrum, but you focus it on some subset of difficult  
17 bugs. Like it covers all the Enterobacteriaceae but  
18 you can also treat CRE.

19 When I talk about pathogen-focused pathways  
20 and I think most of the time when we're discussing it  
21 over the next day or two, we're really talking about  
22 number one in in this. It's so narrow that you don't



1 have the choices implicit in versions two or three of  
2 these conceptual drugs. Next slide. All right. The  
3 implications of some of this, and the future economics  
4 of antibiotics all collide. Next slide, please. So  
5 the current economic model for antibiotics is broken.  
6 The current approach is that we develop a new drug.  
7 Everyone is delighted to have the new drug. They clap  
8 you on the back and say, wow, that's fantastic. Thank  
9 you for doing all that hard work. Matter of fact,  
10 this is so important as a drug, we're not going to use  
11 it. And as a consequence, it's entirely rational --  
12 stewardship, hold the drug back. You know, that's  
13 really what we as a community should do. It's what I  
14 did when I was a hospital epidemiologist.

15 From an economic perspective, of course,  
16 you've just spent \$500 million bringing that drug to  
17 market and that's a financial loss. And many analyses  
18 show exactly the same thing. It is not -- it is  
19 irrational to start antibiotic R&D under the current  
20 development models. And the problem that underpins  
21 all this is that we have a basic -- what amounts to a  
22 pay per use model that reimburses for only one portion

1 of what an antibiotic does. Next slide, please. So  
2 I'd like you to think about antibiotics as the fire  
3 extinguishers of medicine or sometimes another way to  
4 think of them is think of them as the firemen of  
5 medicine, the firepersons of medicine, to be gender-  
6 neutral.

7           So think about fire extinguishers. They  
8 have two roles. One is to put out fires, obviously.  
9 But the other role is to make it safe to be in a large  
10 commercial building like this one. So how often have  
11 any of you used a fire extinguisher? I hope it's  
12 zero, except in training, which is kind of fun. But  
13 in real use, I hope zero. And yet, would you be happy  
14 to be in a building without a fire extinguisher? You  
15 haven't needed it all these years. Would you be happy  
16 to forego it? Think about the firemen down at the  
17 corner fire station, which isn't too far away. When  
18 should you pay the firemen? Per fire? No, obviously  
19 not. So if you think of antibiotics as being the fire  
20 extinguishers or the firemen of medicine, they have  
21 the same two uses. You use them to put out fire, but  
22 equally you use them to make it rational to go into

1 the hospital, get your hip replaced, get your cancer  
2 treated, take care of the premature baby, all those  
3 things that antibiotics make available so that every  
4 day you walk in and you look at the antibiotics on the  
5 shelf and you gaze at them lovingly and say, boy, I'm  
6 glad I'm not going to use that today but I'm glad it's  
7 up there.

8           Next slide. So the buzzword here is de-  
9 linkage and we have to find economic models that  
10 separate reward from usage. There's a big project  
11 going on in Europe called DRIVE-AB that's working on  
12 this idea, things like lump sum access fees,  
13 insurance-like models. In the United States, the  
14 presidential advisory council has taken up the charge  
15 to try to sort this out and I know that others in this  
16 room are very interested in this topic. Don't yet  
17 have an answer to this. But we have to find ways to  
18 pay for the value -- both values of the fire  
19 extinguisher.

20           Next slide. Now, there's an implication for  
21 the developers in the room. Fire extinguishers come  
22 in different categories and you actually need one of

1 each. If you've had fire training, you've learned  
2 that for paper, wood and plastic, you use certain  
3 kinds of fire extinguishers. But for electrical  
4 equipment, you use another kind. Antibiotics are much  
5 the same way. Incremental extensions of fire  
6 extinguishers are nice. This one's a little lighter  
7 or something, whatever. But that only gets you so  
8 far. The real value is when you create a kind of fire  
9 extinguisher for a category that doesn't yet have a  
10 fire extinguisher. So think about that. Strong  
11 scientific value, novelty in mechanism, lack of cross-  
12 resistance. This is the best way to get your fire  
13 extinguisher bought in the future.

14 Next slide. Some common mistakes, and so  
15 now I'm going to weave this back into some of the  
16 themes I've been pointing at. Next slide. So lack of  
17 dose justification. Paul Ambrose is about to give a  
18 talk on this that you're going to enjoy. But let me  
19 just say that my version of this history is you can't  
20 do too much. One animal model plus one isolate equals  
21 inadequate. You need clear data on the PD driver,  
22 clear data on the PD index magnitude, use those

1 preclinical data to conclusively prove you have a dose  
2 that gives the right exposure and then the last line,  
3 please, do not forget to prove that you can get that  
4 exposure in the target population. I got it right,  
5 Paul?

6           Next slide. Misreading regulatory feedback.  
7 For Phase I and Phase II studies, this is important to  
8 know that the agencies will only tell you to stop if  
9 you're likely to hurt somebody. You're free to use  
10 any endpoint you'd like for dose finding. You want to  
11 look at cytokines, you want to look at toenail color,  
12 anything you want. But acceptance of that exploratory  
13 endpoint does not endorse that endpoint for a pivotal  
14 trial. The other aspect of this is that following  
15 regulatory advice, as I heard someone once say, is an  
16 underused strategy. Go talk to the agencies. They  
17 really will make time to help you, and listen closely.  
18 It is very tempting to hear what you want to hear. We  
19 have all been guilty of this. I have definitely been  
20 guilty of this. Pay close attention when you hear the  
21 words sponsor risk. They see more stuff than any of  
22 us see. Listen closely.

1           Next slide. Unrealistic expectations,  
2           expecting superiority over a fully dosed comparator  
3           that is really pushed pharmacodynamically to its max.  
4           This better be rare and you must, must, must not  
5           deliberately enroll subjects whose infection is likely  
6           due to a comparator-resistant isolate, unless of  
7           course there are no other options. But then, in that  
8           case, it's Ebola and we've failed as a community.  
9           Also do not chase the really hard indications first.  
10          Yes, I know endocarditis would be a great indication  
11          to have. But you'd really better learn something  
12          about your drug in a more ordinary setting before you  
13          cast all of your fortunes on that very difficult  
14          pathway.

15          Next slide. I want to be labeled for the  
16          treatment of CRE. I want everybody to understand that  
17          that never happens. Instead, your drug will be  
18          indicated for the treatment of infection X caused by  
19          strains of Y that are susceptible to your drug. It  
20          won't say that are resistant to other drug and that's  
21          because, especially across compound classes,  
22          resistance to one drug doesn't have a one-to-one

1 linkage to susceptibility to another drug. So the  
2 fact that it -- the fact that it is resistant to a  
3 carbapenem, does it make it susceptible to your drug?  
4 No, of course not.

5 Next slide. Some conclusions. Next slide.  
6 So my key points. Seek novelty. Get it registered.  
7 Justify the dose. Lots of preclinical PK/PD data. If  
8 at all possible, do a standard non-inferiority study  
9 for a standard comparator versus a strong -- a  
10 standard indication versus the strongest comparator  
11 you can come up with because, remember, even though  
12 I'm calling that UDR, if you use a carbapenem, it can  
13 be R'd to everything but that carbapenem and that  
14 covers a lot of ground. Seek the super difficult bugs  
15 on the side. Don't make this pivotal. And finally,  
16 keep it simple. The required number of miracles  
17 should always be less than one. Thank you.

18 [Applause.]

19 DR. MARKS: Thank you, John, for that  
20 points-to-consider approach across a broad range of  
21 things. I especially like the fire extinguisher  
22 model. That seems to be evolving nicely as an

1 analogy. I think all of us keep looking for that dry  
2 chemical approach. But the organisms stay ahead of  
3 us. You also talked about the importance of PK/PD.  
4 So next, we're going to have Paul Ambrose, who's the  
5 president of the Institute for Clinical  
6 Pharmacodynamics, has some approaches in here which  
7 clearly outline and show the predictable failures and  
8 successes. The title of his talk is "Pharmacokinetic  
9 Considerations in Unmet Need Programs." Thank you,  
10 Paul.

11 PHARMACOKINETIC CONSIDERATIONS IN UNMET NEED  
12 PROGRAMS

13 DR. AMBROSE: Thank you. It's certainly my  
14 pleasure to be here today. Here are my disclosures.  
15 I'm happy to talk about those to anyone who cares.  
16 This doesn't advance? Advance. So I brought in my  
17 talk to pharmacometric considerations in programs of  
18 unmet medical need. I felt pharmacokinetics just too  
19 constraining. Next slide, please.

20 So let me start off by saying we haven't  
21 been doing a really good job at picking doses for our  
22 Phase III antibiotic development programs. And the



1 goal of my talk here today is to share with you a way  
2 of thinking so that we can do a better job in the  
3 future, right? And so, what's really critical to  
4 remember is that antibiotic development programs fail.  
5 It's loss often about bad drugs and much more often  
6 about bad decisions. And that's a really bold  
7 statement for me to get up here and say, but it's  
8 really true. Consider our place in drug development.  
9 As a group, we have participated in many, many of the  
10 drugs that have reached regulatory approval over the  
11 last decade or so and also some of the failures. And  
12 we've been behind the scenes looking at how decisions  
13 are made. And so, I think we have a perspective that  
14 not many people really have.

15 So from our perspective -- okay, advance,  
16 please. It's hard to do it without the slides. So a  
17 lot of folks in rooms like this really focus on  
18 superiority versus non-inferiority over time. That's  
19 what really the focus has been. And for me, that's an  
20 important question, but it's the wrong question. It's  
21 the less important question. The more important  
22 question is how do I ensure that my antibiotic is

1 dosed correctly so that the drug not only makes it  
2 through the regulatory process, but reaches the hands  
3 of clinicians and helps save patient lives. That's  
4 really the most important question. And I feel if we  
5 spent half of the time arguing about how to get the  
6 dose right as we've spent arguing about inferiority  
7 versus non-inferiority, I think by the end of today's  
8 presentation, you'll agree with me that we'd have more  
9 antibiotics on the market today to treat sick patients  
10 than we do at the moment.

11 So let me show you what I mean. Superiority  
12 can be found on an exposure-response function. So  
13 this is just a made-up drug. You see drug exposure is  
14 a logit function there. And you see the relationship  
15 between AUC to MIC ratio in response. The green data  
16 represents a dose of this drug, which happens to be  
17 three times the dose of the red dosing regimen. You  
18 can see the green regimen is up on the plateau of the  
19 exposure-response relationship and the red data -- the  
20 red distribution of patient exposures is down on the  
21 curve. The green regimen is superior to the red  
22 regimen, right? It's associated with a much better

1 probability of response than the red regimen. This is  
2 really what I'm talking about.

3 We need to push our doses up that exposure  
4 response curve. And the further you push them up the  
5 exposure-response curve, the harder it is to prove  
6 superiority, right? Right? More and more cures,  
7 fewer and fewer failures related to study drug.  
8 That's the result. And sadly, it's very rare that we  
9 actually do this in our clinical trials. But  
10 occasionally, we do. Most recently, The Medicines  
11 Company studied meropenem-vaborbactam, a brand new  $\beta$ -  
12 lactamase inhibitor, a complicated urinary tract  
13 infection. You can go to the Web and see the results  
14 of that trial.

15 They enrolled hundreds of patients. How  
16 many failures? Four. Four failures. They optimized  
17 meropenem not only with dose but with duration of  
18 infusion. Four failures, or 1.6 percent. I'm not a  
19 statistician, but I'll tell you it's got to be  
20 thousands of patients to show superiority to that  
21 regimen, right? So the further we push up that dose-  
22 response curve, the harder it is to prove superiority.

1 Unfortunately, we don't often pick doses that sit on  
2 the plateau of our exposure-response functions. We  
3 pick them on the slope, in the middle of that slope  
4 and sometimes towards the bottom.

5 Next slide, please. So if my hypothesis is  
6 correct that this pharmacology underlies all of this  
7 stuff, right, our successes in drug development as  
8 well as our failures, then we should be able to  
9 predict our failures as well as our successes. So can  
10 we predict our failures? Yes, and right now, I'm  
11 going to take you to some uncomfortable places.  
12 Before we get on how to do it better, we're going to  
13 visit some uncomfortable places. We're going to go to  
14 those programs that failed. And by going there, my  
15 goal is not to point fingers at anybody in the  
16 audience or cast aspersions on anyone. My goal is to  
17 set the groundwork on how we can do this better in the  
18 future. So first, you have to believe -- first, I  
19 have to demonstrate for you so that you can believe  
20 that pharmacology underpins all of this stuff.

21 Next slide, please. So this is daptomycin  
22 and this is the exposure-response relationship for

1 daptomycin in the animal model. It happens to be the  
2 neutropenic mouse thigh infection model, the data  
3 generated by William Craig. And you can see AUC-to-  
4 MIC ratio is the PK/PD driver for daptomycin on the x-  
5 axis there and change in log<sub>10</sub> CFU on the y-axis. And  
6 you can see as you drive exposure up, more and more  
7 bacterial killing. We all remember that daptomycin  
8 was studied versus ceftriaxone in patients with  
9 community-acquired pneumonia and we all remember that  
10 trial was stopped for lack of efficacy in the  
11 daptomycin arm. So let's take a look at that.

12 Next slide, please. The red distribution of  
13 AUC-to-MIC ratios is a simulation of the exposures in  
14 those patients. You can see the median, the 25th and  
15 75th percentiles defined by the edges of the box and  
16 the bar and whisker plots for the range of data. You  
17 can see that the exposures lie -- wow, they lay on the  
18 bottom of the exposure-response curve. I'm sure  
19 Cubist thought they'd be near the top. But they sit  
20 near the bottom. Did they do this intentionally? And  
21 the answer is absolutely not. How did they pick their  
22 dose? They picked dose of 4 mg/kg.

1           But how? Well, it's the same dose they used  
2 in skin infections, where the dose worked. They also  
3 noted that they were much more active against  
4 pneumococcus than S. aureus. In fact, they were  
5 eightfold more active, right? And they had a couple  
6 of animal models. They had Bill Craig's mouse thigh  
7 model. They also had a hematogenous pneumonia model.  
8 But what they didn't have is they based their  
9 decisions on the wrong model. They didn't use the  
10 standard murine lung pneumonia model. Had they used  
11 that model, they would have seen the impact of binding  
12 to pulmonary surfactants in that animal model and they  
13 would have seen that it didn't work versus ceftriaxone  
14 in that animal model and they would have had the  
15 opportunity to abandon the program, even before it  
16 started. Instead, they executed that model post-  
17 mortem.

18           Next slide. So ladies and gentlemen, I  
19 think the daptomycin program was entirely predictable.  
20 Their fatal mistake was using the wrong animal model.

21           Next slide. What about tigecycline? This  
22 is again data from Dr. Bill Craig, set up identically

1 as before. As drug exposure goes up in the mice --  
2 this happens to be Acinetobacter -- you see more and  
3 more bacterial killing. We all remember that  
4 tigecycline was studied in hospital-acquired and  
5 ventilator-associated pneumonia. Next slide. And it  
6 failed versus meropenem. Here are the observed  
7 exposures, the observed AUC-to-MIC ratios from these  
8 patients. You can see the median AUC-to-MIC ratio was  
9 just a little bit short of net bacteriostasis in the  
10 animals. And a large number of patients stretching  
11 with AUC-to-MIC ratios towards zero. Well, this can't  
12 be good, right? Tigecycline did not meet the criteria  
13 for non-inferiority. Why did they pick this dose?  
14 Why did Wyeth pick it? Well, they worked in skin  
15 infections. It worked in intra-abdominal infections  
16 and their sponsor perceived they had a safety concern.  
17 So they were going to go with the maximum predicted  
18 dose.

19 Well, next slide, their critical mistake in  
20 all this was the maximum tolerated dose was just  
21 insufficient, right? Don't go forward with a dose  
22 just because it's safe but your preclinical data might

1 suggest you've got a long way to go. So again, ladies  
2 and gentlemen, tigecycline's failure was completely  
3 predictable.

4 Next slide. What about ceftobiprole? This  
5 is again data from Dr. Craig, same as before. More  
6 drug in the mice, more time we see it in the mice,  
7 more effect for ceftobiprole. Next slide. Here's the  
8 distribution of time above MIC in patients treated  
9 with ceftobiprole. You can see they're not -- their  
10 median value is not even at stasis. Well, how did  
11 this happen, right? Well, in Dr. Craig's animal  
12 model, he noted -- he noted that the time above MIC  
13 needed for efficacy was the same in pneumonia and in  
14 thigh models which suggested that you were getting  
15 very strong lung penetration or very strong ELF  
16 penetration. In fact, some number approaching a  
17 hundred percent, right?

18 So what did the sponsor do wrong? Well,  
19 they elected -- they elected, against the counsel of  
20 their advisors, to do their ELF penetration study in  
21 people concurrently with their Phase III program. And  
22 why? The why was to save time. They were warned.



1 They were warned that penetration of cephalosporins  
2 into ELF is highly variable, going anywhere from 20  
3 percent to a hundred percent. That was until they set  
4 a new low. Their drug penetrated 15 percent into ELF  
5 and this is the expected exposure distribution.

6 Next slide. It should be no surprise,  
7 ceftobiprole was predictable. But had they done their  
8 ELF study before launching their pneumonia programs,  
9 they would have had the opportunity to change dose,  
10 change interval or abandon the program altogether.

11 Next slide. Doripenem, again, exposure-  
12 response in the thighs of mice, data from Bill Craig  
13 again, same as before. You drive exposure up, good  
14 things happen. Doripenem was studied versus meropenem  
15 in ventilator-associated pneumonia. Let's look at  
16 their exposures on the next slide. A little bit  
17 better here, right? The median exposure is associated  
18 with bacterial killing. But look at the variability  
19 and drug exposure at the dosing regimen study. It  
20 stretches towards zero. This isn't good, right? You  
21 can't have that many patients with exposures that  
22 stretch towards zero and expect that you're going to

1 be approved. So again, next slide, their fatal  
2 mistake was not accounting for drug clearance.  
3 Increased drug clearance in VAP patients was just not  
4 accounted for in their dose regimen selection.

5 Next slide. So here we come to meropenem.  
6 These are data from, this time, George Drusano's  
7 laboratory and this is in mice. It's an ELF of mice.  
8 So it's an ammonia model this time. And as you drive  
9 time above MIC for meropenem up in the ELF of mice,  
10 you get more and more bacterial killing. Now let's  
11 look at meropenem. Next slide. Is it any wonder?  
12 This is a 2 g dose every eight hours with a standard  
13 infusion of meropenem. The median exposure is up on  
14 the plateau of the exposure-response relationship, as  
15 are most of the patients that would be simulated.  
16 Notice the variability of penetration into lung  
17 tissue. Very high. So you get that little tail that  
18 goes towards zero. But the vast majority of people  
19 sit up on top.

20 This, by the way, ladies and gentlemen, is  
21 why you should be thinking of combination therapy in  
22 patients with hospital-acquired pneumonia because you

1 will always have this subset of people with poor  
2 exposures down low. So combination therapy is the way  
3 to go. So this is what you want your drug -- if  
4 you're developing something for hospital-acquired  
5 pneumonia or ventilator-associated pneumonia -- this  
6 is what you want your drug to look like. You want it  
7 sitting up on top of the exposure-response curve, not  
8 halfway down, not at the bottom, but at the top if you  
9 want to do the best for patients and the best for your  
10 program. Next slide. So meropenem, it's predictable  
11 it would be successful. It's really clear why doctors  
12 used this drug so much and in such severely ill  
13 patients.

14 Next slide. So just in case you thought I  
15 may have cherry-picked and just picked those four  
16 drugs, I picked them because they were in ventilator  
17 and hospital-acquired pneumonia programs. These are  
18 data that we presented a few years back at ICAAC, when  
19 it was called ICAAC, and we looked at the probability  
20 of PK/PD target attainment based on Phase I data and  
21 microbiology data available at the time that doses  
22 were picked versus the probability of approval by the

1 U.S. FDA. You can see as the drug exposure goes up or  
2 the probability of target attainment goes up, so does  
3 the probability of approval. And there's a mix of HAP  
4 and VAP programs in this particular collection of  
5 studies. There are 20 studies involving 17 drugs, 14  
6 failures and six successes.

7 So you might note that little red circle on  
8 the bottom, all the way towards 100 percent target  
9 attainment on the bottom. There are no guarantees.  
10 That drug happens to be garenoxacin. You might  
11 remember garenoxacin developed for community-acquired  
12 pneumonia. It failed, not because it had insufficient  
13 efficacy. It failed because it had safety issues.  
14 But there are no guarantees. But the further you  
15 drive your target attainment up, the better your  
16 chances are.

17 Next slide. So hopefully I've convinced you  
18 that failure is predictable and now we're going to  
19 answer the question, well, I've got my shiny new drug,  
20 how am I going to keep my NDA on track. Next slide.  
21 I think it's a proven approach and it's PK/PD embedded  
22 in your development program from the very beginning

1 with a very deep collection of animal studies, PK/PD  
2 in design. It's getting PK early and throughout your  
3 development program. It's learning at each step and  
4 reassessing your beliefs about your drug and adjusting  
5 dose as necessary. And if you do all those things,  
6 you'll succeed. But I can tell you that our problems  
7 are sometimes much more basic than that, and I'll  
8 point out two challenges that we see when we talk to  
9 sponsors we work with all the time.

10           The first one is, well Paul, we didn't work  
11 in the animal model. That's because our drug's got a  
12 unique mechanism of action. The laws of pharmacology  
13 don't apply to us. And they don't say it that way,  
14 but it's essentially what they're saying. Well, let  
15 me assure you I haven't seen an antibiotic yet that  
16 the laws of pharmacology simply don't apply. So if  
17 you're thinking that your drug is special, it's  
18 probably not. It really is just about killing  
19 bacteria. That's what it does. If it's not killing  
20 bacteria in the animals, you've got a big, big  
21 problem.

22           The second problem is people want

1 checklists. We all want checklists, right? And  
2 people, they feel good about checklists. They don't  
3 have to think. But I'm sorry, drug development  
4 requires thinking, right? I've got a checklist. I've  
5 got my MIC data. I've got my animal model. I've got  
6 my Monte Carlo simulation. I'm ready to start three,  
7 Phase III. No, you're not. Well, I don't want to do  
8 those studies, Paul. They're not required by the FDA.  
9 The EMA doesn't make me do them, so I don't want to do  
10 them. I can save time. Well, I hope I can show you  
11 in a little bit that this is a very foolish approach  
12 to drug development. It's actually very high risk.

13           Next slide. So let's start off with the  
14 MIC. Pathogen susceptibility, the patient population  
15 matters. These are data from Dr. Ron Jones. They  
16 were actually developed after the workshop that the  
17 FDA put on, on HAP/VAP a number of years back. But  
18 it's looking at the percent susceptible in patients  
19 with hospital-acquired pneumonia versus ventilator-  
20 associated pneumonia. And the first number is always  
21 hospital-acquired pneumonia, followed by, after the  
22 slash, ventilator-associated pneumonia. You notice

1 all of them bolded, many of them bolded. That's  
2 telling you that there's greater than 5 percent less  
3 susceptibility in the ventilator-associated pneumonia  
4 patients. So patients with ventilator-associated  
5 pneumonia oftentimes have higher MICs than those that  
6 don't. Now, this seems really obvious to any  
7 clinician that treats patients -- that treats  
8 patients. But I don't think we always fully  
9 appreciated this. This happens across pathogens.

10 Next slide. What about pharmacokinetics?  
11 Pharmacokinetics also differs on patient population.  
12 Many drugs are renally cleared. So here's creatinine  
13 clearance in 600 or so patients with hospital or  
14 ventilator-associated pneumonia. The red represents  
15 ventilator-associated pneumonia and the yellow or  
16 gold, hospital-acquired pneumonia. And you might  
17 notice that there's a cluster of patients. There's  
18 more red at higher creatinine clearance values. These  
19 patients -- the subpopulation of patients that are  
20 really pushing drug through their clearing organs,  
21 right? So they're getting rid of drug fast. That  
22 means there's low AUCs in these patients, right?

1           And there's certainly an ICU subpopulation  
2           that are hyper-clearers, right? People that have had  
3           motor vehicle accidents and so forth clear drugs very,  
4           very fast. So you have to account for these  
5           differences in clearance. And this may look subtle to  
6           you and those MIC shifts I showed you may look subtle  
7           to you. But they do make a difference. Consider the  
8           next slide. This I showed to you before. This is  
9           tigecycline in patients with hospital-acquired and  
10          ventilator-associated pneumonia. Next figure. This  
11          is those same patients stratified by whether they had  
12          ventilator-associated pneumonia or hospital-acquired  
13          pneumonia. The difference in the box plots, notice  
14          the hospital-acquired pneumonia patients did better,  
15          higher exposures than the ones with ventilator-  
16          associated pneumonia. In fact, if you remember the  
17          clinical trial, tigecycline did about as good as  
18          meropenem in patients with hospital-acquired pneumonia  
19          but really tanked in those patients with ventilator-  
20          associated pneumonia. I say it's no wonder. Look at  
21          the difference in MIC to AUC ratios in these patients.  
22          Next slide. So as you're going through and



1 building your dose justification, I can't encourage  
2 you enough to pressure test your dosing regimens. A  
3 lot of sponsors, they just want to do that -- they  
4 just want to do that mouse study. They want to get  
5 their PK/PD target and that's it.

6 I encourage you to put into very challenging  
7 systems, like the hollow fiber infection model, where  
8 you can test your drug at high inocula, much higher  
9 than you can do in the -- generally do in the animals  
10 for long periods of time, certainly longer periods of  
11 time than you can do in any animal system and look at  
12 the relationship between drug exposure and resistance  
13 emergence on therapy. And select your doses, if you  
14 can -- if you've got this safety headroom to select  
15 your doses to shut that down, that'll increase the  
16 lifespan of the drug and increase your chances of  
17 success from an efficacy perspective in your clinical  
18 trials.

19 Next slide. So an NDA that arrives to the  
20 FDA on time but with empty boxcars is useless. People  
21 are in a really big hurry. They just want to get done  
22 as fast as possible. I mentioned before they want to

1 skip studies. If it's not required, I'm not doing it.  
2 Let's go, full bore ahead. I hope, again, to  
3 emphasize that this is a foolish proposition.

4 Next slide. Here's a typical Gantt chart  
5 that we see from some companies these days with these  
6 accelerated clinical programs. What do you see?  
7 Let's start off. You've got a SAD study, right, that  
8 they're probably doing ex-U.S. And then, when that  
9 finishes, they're going to file the NDA and they're  
10 going to tell the FDA the dose, right there. There's  
11 our dose, right? Well, what's wrong with that? You  
12 haven't done your MAD study yet. You haven't done  
13 your multiple dose study. You don't know if you've  
14 got nonlinear pharmacokinetics or any other  
15 pharmacokinetic issue. And by that time, you're  
16 filling your vials for your clinical trial already.  
17 You're blasting ahead. By the time you finally find  
18 out it's nonlinear pharmacokinetics, there's no way  
19 you're going to change your dose. You're going to  
20 say, well, we're already too far down the road. We're  
21 going to go. That's exactly what's going to happen.

22 And then look what else they do. They put

1 the BAL study, the epithelial lining study. They  
2 stack it right on top of the Phase III program. I  
3 already showed you how it's like running across the  
4 street and eventually you'll get hit by a bus if you  
5 run back and forth enough times. But this is exactly  
6 what we're seeing. And I also think most importantly,  
7 look at the time durations between steps. You don't  
8 see any time for thinking. Everybody's in a really  
9 big rush. No one's stopping, thinking, analyzing  
10 their data.

11 As a group that analyzes data for a living,  
12 I can tell you that people think that this is going to  
13 be done and you push a button and it's done in a week,  
14 right? It's not. Data analysis and looking at -- and  
15 letting data drive your decisions takes time. I think  
16 we all need to slow down and take a deep breath and  
17 make sure our studies are being done sequentially, in  
18 a way that makes sense. And concurrently, if we can -  
19 - if it makes sense to do, but just not race to the  
20 end because you could just be running off a cliff.

21 Next slide. So finally, a warning. Develop  
22 the drug you have, not the one you wish you had. You

1 know, when you hear people come up with their new  
2 drug, and you're laughing but it's true. Think of all  
3 the drugs out there. My drug treats resistant CRE,  
4 quinolone-resistant DAP,  $\beta$ -lactam-resistant DAT. It  
5 works in lung, urine, feces, everywhere. It's  
6 wonderful. Come on. There's no drug like that. So  
7 you sell it to your investors on these false premises.  
8 You get a lot of money and it drives you to do really  
9 stupid things. So slow down, develop the drug you  
10 have, not the one you wish you had. And with that,  
11 next slide, thank my colleagues who continue to inform  
12 my thinking. Thank you very much.

13 [Applause.]

14 DR. MARKS: All right. Thanks, Paul.  
15 Thanks for sharing your insights over your years  
16 working in the field. And now, I'd like to invite Joe  
17 Larsen up to the podium. Joe is the deputy director  
18 for BARDA, the Biomedical Advanced Research and  
19 Development Authority. And Joe's -- I'm sure probably  
20 everybody in the room is familiar with Joe. BARDA has  
21 played a very important role in the space of  
22 antibacterial drug development, both from the

1 standpoint of product development and also pushing  
2 forth the science in the field in general and looking  
3 at new and novel ways to develop new antibacterial  
4 drugs. And he's going to tell us a little bit more  
5 about that. Thanks for joining us here today, Joe.

6 BARDA'S MARKET RESEARCH FOR A CLINICAL TRIAL  
7 NETWORK FOR ANTIBIOTICS

8 DR. LARSEN: Thanks, Ed. And good morning,  
9 everybody. Can I get the next slide, please? So I'm  
10 an employee of the U.S. federal government. Uncle Sam  
11 has vetted me for any conflicts of interest. Next  
12 slide. So as Ed said, BARDA's been involved in  
13 antibacterial drug development since 2010. We  
14 basically form public-private partnerships for the  
15 development of new antibacterial drugs. We've been  
16 involved in one way or another in Phase III clinical  
17 trials for a number of the companies that we support,  
18 and we plan to be involved in Phase III clinical  
19 development of other -- with additional companies in  
20 the future.

21 Next slide. So the problem that we see with  
22 this is that every single time BARDA goes out to do a

1 clinical trial, it sets up that clinical trial de novo  
2 and pays for all -- to build and pay for all the  
3 infrastructure needed to conduct the trial each time  
4 we want to do one. So we wondered if there was a  
5 potential for efficiencies to be built into the  
6 system, perhaps through the development of a clinical  
7 trials network, to do regular registrational Phase III  
8 and Phase II clinical trials.

9 Next slide. So Ed already showed another  
10 diagram in his talk -- he stole a little bit of my  
11 thunder, that -- but his diagram I think, frankly, was  
12 a little bit better than mine -- but talks about the  
13 way that this would potentially work. And it would be  
14 that there would be a clinical trials network for a  
15 standard body site indication that would be  
16 continually running the standard -- enrolling the  
17 standard of care as the control arm in that trial.  
18 And then, over time, investigational products would be  
19 incorporated into the clinical trials network and  
20 compared to that common control arm. And this is a  
21 diagram -- a notional diagram of how this potentially  
22 would work.

1           Next slide. So as a first step in trying to  
2 understand this -- and this is a really great  
3 opportunity here to be speaking about this publicly  
4 because BARDA's perspective on this is that, A, we  
5 want to really hear from industry if this is something  
6 that people think is needed and would be helpful. B,  
7 we also want to understand from both a technical and  
8 cost perspective, you know, what this would cost and  
9 some of the challenges that would exist for us to be  
10 able to implement this. But we also want to hear from  
11 industry some things that we're not thinking about.  
12 And so, I'm going to highlight today other concerns  
13 and risks that have been brought up. But we are --  
14 BARDA very much wants to hear from industry related to  
15 this to make sure that we're thinking about this in an  
16 appropriate way.

17           So when the government wants to understand  
18 something in the market, we do market research and we  
19 issue something called a request for information. And  
20 so, we issued a request for information on February  
21 4th, received responses back on April 11th, and we  
22 received 11 responses, eight of which were through

1 standard CROs that gave us technical approach and cost  
2 data on how they would establish this network. And  
3 I'll share that information with you all today in a  
4 way that's been scrubbed for the individual responding  
5 companies. But we also received three responses from  
6 antibiotic developers, which were immensely helpful  
7 and those weren't providing technical or cost data.  
8 They were providing narratives of saying, hey, if  
9 you're -- if, BARDA, you're going to go forward with  
10 this, you need to be thinking about the following  
11 things. And that was extremely helpful to us. And  
12 again, this is something that we would encourage  
13 additional industry partners to come forward with and  
14 have that conversation with BARDA.

15 Next slide. So what did we assume? So we  
16 issued this request for information and we assumed a  
17 10-year period of performance. We assumed there would  
18 be an initial setup period for about a year and that  
19 three investigational antibiotics would be brought in  
20 to the network and then compared to a common control  
21 arm. We sought information for complicated urinary  
22 tract infection, complicated intra-abdominal infection



1 and nosocomial pneumonia. We told the respondees that  
2 rough orders of magnitude -- we didn't need things  
3 down to a dollar and cent, but just to a general level  
4 of what they felt this would cost. And we bucketed it  
5 in two different kind of levels of patients, 500  
6 patients and 1,000 patients for cUTI and cIAI and 3600  
7 and 600 for HAP/VAP.

8           Next slide. So every single time you do  
9 something like this, you realize all of the things  
10 that you should have specifically asked for. And so,  
11 there's some important caveats to this information  
12 that need to be taken into consideration. And so, not  
13 everybody followed the instructions or provided the  
14 level of information that we would have liked.

15 Indirect rates weren't provided in many different  
16 responses and that basically could increase cost by  
17 about 35 percent. Different responses use different  
18 assumptions in terms of how the network would work and  
19 what we were asking for. And investigator site costs  
20 were not included in certain responses and BARDA's  
21 clinical staff also felt that that would increase the  
22 cost by about 40 to 60 percent. So you're going to

1 see in a few minutes lower numbers. And then, at the  
2 end, I'm going to basically put out what we -- what  
3 BARDA thinks this entire endeavor would cost.

4 Next slide. So this is the summary of the  
5 various costs. And I've averaged them up and then I  
6 also provided the max and minimum values to give you a  
7 sense of the level of variability in the responses  
8 that we received. But in general, the average cost  
9 was about \$20 million for cUTI, cIAI and HAP/VAP at  
10 the lower levels and then approximately, you know, \$25  
11 to \$35 million for the thousand patient levels.

12 Next slide. Also we wanted to understand  
13 the cost of this, just to maintain the infrastructure.  
14 And so, we called that warm-based cost. That would be  
15 just having the network, just enroll the control arm  
16 so that it would be operational. And the mean cost  
17 there, it ranged a little bit by the number of  
18 patients people felt would be enrolled into the  
19 standard of care, was about \$40 to \$55 million with  
20 the maximum values being about \$82 million and the  
21 minimum values being \$22 million.

22 Next slide. Also, just to give you

1 additional sense as to some of the variability in the  
2 information that we received, this is the number of  
3 clinical trial sites, which I think is directly  
4 proportional to the cost that was reported out in the  
5 responses. One response thought that just 75 sites  
6 total would cover it. One respondee did not report  
7 the number of clinical trial sites that would be  
8 required. But on average, for the lower levels, it  
9 was about 100 to 125, 130 and for the larger bucket it  
10 was around -- basically around 175, 180 sites.

11 Next slide. So one of the questions that  
12 came in, in some of the responses from industry, was  
13 really a lot of questions about how this would be ran  
14 and who would govern this. And also, there was some  
15 questions related to if this could be adapted to drug-  
16 resistant pathogens exclusively to do those type of  
17 trials. And I think our opinion at this point is that  
18 if this was to go forward, it would focus on standard  
19 non-inferiority trials and not focus on resistant  
20 pathogens for all the reasons that I think we've heard  
21 today already.

22 We are envisioning that this would be an

1 ACRO that would be administering this. Some questions  
2 felt that -- they questioned who should lead this  
3 effort and some of the respondees felt that it should  
4 be led by a group of academic investigators. We were  
5 actually walking into this thinking that BARDA would  
6 actually lead this effort. But that's of course open  
7 for discussion as things evolve. And then there was  
8 the overall question of what would be the  
9 organizational structure. And I would say several of  
10 the CROs in the responses did provide an  
11 organizational structure and a governance structure as  
12 part of their proposals. But I think that's getting  
13 down to a level that's a little too deep for us to be  
14 presenting here in public.

15 Next slide. So what are the overarching  
16 challenges of setting something like this up? In my  
17 mind, the number one is financing, right? If we're  
18 going to build this infrastructure, it has to be  
19 maintained because ultimately if this is kind of --  
20 ultimately, it would be an economic incentive for an  
21 antibacterial development because efficiencies will be  
22 built in by having a common control arm. But if

1 industry can't rely on that as a network as being  
2 there and being operational, then it's not a  
3 functional incentive.

4 I think initially in order to gain interest  
5 into a network like this, BARDA or other partner  
6 organizations would have to finance the clinical  
7 trials in its entirety to show that the network itself  
8 was competent and could actually execute. And then,  
9 over time, I could envision a model where we would  
10 then switch to a fee-for-service where companies would  
11 pay themselves to actually tap in and utilize the  
12 network. But of course, because of some of the  
13 efficiencies that would be realized, their clinical  
14 trial may be less expensive or may be able to be done  
15 more rapidly.

16 One of the big questions we also have is  
17 that are there sufficient products in development to  
18 warrant this investment. There are not a lot of  
19 antibiotics in clinical development. And if you look  
20 down to the preclinical pipeline, I would not describe  
21 it as vibrant and robust. But nevertheless, I think  
22 there probably is enough to support standing up and

1 having a network. And once that network was also in  
2 place and operational and demonstrating to be  
3 competent, it may spur others to enter into the field  
4 to start doing antibacterial drug development because  
5 they saw that there was a favorable clinical landscape  
6 for development.

7 The big risk -- you know, the big risk for  
8 us is uncertainty, right? If we build it, will  
9 industry participate? Because the last thing I think  
10 any of us wants is what's going to end up being, you  
11 know, a several hundred-million-dollar white elephant.  
12 And so, it's going to need to be -- again, as I  
13 mentioned, we would have to pay probably for the first  
14 few drugs to go into this network to demonstrate its  
15 competence and then switch to a fee-for-service-type  
16 model.

17 Next slide. So just to be transparent in  
18 the responses from the three companies that responded  
19 -- and they cited a number of different challenges  
20 with this. And I would bifurcate those challenges  
21 into two buckets, one related to the protocol and how  
22 the trial would be designed utilizing a common

1 clinical protocol and the second being bucketed in  
2 terms of operational challenges of actually being able  
3 to run a network like this.

4 So there was a lot of questions about the  
5 flexibility of the master protocol itself and all of  
6 these questions were basically around how can I  
7 position my drug in the most favorable light related  
8 to the specific, you know, circumstances of my  
9 product, which are understandable. There were  
10 questions about how regulatory updates, auditing and  
11 compliance would be conducted. I would suggest that  
12 they would be conducted the same way for any other  
13 regular CRO. The selection of the standard of care  
14 was cited as being problematic.

15 One suggestion was to create a global  
16 standard of care map to suggest an aid to management.  
17 And they also submitted that getting sites to agree  
18 globally would be a significant challenge in the  
19 standard of care. Endpoint selection was cited as a  
20 challenge, also coordination between FDA and EMA was  
21 cited as a challenge and something that was needed to  
22 be addressed -- could be addressed perhaps through a

1 network like this. Questions over the data monitoring  
2 committees, whether it was the network or the sponsor  
3 that would be involved in this.

4 I mentioned again addressing product  
5 specific safety and efficacy objectives. Data  
6 blinding was a concern, how to handle dose  
7 adjustments. IV to oral switches was cited as a  
8 concern. And also, this last piece I think is really  
9 important and it is something that I don't think we  
10 thought heavily enough about when we put out this RFI,  
11 which was related to the handling of proprietary data.  
12 And basically, the construction of all the IT  
13 infrastructure that would be necessary to go into  
14 something like this we didn't even really put anything  
15 in there related to that. And the last thing that we  
16 would want to happen is a government-sponsored  
17 clinical trial network, you know, fumbles with some of  
18 the proprietary data and that would be a really quick  
19 way for anybody -- everybody to lose confidence in  
20 this type of incentive going forward.

21 Next slide. So after factoring in some of  
22 the variability that we received in our responses, I



1 would say the annual cost to establish this  
2 infrastructure is probably somewhere between \$60 to  
3 \$100 million annually. I think we probably would be  
4 comfortable subscribing about \$75 million to -- and  
5 that accounts for the fact that some of these things  
6 doesn't account for startup costs or investor site  
7 costs.

8           If I were to finance this at a level that  
9 included standard of care in three investigational  
10 drugs to cover all of the risk and the things that we  
11 haven't thought about to date, I would think that this  
12 would need to be financed at a level of about \$200 to  
13 \$250 million per year. And I think that, you know,  
14 going forward, there's a number of key challenges that  
15 we're going to need to think through and discuss with  
16 our industry partners too before something like this  
17 would be implemented.

18           Next slide. So there are some alternative  
19 approaches that are being discussed and a lot of these  
20 discussions are going on in the EU. So you know, we  
21 asked for a large, standalone network to do  
22 registrational trials that would be functioning, you

1 know, explicitly on that. And the challenge there, in  
2 my mind, is one -- the most significant one to me is  
3 getting the level of financing required to actually be  
4 able to launch this. And the question is are there  
5 other models that could be examined that wouldn't  
6 require as big of a financial lift.

7           And there's some discussion in the EU with  
8 some folks that are suggesting that instead of  
9 building a gigantic, you know, standalone network,  
10 could you utilize existing networks and, you know,  
11 have them be governed in a common way, operating under  
12 I guess a common strategic network to be able to do  
13 this type of work without having to recreate the  
14 infrastructure. I don't know the answer to that. But  
15 I would say I think then the coordination of all of  
16 those different parties then becomes the challenge and  
17 I think those are equally challenging. There's also -  
18 - you know, I'm looking forward to the discussion  
19 about innovative clinical trial designs later today.  
20 Maybe that's the answer to some of this.

21           Next slide. So for next steps for us, we  
22 first need to think about the pathway to financing

1 this. And there's currently a working group that's  
2 being ran out of the Wellcome Trust where we're having  
3 a lot of discussions on the protocol, the operational  
4 considerations and as well as the financing  
5 considerations and they're having a meeting in October  
6 where we're going to begin to discuss many of these  
7 things. And there's clearly other partners besides  
8 BARDA that are looking to try to finance something  
9 like this. And if we could all come together, it  
10 might be a much easier path to being able to finance  
11 something like this.

12 The information that we've received to date  
13 is very helpful. We'd be very open to receiving  
14 additional information from folks in industry because  
15 we really need -- if this is going to go forward, we  
16 need to begin to think about what a potential request  
17 for proposals would look like and the RFI was helpful  
18 in that regard, but I don't think we're all the way  
19 there yet. We need to continue to discuss and think  
20 about the ways that we can overcome the challenges  
21 that were provided to us and highlighted to us. And  
22 then, we also need to think about the most appropriate

1 governance structure to run something like this.

2 Next slide. So again, I just would say that  
3 we are very interested in hearing from industry  
4 related to this and would appreciate all of your  
5 feedback. My email and phone number is there. Don't  
6 hesitate to reach out to me if you want to discuss  
7 anything that I've presented today. Thank you.

8 [Applause.]

9 DR. MARKS: Thank you, Joe. I think a very  
10 fertile area for questions and conversation when we  
11 get back from break. We're thinking about maybe  
12 coming back from break around 11:20 and then add  
13 hopefully a few minutes onto your lunch break to  
14 facilitate interaction and dialogue among various  
15 stakeholders. So why don't we come back around 11:20?  
16 Sorry?

17 DR. COX: 10:50.

18 DR. MARKS: I'm sorry, 10:50. What did I  
19 say? 10:50, sorry. Yeah, why don't we do that, or  
20 come back around noon, you know? 10:50. Thank you  
21 very much, and we'll kick off with Ian, yeah.

22 [WHEREUPON, the foregoing went off the

1 record at 10:23 a.m., and went back on the record  
2 at 10:57 a.m.]

3 DR. MARKS: So we'll get started again very  
4 shortly. Thank you.

5 DR. COX: So maybe just to get started, one  
6 sort of logistical issue first. An ounce of  
7 prevention is worth a pound of cure. We found this  
8 behind the podium. If you're wondering what it is,  
9 it's a hotel card. So if people might just check  
10 their pockets, if somebody was up in the vicinity of  
11 the podium, if they're missing their hotel card, come  
12 to me and I will get it back to you so that you're not  
13 locked out of your room when you get back there.

14 DR. MARKS: All right. Thanks for --

15 DR. COX: If somebody doesn't have a hotel  
16 and they're interested in a hotel, come up and talk to  
17 me.

18 [Laughter.]

19 DR. COX: No, I'm kidding.

20 CLARIFYING QUESTIONS (PANELISTS AND  
21 AUDIENCE)

22 DR. MARKS: Thanks, everyone, for coming

1 back promptly. We're going to move into the questions  
2 section. And just taking moderator's prerogative, I  
3 thought I'd start off with the first one. We hear a  
4 lot about regulatory harmonization and the need for  
5 the U.S. and the EU to work together in terms of  
6 antimicrobial resistance. So I thought maybe Ed and  
7 Marco, you could share with us sort of what you do  
8 now, your thoughts about where this might go in the  
9 future, and if you could share that with us, start off  
10 with either -- Marco, you want to start first or --

11 DR. CAVALERI: Yeah. I think, as I said, in  
12 the context of TATFAR but also behind TATFAR itself in  
13 the recent years we had more and more chances of  
14 discussing the way forward on the development of new  
15 antibacterial agents between FDA and EMA. And also,  
16 we established regular contact with those, clear  
17 recommendation in the TATFAR set of recommendation  
18 around having a regular teleconference.

19 So what is happening is that every month we  
20 sit down for a conference between FDA and EMA in which  
21 we discuss development plans that have been proposed  
22 to both agencies or one agency but maybe with the

1 knowledge that the other agency will be involved later  
2 on in which we touch base around what is the current  
3 view of each agency with respect to the development  
4 plans and how much we can converge into finding, you  
5 know, a single, settled requirement for the developer,  
6 at least how we can define the boundaries around what  
7 can be acceptable and what not.

8           And I think this has really been important  
9 and efficient in, you know, cross-fertilizing the  
10 views between Europe and the U.S. and helping us in  
11 having a common understanding of the way forward but  
12 also of what would be the scientific basis and the  
13 evidentiary standards that would be required in both  
14 the regions. And maybe to add that we do recognize  
15 that in certain type of infection indication, we are  
16 requiring different primary endpoints.

17           And for the time being, we found a solution  
18 by way of different statistical analysis plan, which  
19 so far works very well and in deed there has not been  
20 a single case to our knowledge in which a company had  
21 to redo a pivotal clinical trial in order to satisfy  
22 the requirement of the FDA or the EMA. But save that,

1 I think we are putting efforts into looking into the  
2 future of building more rigorous scientific  
3 understanding of how to assess the benefit of an  
4 antibiotic and antibacterial agent in the context of  
5 this type of infection in order maybe to come up in  
6 the future with some primary endpoint that could be  
7 agreed by both agencies.

8 So it's a journey. But I think we are -- we  
9 understand the value of that and we are putting  
10 efforts in order to do the best we can to convert  
11 today and also with a view that in the future there  
12 might be more chances of converging once new ideas and  
13 new options for primary endpoints on how to design  
14 clinical trials in these types of infection and also  
15 for unmet need will come up. So I don't know, Ed --

16 DR. COX: Yeah. No, thanks, Marco. Very  
17 helpful and very complete. You know, just to sort of  
18 reiterate, so you're hearing the same thing from both  
19 folks. I mean, agreed TATFAR has been a helpful  
20 vehicle for us to interact. And as Marco said, you  
21 know, within TATFAR, I think the first version of that  
22 report, we noted that in fact the clinical trials that



1 are used in Europe are essentially, you know, the same  
2 clinical trials used here and if there's an instance  
3 where there's different endpoints, then we would find  
4 a way to make those clinical trials useful for both  
5 places by a different statistical analysis plan.

6 And as Marco's noted, we continue to work on  
7 the endpoints. And I think, you know, a number of  
8 folks in the room here today have been involved with  
9 the efforts through the FNIH to work on endpoints.  
10 And you know, we see this as an area where, you know,  
11 the science, you know, will essentially, you know,  
12 bring us to the set of options that, you know, we  
13 think will be, you know, helpful to the future and get  
14 us to a greater degree of common understanding because  
15 if the science is there, it should work really for  
16 both groups.

17 We also -- just to add a couple of things,  
18 we share guidance documents in development, which is  
19 helpful too so that we, you know, have both the  
20 scientific exchange and the opportunity to learn from  
21 each other. Similarly, with regards to development  
22 programs, we're sharing comments, you know, with each

1 other and also having, you know, the opportunity to  
2 discuss the comments. Sometimes the comments are very  
3 clear, but having that opportunity to talk with each  
4 other, you know, can be even more helpful.

5 We're able to do that under a  
6 confidentiality agreement and we do -- for those that  
7 choose to take sort of a formal approach, there is  
8 also parallel scientific advice that is available to  
9 those that do it. And we've done a few of those and  
10 worked with Marco and his group on that and very much,  
11 you know, appreciate those opportunities to work  
12 together in that formal approach when people choose to  
13 go that way. And maybe I'll stop there, but yeah.

14 DR. MARKS: Thank you, Ed and Marco. Maybe  
15 now we'll open it up to the panel for questions.  
16 Aaron?

17 MR. DANE: Yeah. So it's probably mainly  
18 for Marco and Sumathi, but partly for John in terms of  
19 the -- so when you were talking about when we get into  
20 the unmet need and the sample sizes are smaller, so  
21 clearly we can't do the traditional statistical  
22 criteria that we usually do and apply. Sometimes we

1 can still do something. But if we're in a situation  
2 where the numbers are even smaller than that and all  
3 of you outlined that, how do you see that data being  
4 used? Because I guess it's -- we get some data and  
5 then we've got to figure out when does it help us feel  
6 better and when does it concern us if we're only  
7 dealing with a handful of cases.

8 DR. CAVALERI: Yeah. I think it will have  
9 to be looked at on a case-by-case basis. I think it's  
10 very difficult to say this is the threshold. Below  
11 this number it will be impossible to draw conclusion  
12 about if we can do that because it will vary. And of  
13 course, here we're entering into a bit of uncharted  
14 territory in the sense that indeed we are talking  
15 about very small trial with a very heterogeneous  
16 population. And so, the interpretation of the data  
17 might be a challenge anyway. What we are trying to do  
18 is to come up with the idea that it will be  
19 challenging, but it will not be impossible.

20 And therefore we are opening to consider, in  
21 light of the unmet need and the potential benefit that  
22 would derive despite the uncertainties, it might still

1 be possible to draw a conclusion on a positive  
2 benefit-risk despite a data set that is very small.  
3 So yeah, I think it's difficult to reason in terms of  
4 absolute numbers here. And you know, each pathogen  
5 will have different considerations. The data may show  
6 something different. Of course, the PK/PD package is  
7 essential and that will be, as I said, one of the  
8 pillars of the evaluation of antibacterial agent in  
9 the context of this unmet medical need with limited  
10 clinical development.

11 DR. DUDLEY: Yeah. I think maybe along  
12 those lines of what Marco was talking about -- Paul,  
13 I'm going to kind of surprise you on this a little  
14 bit. Maybe you could talk a little bit about how the  
15 approaches that your group has taken, with taking  
16 smaller data sets and modeling exposure-response,  
17 which then does give an idea of the magnitude of  
18 treatment effect. And I'm thinking of some of the  
19 tigecycline work that you guys did a few years ago  
20 where you looked across the various exposures of  
21 tigecycline and were able to sort of quantify the  
22 treatment effect that was seen in a variety of

1 infections and whether that will help with these small  
2 data sets.

3 DR. AMBROSE: Sure. We did a couple of  
4 analyses, both involving tigecycline, but one of a  
5 more frequentist nature and one a more Bayesian in its  
6 thought process. And not surprisingly, with the  
7 frequentist approach, with an exposure-response  
8 relationship, your confidence bounds get really,  
9 really, really wide. And we were able to calculate  
10 sample sizes and they were quite large based on that  
11 approach.

12 But when we took a more Bayesian approach  
13 and we acknowledged -- we allowed some of the animal  
14 data to inform our exposure-response analyses of the  
15 clinical efficacy data, such as the direction of the  
16 exposure-response relationship, we were able to  
17 tighten those confidence bounds I think quite a bit  
18 that allowed for the calculation of a much smaller  
19 sample size with which to do those studies. So I  
20 think those things are possible to open to other  
21 statistical approaches. And it looks like by this  
22 agenda, we are.

1 MR. DANE: Yeah, and I think for me, it's --  
2 just so I'm not misunderstood, I'm not thinking we  
3 need any statistical -- traditional statistical  
4 criteria. It's just that idea of assuming we rely  
5 more heavily on the PK/PD information, assuming we  
6 count all these other things, how are we going to use  
7 the data that we do generate, because it is difficult  
8 and it's just having that feel for what -- how are we  
9 going to react to whatever we see as we're trying to  
10 plan a study.

11 DR. COX: Sam, do you want to --

12 DR. BOZZETTE: -- change directions -- so  
13 John, I mean, your tier C drugs, it seems like there's  
14 going to be a mix, no matter what control arm you pick  
15 -- there's going to be a mix of organisms that are  
16 resistant and sensitive. So I'm wondering if you  
17 could say a little more on what those trials would  
18 look like. Do you need different control arms based  
19 on the sensitivities? Do you enroll people right away  
20 or do you wait until sensitivities are available,  
21 which unfortunately takes a while unless you have a  
22 molecular marker. Just what are those trials going to

1 look like?

2 DR. REX: So your first question was about a  
3 mixture of susceptible and resistant in the control  
4 arm, susceptible and resistant to the control  
5 comparator -- to the chosen comparator. And what I'd  
6 argue here is that you should -- there are very few  
7 organisms for which I can't design an active control  
8 arm. It's actually pretty rare right now, you know,  
9 which is good, okay? So in the most general case --  
10 like tomorrow, we're going to discuss at some length a  
11 pseudomonas-specific drug. You know, most of the  
12 time, pseudomonas, if I put one -- I can pick one  
13 thing and probably put something else with it and it'd  
14 be pretty rare that my comparator regimen for that a  
15 pseudomonas would be inactive.

16 So in that circumstance actually, you know,  
17 my problem really is that pseudomonas is just not all  
18 that common as an organism. And so, I end up with  
19 relatively small numbers. And that actually leads --  
20 so the question from just a moment ago where somebody  
21 said to Paul, can't -- well, if I use  
22 pharmacodynamics, can I prove to myself that the

1 magnitude of the effect size relate to placebo is  
2 larger, which will let me use a smaller study, right.  
3 The problem that you get into is let's pretend we  
4 actually say, well yeah, the effect size -- without a  
5 drug, it's -- you know, there's like an 80 percent M1.

6           So let's actually have a really big effect  
7 size and design a small trial. When you get down into  
8 groups of like -- the denominator's 50 and 50 on each  
9 side of the equation, the problem there is that if  
10 both are active and you're expecting them both to be  
11 active, then you have almost no wiggle room for a  
12 little bit of heterogeneity. We'll actually show that  
13 tomorrow, that a movement of one patient from success  
14 to failure can actually dramatically alter your view  
15 of the data set. So you don't get out of the box by  
16 arguing for a smaller data set. You get into another  
17 box. You get into another problem.

18           So the difference -- so you know, that's how  
19 I think about this. And so, different control arms,  
20 well, I'm not too fussed about it being -- if I do  
21 drug A -- tier C drug versus per patient design  
22 therapy, if every one of those patients is on active



1 therapy, I think that's actually perfectly fine  
2 because that's what you do in the real world anyway  
3 and I'm expecting them all to be good and I'm not  
4 expecting to beat that therapy. It's a little  
5 messier. They're going to be -- the AE profile stuff  
6 may be harder to interpret. But it doesn't bother me  
7 that much, provided that you believe that most of the  
8 time the comparator was an active drug. I see that  
9 Paul wants to jump in on this.

10 DR. AMBROSE: Yeah, a little bit of  
11 sideways direction, like PK/PD often hits people. You  
12 can show pre-clinically in any number of models that  
13 it's not the resistant determinant that predicts  
14 efficacy. In other words, if you hit the right  
15 exposure, AUC-to-MIC is big enough, you kill the  
16 susceptible bug just like you kill the resistant bug.  
17 There's nothing magic about that. I can't think of  
18 examples at all where that relationship really begins  
19 to break down over clinically achievable  
20 relationships.

21 What's different in the patients with  
22 infected -- infected with MDR or XDR is a different

1 patient population. They're often much sicker and  
2 there are other comorbidities or other reasons they're  
3 dying. But again, as John pointed out, you can't do  
4 much about that. So to me, optimize your dose and I'm  
5 less concerned with the numbers of patients you have  
6 in XDR or MDR study, as long as you've already  
7 demonstrated that it's drug exposure that matters, not  
8 its label.

9 DR. COX: Maybe another question for Paul.  
10 So Paul, just in follow-up to your presentation, you  
11 were talking about patients who have low exposure to a  
12 particular drug, arguing for, you know, maybe going in  
13 with a couple of drugs. And I'm wondering can the  
14 patient that -- you know, your thoughts on predicting  
15 the patient who's likely to have a low exposure to a  
16 particular drug and I didn't know if you were  
17 suggesting, you know, doing a TDM or just sampling a  
18 level. And then, beyond that too, if you do have a  
19 drug that, you know, the patient's got a low exposure,  
20 should you keep the drug around? Should you stop the  
21 drug? Thoughts on that? And then, if you're going to  
22 pick a second drug, how do you avoid having the same

1 problem with the second drug, you know, if this is a  
2 patient characteristic that they're clearing the drug  
3 a little more quickly? If you pick a second drug  
4 that's maybe not -- that's secreted similarly or has a  
5 similar metabolic profile. So any other thoughts on  
6 that? I thought that --

7 DR. AMBROSE: Sure, and you'll probably have  
8 to remind me of some of the questions that I miss in  
9 that list of them. But to start off with the first  
10 one, I think which is am I talking about needing TDM  
11 because of variability in drug exposure. Well,  
12 certainly if your drug's got unpredictable clearance,  
13 TDM long-term is a useful thing. But the reality is I  
14 think the outcome of an infection is dictated by early  
15 drug exposures. That first 48 or 72 hours, I think  
16 all doctors all instinctively know this.

17 And so, it's really important to have the  
18 right dose up front and that means pushing the drug  
19 exposure. We're not really going to have that much  
20 time for TDM. The event window's too short. It's not  
21 like HIV where we're going to be treating for years  
22 and we can move the drug concentrations up and down at

1 will, right? It happens all too fast. So especially  
2 for, you know, pseudomonas pneumonia, where half the  
3 patients that are going to die are dead within the  
4 first 48 hours or so. So to me, it's pushing that  
5 exposure up front. I won't argue against TDM for  
6 certain drugs. But I would push back and say pushing  
7 dose is probably your safer bet.

8 The second question was --

9 DR. COX: Can you predict who's going to  
10 have these problems?

11 DR. AMBROSE: Yeah. You know, if it's a  
12 renally cleared drug, that's your first hint. So if  
13 you've got someone that's really hyperdynamic, they  
14 might be a patient that's very high creatinine  
15 clearances, they might be a patient that's going to be  
16 at risk. It'll be simple things like that. And  
17 oftentimes our doses are not selected to cover those  
18 patients, right? We start with normal renal function  
19 and we kind of match our AUCs going downward into  
20 various renal function categories in a downward  
21 direction. But we don't go in an upward direction.  
22 So maybe that's something that we could think of.

1           And the second -- the last one I think was a  
2 question related to if you've got a drug that's got  
3 variable exposure, what is it that you do. You stop  
4 the drug or try to add something else. I think you  
5 put them on the drug that has probably the least  
6 variability that you can get to that has a dose that  
7 can account for that variability, number one. And  
8 number two, in some effect sites, like the meropenem  
9 slide I showed, I think that's really important for  
10 everyone to recognize there was this tail of exposures  
11 that approached zero, even with this close to  
12 pharmacodynamically optimized drug and why. And  
13 that's the high variability and penetration into the  
14 lung.

15           So the only way to overcome that is protect  
16 that fraction of patients as a second drug. You may  
17 have to begin to think about inhalation as an  
18 alternative route, you know, breaking on through from  
19 the other side. But I'm not aware of any data where  
20 people have two drugs into a patient, measure the ELF  
21 and see where varying levels of penetration of drug A  
22 influence drug B at all. I don't think any of that

1 data even exists. So at this point, you know, I think  
2 that's an open field. But I think that data is a  
3 clear argument for combination therapy in some  
4 indications.

5 DR. COX: Ian?

6 DR. FRIEDLAND: I had a question for Sumathi  
7 and maybe Marco can also answer this. Of those  
8 different study designs that you outlined, can you  
9 give us some indication of which of those -- you know,  
10 maybe in order of frequency, which of those responses  
11 actually have undertaken? You know, so have people  
12 actually done nested superiority trials? Are people  
13 doing superiority trials? Are people doing external  
14 control trials, for example?

15 DR. NAMBIAR: The vast majority really have  
16 been non-inferiority trials. There's been one person,  
17 maybe two who've attempted to do superiority trials.  
18 But really the vast majority is non-inferiority. We  
19 really have not used external controls. We haven't  
20 seen a lot of proposals for external controls. We've  
21 used external controls more recently in the context of  
22 an anti-fungal drug that was approved over a year ago.

1           But I think the vast majority are non-  
2 inferiority trials. And for Gram-negatives, it's  
3 usually intra-abdominal and UTI, either or both.  
4 HAP/VAP typically has been the second indication,  
5 which I think makes sense. I think, you know, you at  
6 least have the evidence that it works among the other  
7 body sites. And those trials are certainly a lot  
8 easier to do than a HAP/VAP trial. So most of the  
9 HAP/VAP programs have been the second indication that  
10 people use.

11           DR. COX: Marco, anything to add? You're  
12 seeing a lot of the same programs we're seeing, so I'm  
13 guessing it's fairly similar, but --

14           DR. CAVALERI: Yes. It's fairly similar.  
15 Of course we're seeing some proposals around MDR  
16 pathogens and in novel approaches as we were proposing  
17 in the addendum. But I agree with Sumathi the  
18 majority are still in the non-inferiority.

19           DR. COX: And Nick?

20           DR. KARTSONIS: Yeah. I had sort of a  
21 follow-up question to the non-inferiority question to  
22 Sumathi, which is now that sponsors have come with

1 these non-inferiority margins, have there been  
2 situations where you've allowed a wider margin? And  
3 if so, can you give us some guidance in terms of what  
4 a wider margin means?

5 DR. NAMBIAR: I was hoping that wouldn't  
6 come up. But yes, we have -- we have allowed wider  
7 non-inferiority margins and I think some of that  
8 information is available in the public domain. So  
9 there's no secret here. I think particularly we've  
10 done it in the context of complicated urinary tract  
11 infections. We've allowed for a non-inferiority -- I  
12 mean, traditionally it would be 10 percent.

13 But in an unmet need program, we've allowed  
14 up to 15 [percent]. But I think the important point  
15 is that we need an adequate justification for why you  
16 think the product meets an unmet need. It's not just  
17 a question of widening the margin because someone  
18 wants to get the trial done in a shorter period of  
19 time. And I think more recently, I think Ed and I  
20 keep saying there are many flavors of unmet need.

21 More and more we are seeing people, you  
22 know, make -- it'll be a very tiny incremental benefit



1 and they'll say, here, I'm able to address an unmet  
2 need and the answer to that is no. We're not willing  
3 to. I think you also have to keep in mind safety  
4 concerns. So widening the non-inferiority margin,  
5 getting a smaller sample size might be one solution to  
6 the problem.

7 But we do come across products where you've  
8 seen a safety signal and in that instance, you know, a  
9 smaller program is not appropriate. So it's less  
10 about the number. I think a lot of it really depends  
11 on what the drug has to offer and whom you are trying  
12 to study. So and for HAP/VAP, again, we have allowed  
13 margins of up to 12.5 [percent] that we consider as  
14 wider margin and programs that do such trials will  
15 have a limited use statement in labeling.

16 DR. COX: Aaron? Yeah.

17 MR. DANE: Yeah, again, it's a follow-on to  
18 a comment you made around external controls, where I  
19 can see, particularly in the resistant pathogen area,  
20 that there really isn't any data out there to be able  
21 to use. But I mean, what's your view on using  
22 external controls if you're in one of the body site-

1 type approaches, and there are recent clinical trials  
2 that could be used in that way? So is that something  
3 that you would be amenable to doing? Because that  
4 could make trials a lot more feasible if that control  
5 arm data could be used across the trial in that way.

6 DR. COX: I'd welcome thoughts from other  
7 people on this. But you know, for non-inferiority  
8 trials, I mean, people have been successfully doing  
9 those in a variety of different areas. So I mean, I  
10 don't think there's any tremendous barrier to doing  
11 that. I mean, you know, we do see as we look across  
12 trial to trial, we do see variation. And I guess the  
13 question is are you reducing or increasing variability  
14 or, you know, what is the comparability of the  
15 external control compared to the patients that are  
16 actually in the trial.

17 And you know, when people do external  
18 controls, I mean, we talk about the importance of, you  
19 know, having a protocol that would essentially enroll  
20 patients in the external control that would be, you  
21 know, similar to the trial that you had been enrolling  
22 the test drug patients into. So there's a lot of

1 things to think about. But, you know, ICH E10 talks  
2 about historical controls and some of the issues  
3 around them.

4 So you know, trying to overcome those and,  
5 you know, one of the topics that's come up too in the  
6 context of the clinical trial network discussion would  
7 be is this would sort of be an ideal sandbox to try  
8 and work through these issues because there's an  
9 opportunity to have the same protocol in place over a  
10 period of time and really try and examine and explore  
11 what's really going on. You know, are the patients  
12 behaving, you know, sufficiently similar with regards  
13 to outcome when a similar protocol is applied. It'd  
14 be interesting to see that, how do things change. A  
15 new drug gets approved. It might change the standard  
16 of care. Does that change what we see and how do we  
17 figure all that in? So probably more questions to  
18 your question than answers, but --

19 MR. DANE: Well, no --

20 DR. COX: -- I think those issues are, you  
21 know -- are out there.

22 MR. DANE: I mean, in the meantime, that's

1 what I was thinking, is that, you know, if we've got  
2 relatively recent trials, that's closer to that  
3 network, if you like, is that, you know, rather than  
4 having to rely on something from 20, 30-plus years  
5 ago, if we can say, well, these trials were conducted  
6 fairly recently and the designs were sufficiently  
7 similar and we'd have to go through all that, does  
8 that allow that information to be used, which then  
9 reduces the burden on the future studies.

10 DR. COX: Yeah. Yeah, I mean, if you -- I  
11 mean, if you look at, you know, trial A was in these  
12 sites, trial B was in those sites and maybe the  
13 patients are somewhat different as you move from site  
14 to site, so the reason that the numbers are different  
15 is not just, you know, variability but in fact patient  
16 differences. So it's -- you know, and then, you know,  
17 we see protocols and oftentimes there are subtle  
18 differences or differences that exist within, you  
19 know, the definition of what a success is.

20 And you know, that can change your numbers  
21 significantly. So when you look at historical reports  
22 in the literature for outcomes for particular disease

1 conditions, and then you look at the results of the  
2 clinical trial, because of the way the endpoint was  
3 defined in the clinical trial, it can lead to, you  
4 know, in some instances, markedly different numbers.  
5 So you know, it's a question of are you really apples  
6 to apples or are you apples to oranges. And if you  
7 are apples to oranges, why is that?

8           So I think there is still, you know, some  
9 work to be done there. And I know -- I'm thinking of,  
10 you know, the endocarditis trial and the definitions  
11 in the literature with regard to successful  
12 endocarditis and the definitions -- the first success  
13 within the clinical trial for dapto, for right-sided -  
14 - or for bacteremia, I should say, you know, really  
15 led to some fairly different numbers. And so, there's  
16 a lot to sort through in that. It's not just --

17           MR. DANE: So it's possible. But it would  
18 be difficult and there'd be a lot of steps to go  
19 through I guess is the --

20           DR. COX: Well, I mean, I guess -- I mean,  
21 you can think about, you know, what is the problem  
22 you're trying to solve and how big is the problem.

1 And if you're able to do, you know, well-done non-  
2 inferiority trials, I mean, you know, go forth. If  
3 there are issues that you're trying to solve and there  
4 are -- you know, we'll talk about areas where it's  
5 particularly difficult to do clinical trials and it  
6 may be worth looking into this a little bit more and  
7 trying to figure things out because you'll take a  
8 problem that's insolvable and make it, you know,  
9 solvable.

10 So you know, I think it's important to think  
11 about the nature of the problem and where solutions  
12 are, you know, most helpful and most needed and, you  
13 know, try and work through it. So does that help,  
14 Aaron?

15 MR. DANE: Yeah, and that's a good point.  
16 So I'm thinking of the situation where it might be  
17 possible to recruit maybe a couple hundred, but no  
18 more. So you're halfway between a really small  
19 development program and the fully powered one. And it  
20 might allow you to do a different randomization ratio  
21 or something like that. So this wasn't the idea of  
22 you just have an uncontrolled study you'd compare it

1 with. You'd have some reference across the two that  
2 you'd compare. But just trying to make those sorts of  
3 situations more feasible, to get something that would  
4 support approval.

5 DR. COX: Yeah, and I think we really will  
6 venture into that area tomorrow, where it is very  
7 difficult to actually get the patients to get to a  
8 powered study. So I'm sure we'll be talking about  
9 that more tomorrow. So Helen, did you want to add  
10 something?

11 DR. BOUCHER: I'll just comment to add to  
12 your point, Ed, about the difficulty in the bacteremia  
13 trial. And I think that there are a couple of issues  
14 that we've already talked about. One goes back to  
15 John Rex's comment about the movement of small  
16 numbers. You know, that was a trial of a small number  
17 of patients and there was heterogeneity, right? We  
18 had different people in different buckets of  
19 diagnoses. And that was something that had to be  
20 accepted to do that, to really try to complete that  
21 trial.

22 At the end of the day, I think that one of

1 the things that was most helpful was that there was a  
2 group of patients that all the patients were well-  
3 characterized, but there was a group of patients in  
4 whom their bad outcome was indisputable where there  
5 was some treatment effect. And I think that that was,  
6 at least sort of our perception of how a conclusion of  
7 success could be made.

8 And so, somehow in this discussion of if  
9 you're going to have a small group, whether it's with  
10 a wide margin or no margin, including patients, at  
11 least some patients in whom it's unequivocal that  
12 there's impact of drug is helpful. And I think that  
13 was at play in the antifungals back in 2001 and back  
14 in 2014 and Nick Kartsonis and I were there in 2001.  
15 You know, so that notion is I think one we can all  
16 agree on.

17 I think the challenging part comes in to  
18 what about the trials where we don't have those  
19 patients, and there's still a need? You know, there's  
20 still a need for an oral drug to treat ESBL UTIs. And  
21 as the clinician who deals with this all the time, I  
22 don't want to forget that we just don't have people



1 with HAP/VAP. We also have young, otherwise healthy  
2 people who have to come and get a PIC line for their  
3 ESBL UTI and they have a need as well.

4 DR. MARKS: Dennis, you wanted to make a  
5 comment?

6 DR. DIXON: Just wanted to echo a comment  
7 made by John Rex on the importance of speaking to the  
8 regulatory agency early and having a dialogue and a  
9 discussion to learn the way forward. That also  
10 applies to funding agencies like NIH and BARDA. And  
11 your comment, John, that there is a strong temptation  
12 to hear what you want to hear, we see that too. And  
13 so, I think people take the encouraging words and they  
14 don't look so much at the sentences or comments that  
15 start with but, however and whereas and that's just so  
16 important to understand the reality in moving forward.

17 And just to comment, I think it was a really  
18 good idea to have this workshop and to have this  
19 discussion openly so that companies out there can  
20 start to learn from others and can get a sense on what  
21 they might want to bring forward to you and have an  
22 early discussion about.

1 DR. MARKS: So we might -- before we go to  
2 Tom, we might just invite if there are people in the  
3 audience that have a clarifying question, just make  
4 your way to the microphone and we'll get to you right  
5 after Tom.

6 DR. LOUIS: Just quickly to highlight  
7 something both implicit but somewhat explicit in  
8 Paul's presentation and that is that the delivered  
9 dose isn't a number. It's a distribution and that  
10 really I would push for distributional thinking on  
11 almost everything. In this case, the biologic effect  
12 is really the integral of that uncertainty  
13 distribution over, in this case, a nonlinear curve and  
14 things could either be much better than you think or  
15 much worse than you think. But in either direction,  
16 it's best to keep that uncertainty throughout the  
17 whole system. I know that's harder than putting down  
18 a number. But you'll have much better assessments and  
19 better trial designs and no magical cure, but at least  
20 a sort of strategic approach.

21 SESSION 2: REAL WORLD EXPERIENCES IN CONDUCTING  
22 SUCH TRIALS

1 DR. MARKS: Any clarifying questions from  
2 the audience? I was just checking to see. Hi, over  
3 here? Any questions from the audience? Okay. Is  
4 that okay? All right, well, with that, we'll move on  
5 to session two, real-world experiences in conducting  
6 such trials. And great to have Ian Friedland, chief  
7 medical officer from Achaogen. His talk is  
8 "Developing Antibacterial Drugs for Patients with  
9 Unmet Need: Experience and Recommendations." Thank  
10 you, Ian.

11 DEVELOPING ANTIBACTERIAL DRUGS FOR PATIENTS  
12 WITH UNMET NEED: EXPERIENCE AND  
13 RECOMMENDATIONS

14 DR. FRIEDLAND: Good morning, everyone. And  
15 I'd really like to start off by thanking the FDA for  
16 inviting us here to come and share our experiences  
17 enrolling an unmet need-type study. So I'm going to  
18 go through some of these positions and give you the  
19 basis for the positions in my talk. I'm going to talk  
20 a bit about the feasibility or actually rather the  
21 infeasibility of conducting fully powered trials,  
22 given the low number of available enrollable patients.

1 And nonetheless, despite the difficulties of enrolling  
2 these types of trials, the data that one can obtain  
3 are critical and provide really important data to  
4 clinicians. These smaller data sets can be highly  
5 descriptive and they can support exposure-response  
6 analyses. But it is imperative that data in this  
7 unmet need population, including outcomes, is  
8 integrated in some shape or form in the product label.

9 So why even conduct these unmet need  
10 studies? We can just do a standard UTI II indication,  
11 get the drug approved. And this slide highlights the  
12 big differences between the standard population, say  
13 for cUTI, complicated urinary tract infection, acute  
14 pyelonephritis, versus a typical unmet need study, the  
15 one that I'll be describing today, which is blood  
16 stream infection and hospital-acquired/ventilator-  
17 associated pneumonia due to carbapenem-resistant  
18 Enterobacteriaceae. The standard UTI study does not  
19 directly address an unmet need, where clearly if you  
20 focus on unmet need, that's going to address that  
21 particular population. In UTI, patients have few  
22 comorbidities. There's low mortality rates, whereas

1 in the unmet need population, there are significant  
2 comorbidities, high mortality rates, multi-organ  
3 failure, very, very different patient population.

4 Duration of therapy could be different.  
5 Doses could be different. The pathogens are clearly  
6 different. John Rex referred to UDR. So it's a  
7 standard UTI trial has usual drug resistance. This  
8 could include something like 15 to 20 percent extended  
9 spectrum  $\beta$ -lactamases. It's very unlikely you're  
10 going to see carbapenem-resistant enteric.

11 Polymicrobial infections are usually excluded, whereas  
12 in the unmet need study, they're all, by definition,  
13 multidrug-resistant. We do see extremely drug-  
14 resistant and even pan-drug-resistant strains. And  
15 polymicrobial infections are common. PK is very  
16 different in the two populations. UTI looks a lot  
17 similar to Phase I-type populations, whereas in the  
18 unmet need population, the PK is much less  
19 predictable. There's much less variation.

20 Significant changes in volume of distribution. And in  
21 our particular instance, we're studying our drug as a  
22 single agent for UTI, but in combination in the unmet

1 need population. So one gets very different  
2 information.

3 So plazomicin is a new aminoglycoside that  
4 Achaogen is developing and this drug has broad  
5 activity against Enterobacteriaceae, including strains  
6 resistant to other classes like carbapenems. And you  
7 can see there on the top line, the activity, the  
8 minimum inhibitory concentration, 50 and 90 of  
9 plazomicin showing potent activity against this  
10 collection of CRE isolates, in contrast with a group  
11 of other commonly used antibiotics. All the values in  
12 red are resistant, with only a few that have some  
13 activity, shown in blue.

14 So this is the basis of our Phase III  
15 program. We have two Phase III trials. Our cUTI  
16 trial, called EPIC, is the basis for registration.  
17 That's the trial that we believe will give us approval  
18 through the FDA and EMA. The CARE study, which is our  
19 study in carbapenem-resistant Enterobacteriaceae, is  
20 providing additional support of data. It's a smaller  
21 randomized trial. Originally we started with just the  
22 CARE study. But later, as that study went on, it

1 became clearer that enrollment was going to be  
2 challenging. We introduced the UTI study as an easier  
3 path to approval. Both studies are expected to  
4 conclude later this year and support a filing in the  
5 second half of 2017.

6 So let's go back to the beginning and look  
7 at our original CARE study design. And this was  
8 originally designed as a randomized, open-label  
9 superiority trial in patients with bloodstream  
10 infections and ventilated pneumonia due to CRE. This  
11 was -- this is a comparative trial versus colistin.  
12 The treatment arm is plazomicin in combination with  
13 either meropenem or tigecycline, so a combination  
14 regimen. Comparator arm is the same combination, but  
15 using colistin this time.

16 Primary endpoint, 28-day all-cause mortality  
17 and we were planning on demonstrating superiority over  
18 the colistin regimen. And this was based on a meta-  
19 analysis at the time showing a 35 percent mortality in  
20 patients treated with colistin. And with a 12 percent  
21 absolute reduction in mortality, we would have 78  
22 percent power with the sample size we calculated. We

1 did get a concession from FDA to do the one-sided  
2 alpha of 0.05. The total sample size calculated  
3 assuming an 80 percent evaluability was 360 patients.

4 So this was the original feasibility done by  
5 our CRO. They did a very detailed exploration at many  
6 sites around the world looking at incidence of CRE.  
7 And this is the summary they came up with. In nine  
8 countries, using 68 sites, in these nine countries,  
9 they projected we could enroll 115 patients per year,  
10 which would mean the study would take -- 360 would  
11 take three, three-and-a-half years to conduct. As it  
12 turned out, the only country which approached the  
13 original prediction was Greece, and we can maybe talk  
14 a little bit later about why Greece managed and why  
15 the rest of the world struggled with this kind of  
16 trial.

17 Early on in the study, we -- when the study  
18 was going slowly, we looked at some of our metrics and  
19 we looked at the number of patients that we  
20 prescreened and by prescreened here, I mean patients  
21 haven't signed consent yet. And you can see of the  
22 almost 700 patients who were originally screened, only



1 14 patients were eligible for enrollment in the trial.  
2 And here are some of the reasons why patients were not  
3 eligible. Science could not prove that it was a CRE  
4 and, very importantly, patients exceeded the 72 hours  
5 of prior antibody therapy that we allowed in the  
6 study. Other important exclusions are things like low  
7 APACHE scores, polymicrobial infections and, very  
8 importantly, emerging colistin resistance that  
9 occurred during the conduct of this trial.

10 If we look at this on a more granular level,  
11 this is the experience from one of our good sites in  
12 Greece, showing that they definitely did see  
13 carbapenem-resistant Klebsiella in their hospital.  
14 And this is a detailed analysis, 17 patients that they  
15 looked at with carbapenem-resistant Klebsiella.  
16 Importantly, none were in ICU and this is important  
17 because most of our investigators are intensivists.  
18 But out of the 17 patients they looked at, only two  
19 could be enrolled and there are the reasons why  
20 patients were excluded -- low APACHE scores,  
21 resistance to colistin. So you can see that even  
22 though these infections are fairly common, these kinds

1 of exclusions are very difficult to predict up front.

2 Because of the slow enrollment, we  
3 implemented two major amendments to the study. The  
4 first one, we tried to loosen or broaden the entry  
5 criteria for the randomized cohort. So we allowed all  
6 hospital-associated pneumonias to be enrolled. We  
7 clarified some of the definitions of pneumonia. And  
8 we also added slightly different endpoint. Instead of  
9 just doing mortality, we did so-called mortality-plus,  
10 which is mortality plus other significant disease-  
11 related complications which are more closely related  
12 to the primary infection. Despite these changes, we  
13 saw minimal impact of this amendment.

14 So we then introduced a second amendment and  
15 the second amendment actually introduced a totally new  
16 cohort and this was a single arm, plazomicin treatment  
17 arm in which all the patients who were not eligible  
18 for the randomized cohort could come into that cohort  
19 and still get treated with plazomicin. And this  
20 included now patients with urinary tract infection who  
21 were excluded from the randomized cohort, lower APACHE  
22 scores and importantly are things like colistin

1 resistance, which was not allowed in the randomized  
2 cohort because colistin was the comparator.

3 And this is a snapshot of enrollment. This  
4 graph is not necessarily to scale. But you can see  
5 the original projection of 360 patients and our actual  
6 enrollment is tracking far short of that prediction.  
7 You can see where we introduced cohort two, which was  
8 the single-arm plazomicin treatment arm that did  
9 result in a bump up of enrollment. Unfortunately, the  
10 randomized cohort still tracks quite a lot below that.

11 So what have we learned from our experience  
12 in the CARE study? The site surveys that CROs perform  
13 -- I think a lot of us do know this -- grossly  
14 overestimated patient enrollment. Of all our sites,  
15 only a small subset, maybe 15, 20 percent, actually  
16 enrolled more than one patient. Superiority studies  
17 like this would only be feasible if many sites in  
18 countries have a CRE incidence similar to Greece. And  
19 those of you who know what the situation in Greece is,  
20 their carbapenem-resistance rate in Klebsiella runs  
21 about 80, 85 percent in ICUs. And clearly we don't  
22 want that situation to emerge in the rest of the world

1 before we can conduct these kinds of trials.

2           There are -- the barriers to enrollment  
3 actually evolved during the trial. For example,  
4 resistance to colistin became more and more of a  
5 problem as the study went on. Site engagement is  
6 critical. These are difficult trials. The VSCAs [ph]  
7 get easily discouraged. We spend a lot of time  
8 talking to our sites, doing site engagement  
9 activities. The studies are expensive. And in this  
10 instance, BARDA's support for this trial was essential  
11 for a small company like us to conduct a trial like  
12 this.

13           But if we are going to undertake these  
14 studies, and we do believe one can get extremely  
15 useful and important information, it is critical that  
16 somehow this information does get included in the  
17 label to ensure that the information is available to  
18 prescribers. And here I'm talking about even efficacy  
19 data in this unmet need population. This is in the  
20 context of we do actually have proven efficacy in the  
21 usual population. It will be a smaller data set. It  
22 will have uncertainty. But I think the nature of the

1 data set, the uncertainty can be highlighted in the  
2 label. The PK is very different in these populations.  
3 The microbiology can be very different. I think it's  
4 a given that we would include safety information in a  
5 different population like this. And this may be the  
6 only source of information on combination therapy.

7           So this is just highlighting how different  
8 the populations are in terms of PK. And the basis for  
9 this is largely differences in renal function. This  
10 is a renally excreted drug. And you can see a very  
11 broad range of renal function that we see in our CARE  
12 study in comparison to our EPIC study, our cUTI study,  
13 and what we'd estimated from population PK modeling,  
14 which is based on Phase I and Phase II. And you can  
15 see on the Phase I/Phase II, our UTI study, we get  
16 mostly normal, mild and moderate renal dysfunction.  
17 But in CARE, now we start seeing substantial numbers  
18 of patients with hyperclearance, which we know it's  
19 this population in particular that has caused problems  
20 in the past. We also get a substantial number of  
21 patients with severe renal failures, including those  
22 who are on continuous renal replacement treatment. So

1 a very different experience. It's very difficult to  
2 design Phase I or Phase II or UTI studies that can  
3 capture this kind of variability. Also interestingly,  
4 because of this extreme variability, we do get a whole  
5 range of exposures, which does make this data set very  
6 rich for doing exposure-response analyses.

7 The microbiology is also unique in the unmet  
8 need population. Yes, in our UTI study, it is focused  
9 on Enterobacteriaceae. Yes, we do see multi-drug-  
10 resistant enterics like ESBLs. We do see  
11 aminoglycoside enterics. But the CARE study is where  
12 we get carbapenem-resistant strains, colistin-  
13 resistant carbapenem strains, tigecycline-resistant.  
14 So kinds of resistance mechanisms and patients with  
15 these infections that you can't get in other kinds of  
16 trials. Also, we do get patients with higher MICs and  
17 this collection of these organisms with high MICs will  
18 help provide a more robust breakpoint assessment. And  
19 we also see bacterial species, maybe a little less  
20 important. But usual UTI is E. coli and this is  
21 focused on CRE. So it's mostly Klebsiella.

22 In conclusion, it's infeasible to conduct

1 rigorous inferential trials in these kinds of unmet  
2 need populations. And here, I'm referring to  
3 carbapenem-resistant enterics, resistant Pseudomonas  
4 populations, Acinetobacter-type studies. But these  
5 studies do provide really important and interesting  
6 information that's critical for clinicians to make  
7 treatment decisions. It is imperative, though, that  
8 these data do get included in the product label. And  
9 I think we would all agree that if the regulatory path  
10 was really clear, the studies in the unmet need  
11 population would be more likely to be undertaken and  
12 funded.

13 This is a last word, if I can get the slide  
14 to move. Thank you. My thoughts based on our  
15 experience in what are considerations one needs to  
16 take into account in thinking about viable study  
17 designs in this unmet need population. We do need to  
18 think what we can do with small studies, try and make  
19 them more efficient. So let's first start with rather  
20 than start with theoretical study design, let's start  
21 with what's feasible and look at this is possibly the  
22 population we can enroll and what can we do with this

1 number.

2           So these kinds of studies, to me what's  
3 feasible is somewhere between 40 and 80 patients,  
4 definitely less than a hundred. And the question is  
5 if you've got that number of patients, what can you do  
6 with that? We can definitely look at different  
7 endpoints, and I think we are working with CTTI and  
8 FNIH on more sensitive endpoints for things like  
9 HABP/VABP. Because of the small number of patients, I  
10 believe we should aim to get all or nearly all the  
11 patients on your study drug, which would then mean  
12 that we need to get control data somewhere else. So  
13 either external controls, shared controls and here is  
14 where I actually think a trial network could be very  
15 useful helping us get control data in this unmet need  
16 population.

17           Clearly designs that allow early institution  
18 of study therapy are very important. Our CARE study  
19 requires the confirmation of a carbapenem-resistant  
20 Enterobacteriaceae. That can take three or four days.  
21 To me, that misses the whole opportunity for drugs to  
22 be started early, to show their true potential. So if



1 we can't come up with study designs where you can use  
2 study therapy early, or at least as early as possible,  
3 I think we've missed the opportunity to really test  
4 the true drug effect. And obviously here rapid  
5 diagnostics can help. I do think we are going to have  
6 to think of pathways that incorporate combination  
7 therapy as a sort of definite simplifier, trial  
8 designs that will allow us to treat polymicrobial  
9 infections, which are common, that will allow us to  
10 start therapy earlier. And lastly, I do fully  
11 appreciate and definitely want to encourage the  
12 harmonization between FDA and EMA because clearly it  
13 is a barrier to sponsors when the two agencies have  
14 slightly different approaches. And thank you for your  
15 attention.

16 [Applause.]

17 DR. COX: Thanks, Ian. We appreciate you  
18 sharing your experiences and your insight. I think  
19 it's helpful to the field in general, and your  
20 willingness to present to the group on that is greatly  
21 appreciated. So now, I'd like to welcome Mike Dudley  
22 to the podium. Mike is the senior vice president and

1 head of R&D at The Medicines Company. And he'll be  
2 talking with us about planning and executing a  
3 carbapenem/ $\beta$ -lactamase inhibitor program focused on  
4 treatment of KPC-producing CREs. Thanks for joining  
5 us, Mike.

6 PLANNING AND EXECUTING A CARBAPENEM/ $\beta$ -  
7 LACTAMASE INHIBITOR PROGRAM FOCUSED ON  
8 TREATMENT OF KPC-PRODUCING CRE

9 DR. DUDLEY: Yeah. Thanks, Ed. And thanks  
10 to you and your colleagues for putting this program  
11 on. I think that all of us in industry are  
12 appreciative of what the regulatory bodies have done  
13 to really advance this field forward. My disclosures  
14 are here. And what I'm going to talk about is really  
15 starting from the beginning of what our thinking was  
16 as we designed this program from really the chemist  
17 bench and then moving all the way through design of a  
18 Phase III program. And it was around actually in the  
19 2008-2009 timeframe when many of us were sitting  
20 listening to the spread of KPC-producing CRE in New  
21 York City that we regarded this as -- even before CDC  
22 -- as an emergent urgent threat that was going to be

1 facing healthcare institutions. It truly was a  
2 tipping point when one was now seeing resistance in  
3 Enterobacteriaceae, the most common infections in the  
4 hospital, to a very effective class of drugs known as  
5 the carbapenems.

6 So in terms of doing that, we went to the  
7 laboratory and designed then a program that was going  
8 to culminate in a new class of  $\beta$ -lactamase inhibitor  
9 based upon a Pharmacophore [ph] which microbiologists  
10 knew about in terms of boronic acids of inhibiting  
11 serine carbapenemase -- serine  $\beta$ -lactamases and  
12 optimized it then to be used for inhibiting the KPC  
13 enzyme. Secondly, we really wanted to work very  
14 carefully on optimizing its properties to work in  
15 combination with the carbapenem antibiotic. And this  
16 program advanced from literally the chemist benchtop  
17 to completion of enrollment in a pivotal Phase III  
18 trial in only six years. And largely a lot of that  
19 was because of the support of BARDA and many other  
20 partnerships that we've had throughout the year of  
21 being able to move this program forward.

22 Now, we optimized it for a carbapenem

1 because we recognized then that we could make use of  
2 the potency of a carbapenem antibiotic against  
3 Enterobacteriaceae and in contrast to cephalosporin  
4 combinations, which would then be subject to so-called  
5 usual drug resistance of ESBLs, we really focused then  
6 on a program that was going to optimize the molecule  
7 for inhibiting serine carbapenemases. And you see  
8 that evidenced here when you look at a very multi-  
9 drug-resistant or XDR-resistant panel, as shown on the  
10 bottom of the slide there, by double-digit MIC90s.  
11 Within this panel, 70 percent of these strains are  
12 inhibited by less than or equal to 0.6  $\mu\text{g}/\text{mL}$  of  
13 meropenem in the presence of 4  $\mu\text{g}/\text{mL}$  of vaborbactam.

14 The second piece that we did too though, and  
15 being mindful of the other part of this, is the  
16 pharmacokinetics. And we wanted to ensure a couple of  
17 things. One was is that we could match the  
18 pharmacokinetics of the partner  $\beta$ -lactam -- here,  
19 meropenem -- with the  $\beta$ -lactamase inhibitor  
20 vaborbactam, both within plasma as well as within  
21 epithelial lining fluid. And we accomplished that.  
22 We saw evidence of that in nonclinical models and then

1 this work done by Keith Rodvold published last year  
2 shows that in fact the penetration into ELF is very,  
3 very high, of course known for meropenem, when given  
4 by a three-hour infusion, but also comparably for  
5 vaborbactam as well. So well-matched microbiology,  
6 well-matched pharmacology to move forward.

7 It was then what do you do then in terms of  
8 designing a Phase III program to go forward with this.  
9 And Ian has covered many of the things -- and others  
10 have covered many of the considerations that we had  
11 here as well because we felt with a program that had  
12 been very mindful from the beginning of focusing on  
13 the pathogen and the infections where the pathogen was  
14 going to be found, we wanted to make sure then that we  
15 would have a Phase III program that would really  
16 reflect and translate a lot of that thinking that had  
17 taken place within the nonclinical and the early  
18 clinical development.

19 So I would just add also not only  
20 understanding exposure-response relationships within  
21 patients, understanding pharmacokinetics in special  
22 patient populations and safety as well. One other

1 issue which I would refer you to is the nice work from  
2 ICPD that actually with tigecycline that also  
3 uncovered also effect modifiers, both with respect to  
4 the patient's protein status as measured by albumin  
5 and how it modulated the exposure-response  
6 relationship in both HAP as well as VAP patients as  
7 well.

8           But also, I think, as we've talked about,  
9 it's important to inform clinicians about the results  
10 -- all the results that occur in Phase III programs in  
11 these patient populations. And I would draw your  
12 attention to even though we were thinking about this,  
13 a very fine viewpoint that Brad Spellberg and  
14 colleagues published earlier this year, that where  
15 they pointed out that for most drugs that are  
16 developed, the appropriate use in the clinic does in  
17 fact mirror the way that the drug was proven to be  
18 effective and safe in clinical trials. And so, a  
19 trial that also is involving these types of patients  
20 that Ian and I are talking about is also going to  
21 empower stewardship going forward because we want to  
22 provide information for clinicians in terms of

1 defining those indications and uses in that treatment  
2 population of patients.

3           So indeed, it's a novel idea. How about  
4 studying a drug designed for CRE in patients with CRE  
5 infection? And that's what we did. We came up with  
6 two trials. It's the TANGO program, TANGO I and II.  
7 TANGO I was indeed a guidance-directed both with EMA  
8 as well as FDA study looking at complicated urinary  
9 tract infections in acute pyelonephritis where CRE are  
10 indeed frequently found. So we rejected the idea of  
11 going, for example, to intra-abdominal infections  
12 because you don't see CRE infections generally in the  
13 usual population of complicated intra-abdominal  
14 infections. Our comparator was piperacillin and  
15 tazobactam. We recently announced the completion and  
16 the results of that trial where non-inferiority was  
17 indeed shown in the primary analysis population with  
18 indeed superiority also shown within that primary  
19 analysis population and in the primary endpoint.

20           Now, TANGO II is a pathogen-focused study,  
21 as you've heard about there. It was a study then that  
22 was designed to go into those patient populations,

1 particularly the complicated urinary tract infections,  
2 HABP and VABP and also bloodstream infections where  
3 patients had known or expected CRE. We designed it to  
4 be a 2:1 randomization so that we -- to get more  
5 exposures again in these patient populations with CRE,  
6 with meropenem and vaborbactam and that study is  
7 ongoing. And here's where kind of we -- more detail  
8 in terms of how we ended up with this. These patients  
9 are randomized, as I mentioned, 2:1 to receive  
10 meropenem-vaborbactam or best available therapy for 7  
11 to 14 days. These are patients with either known or  
12 suspected CRE, as shown on the slide here, with a  
13 diagnosis of infection sites that I mentioned earlier.  
14 It is an open-label design, as you might expect, with  
15 the best available therapy arm, although we've done  
16 quite a bit here to try to reduce bias by having  
17 blinded investigators and adjudication committees,  
18 where needed, that we added as an amended protocol.  
19 And we used pre-specified outcomes I think much like  
20 what Ian was getting at here in terms of cure rates  
21 within these patients with meropenem and vaborbactam.

22 Now, I want to move though in terms of what



1 we -- sort of in planning this trial, what did we have  
2 to begin to think about. Well, one is what is best  
3 available therapy for CRE infections. And these are a  
4 number of retrospective studies that appeared in the  
5 literature here, with some of the learnings from those  
6 studies as well. It's certainly that, I think to Ed's  
7 point earlier, that carbapenems appear to have some  
8 treatment effect, even in this setting of resistance  
9 as well. But there are a variety of other factors  
10 that were identified retrospectively in these studies.

11 So what we did do though is in planning this  
12 trial and ultimately executing it was that we actually  
13 went forward to the sites that were actually -- many  
14 of the sites that were going to actually participate  
15 in the TANGO II trial to generate retrospective data  
16 from those institutions about outcomes and best  
17 available therapy, so somewhat of an external control  
18 approach, but more importantly, to really -- to teach  
19 us about what these patients actually had, how were  
20 they treated and how could we design the protocol then  
21 to optimize their enrollment within the study as well.  
22 And so, Elizabeth Alexander and Jeff Loutit and other

1 colleagues in our group that led this analysis did  
2 this study in these 22 major medical centers, both in  
3 the U.S. and Italy, again in Europe -- many of which,  
4 of course, would be sites in the TANGO II study.

5 And here's what we found. And we found,  
6 perhaps not surprisingly, what we know now is that  
7 many of these patients have comorbidities that would  
8 usually result in an exclusion from the typical  
9 registration trial. So as you scan down this list  
10 here, you can see that many of these patients were  
11 immunocompromised, about a quarter of them. Many of  
12 them had prior transplantation as part of it, chronic  
13 renal insufficiency, septic shock and APACHE scores  
14 with the means somewhere in the 20s.

15 So again, these are very, very sick  
16 patients, oftentimes not the ones that are going to be  
17 currently enrolled in typical registration trials.  
18 These are the primary endpoint which we were  
19 collecting, of course, which included mortality as  
20 well as other factors as well. Overall mortality,  
21 around 28 percent in all these. But note that 18  
22 percent mortality even in patients who had UTIs and

1 acute pyelonephritis. Again, not typical of the types  
2 of patients that you're going to be enrolling with a  
3 UTI or acute pyelonephritis study and the typical  
4 registration trial as well. Many of these patients  
5 spent many, many days related to their CRE infection  
6 in the intensive care unit. As well, many of these  
7 patients being hospitalized certainly related to their  
8 index CRE infection for weeks at a time.

9           Now, what about best available therapy?  
10 What did we learn about that? Well, not surprisingly,  
11 the percentage here of non-susceptibility among  
12 existing antibiotics was pretty high. Quinolone's up  
13 to 90 percent. Even colistin/polymyxin B, up to 25  
14 percent of them were non-susceptible based upon in  
15 vitro susceptibility testing. Now, probably one of  
16 the -- I was trying to figure out how do I summarize  
17 all this in terms of the therapies that we saw. And  
18 we saw everything from one-drug to four-drug therapies  
19 with about two-thirds of patients either getting mono  
20 therapy or three-drug therapy. But there was actually  
21 69 different directed therapy antimicrobial regimens,  
22 okay? Sixty-nine different regimens involving one to

1 four drugs as part of that. I'd say that's not much  
2 of a consensus in terms of what you have and what  
3 you're going to get in these trials because of  
4 differential susceptibilities is lots of variability  
5 in what the control regimens are going to be.

6 So how did this help us then design the  
7 trial that ended up as being TANGO II? And the team  
8 worked then to really expect the enrollment. Our  
9 experience was not unlike that which Ian recounted for  
10 you is that a lot of these patients were getting  
11 knocked out based upon the usual types of exclusion  
12 criteria. So allowing immunocompromised patients,  
13 including those with prior organ -- solid organ  
14 transplants, those patients even on hemodialysis as  
15 well as have severe renal disease and also liver  
16 disease. And then, as shown there kind of in the fine  
17 print, which is always the dreaded language that  
18 knocks out a lot of patients with life threatening  
19 diseases with all sorts of medical complications, we  
20 changed that to simply be those patients broadly  
21 defined as having life threatening diseases with the  
22 subject needs to be surviving more than 72 hours from

1 randomization.

2 Well, finally, let me make a -- it's like  
3 one of those things, Joe, if you've ever asked for  
4 comments, be careful what you wish for. So let me  
5 make a few comments about a couple of things in terms  
6 of clinical trial networks and so forth as we sort of  
7 reflect upon this experience. We believe that the  
8 clinical trial network discussion is a really helpful  
9 one right now. But we believe that those are mostly  
10 going to be useful studying patients with resistant  
11 pathogens like CRE. We don't think that that's going  
12 to be very helpful with doing networks of registration  
13 trials such as in complicated urinary tract infections  
14 and intra-abdominal infections. We already know how  
15 to do those trials.

16 I'm not convinced that there's going to be  
17 much cost savings by being able to cycle through  
18 those. I think that the clinical trial networks and  
19 public funding for that should be used to help us  
20 solve the tough problems, not just saving cost should  
21 be the driver here. But it needs to be helping us to  
22 solve the problems. And one of the problems that we

1 had of course for us was trying to -- could we use  
2 rapid diagnostics, susceptibilities, resistance  
3 testing programs within the context of a trial. That  
4 would be very helpful to have within a trial network.  
5 Help us identify which of those 69 regimens might be  
6 the best available therapy regimen to carry forward  
7 that would be helpful for that. Then that would serve  
8 as a basis for evaluation of these new agents.

9           And of course strategies for managing these  
10 patients as well. And I think Ian would probably join  
11 me in saying we're kind of battle-worn going through  
12 this. And again, if this were part of a -- our  
13 experience was part of a network, it would have been  
14 nice to have this experience preserved in some way  
15 such that we can be able to get the kind of  
16 information that I think we all would like to see as  
17 part of our -- as part of our experience carrying  
18 forward in these patients.

19           Lastly, I'll add our voice as well to the  
20 idea that communicating the experience in these  
21 patient populations and pathogens is of interest, from  
22 a modeling standpoint as well as from descriptive

1 information, with the modeling approaches that we've  
2 touched on and heard about earlier as well. And I  
3 recognize that there are differences between Europe  
4 and the U.S. with respect to this. I know the Code of  
5 Federal Regulations is very specific about this. And  
6 I would just simply say if we need the CFR changed,  
7 let's change it so that we can be able to communicate  
8 this information to clinicians as well.

9 So just in summary, what I think we would  
10 all add here is that, very similar to the points made  
11 earlier, is that don't expect these clinical trials in  
12 these patients with pathogens of interest is to really  
13 yield the same information as guidance-directed  
14 registration trials. Absolutely agree that these non-  
15 inferiority trial approaches are really good ones for  
16 us to really get the pivotal information. But you  
17 need to get information I think in the target patient  
18 population. That really helps us to really understand  
19 these drugs. You don't do these for inferential  
20 testing. I think others have made that point very  
21 well this morning as well.

22 We can use these studies and the

1 information, particularly using PK/PD bridges to get  
2 us there. So information from larger clinical trials  
3 can of course be informative for interpreting these  
4 trials as well. And we would say that these studies  
5 are difficult. There's no question. But they're  
6 important. They're enrollable. And I think that we  
7 need to look at ways that we can basically be able to  
8 make these trials happen here and figure out ways to  
9 have these in the product labeling.

10 And finally, I'd like to thank my  
11 colleagues, particularly Jeff Loutit, Elizabeth  
12 Alexander and others that participated in the TANGO II  
13 and the 506 natural history study investigations.  
14 These are hard things. And I'd also like to thank  
15 BARDA for their ongoing support. Thank you.

16 [Applause.]

17 CLARIFYING QUESTIONS (PANELISTS AND  
18 AUDIENCE)

19 DR. COX: Thank you, Mike. Now, we'll move  
20 over to a brief clarifying questions for the  
21 panelists. And Joe, I might just ask one clarifying  
22 question from you. Thinking back, just help me



1 remember what you were thinking in terms of the  
2 clinical trial network and the focus. Was it on the  
3 non-inferiority trial designs or was it for the drug-  
4 resistant or was it for both?

5 DR. LARSEN: It was for non-inferiority  
6 standard clinical trials. And it was more about  
7 streamlining the fact that we have to pay to establish  
8 the infrastructure to do these trials each time we do  
9 it.

10 DR. BOUCHER: So I wanted to just ask a  
11 question or follow-up about the clinical trial network  
12 because I thought there was some -- that part of the  
13 reason that we didn't have more U.S. participation in  
14 a lot of these trials had to do with the fact that a  
15 lot of academic centers aren't sort of up to speed  
16 with doing high quality registration-type trials in a  
17 reproducibly high quality and efficient way and that  
18 part of the rationale for this network was to do that  
19 because we know we have the patients.

20 But many of us in academia aren't  
21 participants in industry trial and I think it's  
22 because -- it's not necessarily because we don't want

1 to be. It's because we don't necessarily meet the  
2 criteria. We don't perform well enough and as an  
3 academic I can sort of say that. So one idea of  
4 having a trial like Joe is outlining is that people  
5 would be up to speed. They'd have an infrastructure  
6 to be enrolling patients with whichever indication,  
7 whether it's intra-abdominal, UTI -- I mean, they're  
8 slightly different actually.

9 But if we had that kind of infrastructure  
10 going, if we had down to the study coordinators - we  
11 weren't always renting one for each study -- that that  
12 would make it more efficient and I think certainly a  
13 global desire would be to include more of those  
14 patients. So I just would love to hear from Ian and  
15 Mike a little bit more about thoughts.

16 DR. MARKS: So maybe we'll go from John to  
17 Dennis and then we'll come back and see if Ian and  
18 Mike have additional comments.

19 DR. REX: So to pick up on the theme about  
20 the trial network and then segue a little bit, the --  
21 you know, Mike, you're right. We do know how to do  
22 complicated UTI studies. But at the same time, every

1 time we do one, even though I know how to do it,  
2 there's always the six-month ramp-up. You always have  
3 to go out and train all the sites. It takes time to  
4 get going. And that time lag is just a function of  
5 how fast you can roll it out. One of the fundamental  
6 ideas behind the UDR-focused network was that the  
7 network would be on constantly. The sites -- and at  
8 your site, every time you see an intra-ab, you think,  
9 trial network. And maybe they're only going to get  
10 randomized to meropenem because that's the only active  
11 drug. But you're actually paying for a clinical trial  
12 coordinator. The system is up and running and you  
13 bring a new drug in and it's instantly on at a hundred  
14 sites that are already enrolling. And so, the notion  
15 is it's almost an instant-on and instant-off of the  
16 drug that gets dropped into the system.

17           There's a paper that's going to come out in  
18 Clinical Infectious Diseases in a couple of weeks.  
19 Anthony McDonald, the first author, is an economist  
20 with whom I worked and we actually model it -- average  
21 40 percent cost and time savings, if you actually get  
22 one of these networks up and running. So it's not

1 that we don't know how to do it. It's that we --  
2 there's an inherent inefficiency -- every company has  
3 to build a one-off trial network to do its program.  
4 and that just takes time to turn on and turn off. So  
5 that's the trick.

6           So but a question for the agencies.  
7 Listening to these comments about the harder one,  
8 particularly Ian's slide about how different the EPIC  
9 -- different the two groups were in terms of renal  
10 function, it made me think this is the same problem we  
11 have in pediatrics where what we have is the  
12 difficulty with it's an unusual patient group, if you  
13 will. They're relatively harder to get at. And yet,  
14 we would very much like to be enabled to use the drug  
15 in that setting.

16           And the evolution of our thinking in  
17 infectives is moving from I'd like to have an efficacy  
18 study in two-month-olds with your new drug, which  
19 people would say, I'll do that, and then five years  
20 later you couldn't do it, to just give me the PK data  
21 to tell me how do I dose it in a neonate, how do I  
22 dose it in a four-month-old. Could it be that we need

1 to take a page out of the idea of the evolution of the  
2 thinking about pediatrics and say maybe that's kind of  
3 what we're trying to do here, is tell me how to dose  
4 it in, you know, fill in the name of, you know, a  
5 goofy subset.

6 DR. COX: Yeah. No, a good point is the --  
7 you know, as the talks have been going on and we've  
8 been looking at the PK results and seeing some of the  
9 differences in the two groups, you know, it does seem  
10 like a very valuable piece of information that can be  
11 gathered from these different patient populations. I  
12 kind of hinted at this just briefly in my talk to the  
13 issue of generalizability if we are doing, you know,  
14 NI studies because they are feasible and that's where  
15 you can study, you know, the safety and the efficacy  
16 of a drug in a population where you can enroll a fair  
17 number of patients.

18 If the trial and patients with more highly  
19 resistant organisms is one where it's just simply hard  
20 to find the patients. It's hard to enroll. Then it  
21 does seem like, you know, gathering PK data from that  
22 patient population could be particularly informative

1 and could help to, you know, understand better how to  
2 use that drug in that patient population. And if  
3 it's, you know, a more abbreviated program focused on  
4 unmet need, it seems like that's an important piece of  
5 information in essence to bridge over to that  
6 population, if you will.

7           The other thing to think about too is that  
8 is there a way within the NI trials because I don't  
9 think it's the resistance phenotype per se that's  
10 driving, you know, the question about generalizability  
11 here. I think it's more, you know, who are these  
12 patients with regards to their comorbidities and all  
13 the other factors. So to the extent that you can  
14 understand that, whether that be in the patients that  
15 are enrolled in the NI trial because you seek out  
16 patients that are sicker or have greater numbers of  
17 comorbidities, that may also help to bridge the gap to  
18 some extent too.

19           DR. MARKS: So before we go to Dennis, just  
20 quick from Marco. Then we'll go to Dennis and then  
21 back to Mike.

22           DR. CAVALERI: Yeah. Just to add to what Ed

1 was saying, I think, yeah, indeed this is an important  
2 aspect. And I would like also to come back to what  
3 Paul was saying this morning. We are asking  
4 developers to consider straightaway if the new  
5 antibiotic is for unmet need and we'll be using the  
6 ICU to generate PK data in those patient populations  
7 because we know that there is an increased renal  
8 clearance. And we want to see the data and the target  
9 attainment there.

10 So it's pretty clear that we are demanding  
11 this data and it will be very important and would  
12 bring up, you know, important information from the  
13 standpoint of what could be the activity in this  
14 patient population. And pediatrics, as you may know,  
15 we started working on an addendum of our guidance.  
16 And indeed, one of the options that we were looking to  
17 is how much we can use PK data in order to support  
18 extrapolation to the various pediatric age groups.

19 DR. COX: Yeah, and one more quick point  
20 too. I think it may have been in Ian's talk. He  
21 talked about how, you know, the exclusion criteria  
22 essentially -- you know, that the patients wouldn't

1 get into the NI trial. I mean, that gives good reason  
2 I think for us to look back at the exclusion criteria  
3 for the NI trial because we probably shouldn't be  
4 excluding those patients. We should be getting them  
5 into the trial because, you know, we need to know how  
6 the drug works in that group of patients too.

7 DR. MARKS: So, Dennis?

8 DR. DIXON: Just to speak to Helen's point  
9 about the being up to speed or not in the United  
10 States, and I'll limit my comments to a very special  
11 subset of trials, not the usual registrational trial  
12 and network but rather the public health questions of  
13 resistant pathogens, be there Enterobacteriaceae or  
14 non-Enterobacteriaceae for carbapenem resistance. And  
15 with our experience on one large PK study,  
16 observational, and one large -- so large in that case  
17 was 150 -- large in the randomized control trial with  
18 colistin alone versus colistin plus the carbapenem  
19 would be over 400.

20 The primary factor was the density of  
21 infections at the site. And so, quality was not an  
22 issue in the preponderance of the United States sites.



1 We enrolled zero to one subjects per year at most of  
2 them. Closed those sites, added international sites  
3 and now we have a subset that are enrolling three to  
4 five subjects per month. And we have come up with  
5 this concept of alignment of networks rather than  
6 building one we can't afford in the beginning. And  
7 the alignment is our contract-based trial on  
8 carbapenem alone -- colistin alone versus carbapenem,  
9 we're aligning with COMBACT. And we have the hope of  
10 adding up to 10 sites in the next two years that could  
11 enroll in that range.

12 And on paper, if we find those sites, we  
13 will complete the study. How many times do things  
14 work out exactly -- within three years or so. But we  
15 know that time could tell otherwise on that. So it  
16 wasn't the quality, but it was the absolute incidence  
17 of infection, going to places like Greece and other  
18 places in Europe to find those places through census  
19 and site assessment and retrospective analysis of the  
20 subjects relative to the exclusion criteria look like  
21 they would work. So that's what we're hoping to do.  
22 And we also had an all carbapenem study to -- in our

1 colistin study to expand the definition of pneumonia  
2 because the subjects were not meeting the pre-  
3 specified criteria. We've modified that to be more  
4 liberal to improve our numbers.

5 DR. MARKS: So we'll go to Mike. We'll give  
6 Ian an opportunity. And if you have questions in the  
7 audience, if you'd just make your way to the  
8 microphones, we'll get to you next as we head towards  
9 lunch.

10 DR. DUDLEY: Yeah. Let me just kind of  
11 elaborate on a couple of things that John and Helen  
12 have mentioned as well. And I'm sensitive to the idea  
13 of the time lag that it may take. I think there's a  
14 couple of responses to that. One is we're actually  
15 quite aware right now, since we've stopped enrollment  
16 at our UTI trials, that another company has been able  
17 to come in and make very, very good use of that  
18 infrastructure through a CRO. So I guess I would say  
19 that a healthy clinical trials environment, which is  
20 what CROs were designed to do in the first place, was  
21 to basically set up networks where you could do trials  
22 like these is probably what you need.

1           We've gone through somewhat of a nuclear  
2 winter over the last decade with not a lot of  
3 development. So a lot of the stuff has had to be put  
4 together from scratch. But at least we're more than  
5 one program where they haven't experienced much of a  
6 time lag at all and been able to sort of tack on top  
7 of that.

8           Secondly, I don't think clinical trial  
9 network is going to solve some of the fundamental  
10 problems that we have in that. And Helen, to your  
11 point, it's not so much a quality issue. It's an  
12 issue now that oftentimes, for example, the Stop  
13 Sepsis campaigns that say you've got to have  
14 antibiotics in within 24 hours really work against  
15 that. Most of the clinical trials that are done now  
16 in urinary tract and intra-abdominal infections,  
17 particularly in urinary tract infections, are done ex-  
18 U.S. Infectious disease clinicians aren't interested  
19 in doing urinary tract infection studies in a normally  
20 healthy population of patients that are in that; same  
21 thing with intra-abdominal infections.

22           So you know, we're talking about usually

1 different people who want to do those trials. Most of  
2 the trials -- our experience was the same as others',  
3 that most of the urinary tract infection patients are  
4 enrolled ex-U.S. And I don't think a clinical trial  
5 network is going to solve all that as well. I think  
6 that what we -- what we -- if we're going to put some  
7 resource against that, I would say that let's try to  
8 get infectious disease clinicians that are struggling  
9 with CRE and other multi-drug or XDR-resistant  
10 infections engaged by a trial network that's going to  
11 be talking about getting information in those patient  
12 populations. And I think let's help the CRO industry  
13 do what they're good at doing and setting up trials  
14 and having a vibrant pipeline that will make use of  
15 that.

16 DR. MARKS: So thanks, Mike. So we'll go to  
17 Helen quickly. We'll finish with Ian, unless Dan had  
18 something -- so Ian and Dan. Then we'll take lunch.  
19 How about that?

20 DR. BOUCHER: Yeah. So just really quickly,  
21 I hear you on all fronts. And certainly no one's more  
22 enthusiastic about studying CRE than I am. But we've

1 heard from a lot of IDSA members and people in LLG and  
2 other groups that people in America -- infectious  
3 disease physicians in America aren't interested in  
4 studying in a Phase III way these infections, but find  
5 it incredibly difficult with the academic sort of  
6 structure, when you don't have infrastructure to be  
7 running a trial and you can't have a coordinator all  
8 the time because you don't have a budget. And this up  
9 and down is just not tenable for folks.

10 But you know, there is an interest and I  
11 think for our patients, it really matters. But from  
12 the IDSA perspective, you know, it's worth figuring  
13 this out. And I think to Joe's earlier point, you  
14 know, if this network was functioning, we could learn  
15 a lot of other things about natural history of this  
16 disease, about diagnostics, about, you know, even  
17 other drugs that might not be being developed by a  
18 sponsor, but that might be useful to take off the  
19 shelf. And we haven't even touched that subject. But  
20 I think again just to sort of make sure we don't kill  
21 this too quickly, I think that there are some other  
22 potential benefits. And at some level, it still

1 troubles me as a doc to think that I'm going to be  
2 giving my patients drugs that are developed 80 percent  
3 ex-U.S. when we have patients here who have these  
4 infections.

5 DR. MARKS: So, Ian?

6 DR. FRIEDLAND: So I'm going to echo a lot  
7 of what Mike was saying. I definitely do take what  
8 John is saying in that having a little bit more  
9 efficient, shorter start times is valuable to  
10 sponsors. But we can actually run UTI II trials, yes.  
11 Money would be -- having funding would be good and if  
12 you give us the funding, we can run those trials. We  
13 can't run them that well in the U.S. Helen's exactly  
14 right. And it's for other reasons -- they may be the  
15 ones that you think of. For example, UTI -- U.S.  
16 investigators will not treat on an IV drug for seven  
17 days. So we actually can't enroll those patients in  
18 the U.S. But in other countries, that's their  
19 standard of care.

20 So I think there are lots of reasons why the  
21 U.S. goes -- it's not just lack of experience of the  
22 U.S. investigators. But where we do struggle is

1 exactly where Mike Dudley referred to, is if we're  
2 setting up these unmet need populations, different  
3 kind of populations, we don't know enough about them  
4 to really design efficient trials upfront. And then,  
5 we learn as we're conducting the trial of all the  
6 errors we made. It makes much more sense that we  
7 first do the research up front, learn about the  
8 population, learn about the inclusions/exclusions and  
9 then we can design the trials more efficiently. And  
10 that's where I think something like a network could be  
11 very useful, gathering that kind of information for us  
12 before actually conduct the trials.

13 DR. MARKS: Thanks, Ian. Dan, and then  
14 we'll come back.

15 DR. RUBIN: So, first I want to thank the  
16 two groups for conducting trials in this very  
17 difficult area, in the patients with greatest need. I  
18 just have two clarifying questions for Dr. Friedland.  
19 First, could you talk a little about what, if any,  
20 difficulties the availability of ceftazidime-avibactam  
21 during your trial had on your ability to randomize to  
22 a colistin-based comparator and whether that was any

1 factor in the enrollment challenges? And then  
2 secondly, you mentioned the issues with emerging  
3 colistin resistance and the fact that those patients  
4 had to be excluded due to the colistin-based  
5 comparator regimen. I was wondering wouldn't that  
6 emergence of colistin resistance actually make it  
7 easier to show a difference or superiority, if not  
8 using -- if using a best available-type therapy  
9 regimen in your analysis for the future. Thanks.

10 DR. MARKS: So maybe we do it this way,  
11 because we have an hour right after lunch and this  
12 discussion -- ponder that over a sandwich or whatever.  
13 But I did want to get a quick comment from Sam, and  
14 then we'll come back. And Dan, if you'll remind us of  
15 that right at the very beginning, then we'll get to  
16 you. Is that okay? Thank you. Sam?

17 DR. BOZZETTE: I want to quickly pick up on  
18 what Helen and Mike were saying and point out that  
19 there are additional benefits to having clinical  
20 trials networks that are, you know, external --  
21 externalities, if you will -- external to the conduct  
22 of the trial itself. You often increase quality of



1 care and you develop a cadre of clinical trialists and  
2 experts in the field. I think that's what happened  
3 with the AIDS clinical trials groups, for example.  
4 That's worked very well and essentially the whole  
5 notion of the HIV physician came out of that effort.

6 DR. MARKS: Thank you. Okay. No questions  
7 from the audience. So why don't we adjourn? We'll  
8 come back -- since I got the time wrong last time, let  
9 me look --

10 DR. COX: At 1 o'clock?

11 DR. MARKS: At 1 o'clock. Thanks very much.

12 [WHEREUPON, the foregoing went off the  
13 record at 12:21 p.m., and went back on the record  
14 at 1:09 p.m.]

15 PANEL DISCUSSION 2

16 DR. COX: -- we'll start in about one  
17 minute. I'll make a trip outside in just a sec just  
18 to bring folks in if we don't all sort of manage to  
19 get in here.

20 DR. MARKS: All right. Let's go ahead and  
21 get started for the panel discussion. I think where  
22 we left off was Dan was going to restate is question,

1 and then we were going to hear from Ian and Mike, at  
2 least. Dan?

3 DR. RUBIN: Thanks. So the two questions  
4 that were addressed to Dr. Friedland, but anyone else  
5 can chime in, were on the availability of ceftazidime-  
6 avibactam and how that impacted whether it was  
7 possible to enroll in the colistin-compared  
8 superiority trial and then secondly you mentioned the  
9 emergence of colistin resistance and comments on the  
10 rationale for excluding these patients rather than  
11 randomizing them to a treatment regimen or best  
12 available therapy regimen since that may be the one  
13 group where it is possible to evaluate a treatment  
14 effect.

15 DR. FRIEDLAND: So first on this  
16 ceftazidime-avibactam, when we started the trial,  
17 ceftazidime-avibactam was not approved, was not  
18 available and in fact even now most of our patients  
19 are being enrolled in Europe, where ceftazidime-  
20 avibactam is not yet available. But it does speak to  
21 the fact that these kinds of trials do have a limited  
22 lifespan because as new therapies do become available,

1 it does become almost impossible to run a trial now  
2 versus colistin, in which we have more effective  
3 treatments. So I think this is also part of the  
4 problem of these trials, is that you can only run them  
5 for so many years before new therapies become  
6 available and the comparator you chose is no longer  
7 now, you know, a valid comparator.

8           What happened with colistin is when we  
9 started the trials, colistin resistance wasn't as much  
10 of a problem as it has become. So clearly  
11 investigators were keen to engage in that study with  
12 colistin as a comparator. It was one of the few  
13 available options. But it sort of became apparent  
14 that colistin resistance was a problem and in fact we  
15 picked up colistin resistance from our central lab,  
16 that the local sites didn't even know about. And we  
17 actually pointed out to them that they actually had  
18 colistin resistance and then when they started testing  
19 more accurately, they realized that they did have a  
20 problem.

21           They do have alternatives, because it is a -  
22 - it is a required comparator. It's not a best

1 available treatment. It's colistin and they do  
2 theoretically have other drugs available like  
3 tigecycline. So in that situation where they think  
4 they have other therapies rather than colistin, they  
5 will -- they'd be very reluctant to enroll someone in  
6 a trial where they know there's a strong likelihood  
7 you can be resistant to the comparator. So in that  
8 situation, they'd rather not enroll them in the trial.  
9 They'd rather wait to get the colistin susceptibility  
10 result. And then, if it's susceptible, they'll run  
11 the trial. But if it's resistant, then they're going  
12 to look for alternative treatment and not put them in  
13 the trial. So I think that's sort of the situation  
14 we're in now.

15 DR. DUDLEY: Yeah. The only thing I'll add  
16 to that was actually I think we've chatted with Dr.  
17 Alexander, who's running our TANGO II trial. And she  
18 actually thinks that it's actually helped, although we  
19 don't -- again, Avycaz is not available in Europe yet.  
20 But in the United States, it actually has helped the  
21 awareness a bit and that patients don't have to  
22 necessarily be randomized to colistin. So Avycaz is

1 fair game in the best available therapy arm.

2 DR. MARKS: Go ahead, John.

3 DR. REX: Well, if you listen to the theme  
4 there, you know, Avycaz should be increasingly  
5 available towards the end of this year. And then,  
6 you're going to be filing -- you think you're going to  
7 file your NDA when, for --

8 DR. DUDLEY: Publicly we've said second half  
9 -- first half of next year. Okay, so 2017 -- our  
10 utility date --

11 DR. REX: Yeah.

12 DR. DUDLEY: So 2017. So, and then,  
13 plazomicin will come along. So sometime in -- fast-  
14 forward two years from now. There could be two or  
15 three choices that, you know, are -- each one of them  
16 has its quirks. But you know, net of it is it will be  
17 really hard to explain to somebody why they should be  
18 randomized to colistin. The echo over here was thank  
19 God.

20 DR. MARKS: Sam?

21 DR. BOZZETTE: Is a general comment in  
22 order? Okay. This morning -- okay, never mind. In

1 general, this morning's discussions didn't hit the  
2 role of diagnostics much. And I thought that I should  
3 say a couple of words on that. First of all,  
4 diagnostics should be able to provide substantial  
5 efficiencies in the conduct of these trials by helping  
6 to identify who actually has a bacterial infection as  
7 opposed to some other condition that put them in the  
8 ICU and made them toxic and septic-looking. In terms  
9 of rapid identification, and particularly  
10 antimicrobial sensitivity testing, probably through  
11 genotypes, but they have their issues, the whole  
12 genotype/phenotype issue and I think the industry is  
13 working hard to get to rapid phenotypic sensitivity.  
14 And I suppose in the case of genotypes I should say  
15 resistance testing rather than that.

16 And the other thing I guess I would say is  
17 that -- and the thing that really hits me from this  
18 morning is the possibility of a virtuous cycle with  
19 drug development and diagnostics, the idea that  
20 diagnostics could help the conduct of trials,  
21 particularly through patient selection up front, by  
22 allowing people to discontinue or dis-enroll patients

1 when it becomes clear that they don't have the  
2 organism infection of interest. But at the same time,  
3 these trials -- particularly the trials networks are  
4 perfect sources for development of diagnostics. One  
5 of our big problems is that we don't have a lot of  
6 money. And just accumulating the specimen banks is  
7 pretty much shoots our development budget for a lot of  
8 potential diagnostics.

9           So the idea that we could draw from both the  
10 control and the various active arms in a master  
11 protocol context I think is something that would be  
12 tremendously helpful for us. And then, the  
13 diagnostics that are developed through that mechanism  
14 could feed back into the trials, even during the  
15 course of the trials. If a trial's ongoing and we  
16 develop a better way of determining the patients of  
17 interest, that could be incorporated into the trials  
18 as it goes along. So I think this idea of a virtuous  
19 cycle is something that the group should look at, you  
20 know, very seriously. We're going to have some  
21 conversations about how to do that and I hope other  
22 people who are interested in diagnostics and other

1 diagnostic companies could participate as well.

2 DR. MARKS: Any follow-up on that piece? I  
3 mean, I think from most everybody I've ever talked to,  
4 diagnostics are critical in this as part of the  
5 solution. Every report I see that comes out also  
6 calls for that as well. John?

7 DR. REX: Just to extend on that, I really  
8 do think that the diagnostics could make trials more  
9 efficient. But there's something that Ed has -- it's  
10 taken me a while to fully articulate this. The  
11 diagnostics enable you to find the patient. But it  
12 doesn't make the patient with the rare bacteria more  
13 common. So it enables you to find them. It doesn't  
14 create them. And so, if the target organism is --  
15 only occurs, you know, 2 percent of the time, it only  
16 occurs 2 percent of the time. And the test would  
17 enable -- would mean you might miss fewer of them.  
18 You'd be able to find a few more. You'd be able to  
19 find them a little and maybe the patients you enroll  
20 in the trial would be -- once you actually enroll,  
21 would be much more likely to have the target organism,  
22 the ones you actually enroll. But you still have to



1 screen the other 98 who didn't have it in order to  
2 find the two.

3           There's no substitute for running the test  
4 in a hundred people to get those two. And that's  
5 actually one of the things about the trial network  
6 concept focused on the UDR setting where everybody  
7 with intra-ab gets enrolled is that you could actually  
8 inside that be looking for the oddball pathogens  
9 because you're actually going to -- you've got  
10 something to do for everybody in a UDR-focused study.  
11 Everybody with intra-ab in a UDR network gets enrolled  
12 and you can run your diagnostic on them and pick out  
13 the unusual ones and spin them into something else.

14           DR. BOZZETTE: I would agree with you that  
15 the main utility would be the ability to screen out  
16 individuals. You're not going to make more  
17 individuals with disease. But if you have -- if  
18 you're talking about a condition in which there is an  
19 imperative to treat, the difference between only  
20 having to do that with a single dose or two doses  
21 versus following the person for two or three days  
22 should be substantial, I would think.

1 DR. REX: Right. And the big cost is --  
2 it's the enrolled patient that's the most expensive  
3 part.

4 DR. BOZZETTE: Oh, absolutely. Absolutely.

5 DR. REX: I say that -- I should really say  
6 that -- I don't know the precise percentage. But a  
7 big part of our budget isn't just the cost of the  
8 patient. It's the running cost of the site. So I've  
9 got to have the IDP and the pharmacy. I've got to,  
10 you know, go back and audit. I've got to, you know,  
11 do all that stuff just to keep the site up and  
12 running. And so, that's why the patient cost a  
13 hundred thousand dollars. It's not because I spend a  
14 hundred thousand dollars on that patient.

15 DR. MARKS: So why don't we bounce to Nick?  
16 Then we'll do Kert and then our colleagues in the  
17 audience.

18 DR. KARTSONIS: I just want to make an  
19 additional comment about that and then maybe ask a  
20 question to Ian and Mike about their experiences,  
21 because we're doing a resistant infection study right  
22 now for imipenem-relebactam. And one of the things

1 that we've done from a diagnostic standpoint is we've  
2 -- two years' ahead of time, we actually developed the  
3 panels that actually had imipenem, as well as  
4 colistin, as well as imipenem-relebactam and literally  
5 gave them to all of our sites to use as screening  
6 tools, susceptibility panels. That obviously cost  
7 time and money to do that. It's not a simple endeavor  
8 and I can tell you it cost millions of dollars to  
9 implement that.

10 What it has shown us, and it's probably a  
11 poor man's diagnostic, is that, as John has alluded  
12 to, we're picking up 1 to 2 percent of all -- and  
13 we're obviously in geographically enriched regions  
14 that have the resistant infections. But we're still  
15 only picking up 1 to 2 percent of all of the KPCs  
16 and/or resistant Pseudomonas -- you know, carbapenem-  
17 resistant Pseudomonas pathogens and what have you. So  
18 I guess a question I have for Mike and Ian is have you  
19 used any enrichment tools? Have you used any  
20 diagnostics that might help you expand on TANGO II  
21 that you're willing to share or from the CARE study?

22 DR. FRIEDLAND: So we allow our sites to use

1 whatever rapid diagnostics they have available. And a  
2 lot of our sites, like in Greece, do have rapid  
3 diagnostics. We don't have one specific diagnostic  
4 that we -- you know, that we demand. But a lot of our  
5 sites do use their local -- and that has been very  
6 helpful. They can enroll patients sooner with that.

7 DR. DUDLEY: Yeah. My colleague, Jeff  
8 Loutit, is actually at the microphone and we have  
9 actually discussed this. So maybe, Jeff, if you want  
10 to comment on how we have been thinking about  
11 enrichment with the diagnostics and so forth?

12 DR. LOUITIT: Yeah. Thanks, Mike. And this  
13 speaks to the comments from John and Sam as well. So  
14 as part of -- so I work with Mike as part of The  
15 Medicines Company and work with Elizabeth in running  
16 the TANGO II trial. We're part of the consortium to  
17 develop a cartridge through Cepheid to look at  
18 identification of CRE directly from specimens -- so  
19 urinary tract or respiratory tract specimens, et  
20 cetera.

21 What was very -- and we then went out and  
22 found that pretty much every site that we were going

1 to, had the GeneXpert system. So we knew they could  
2 do it. And then, we said, okay, how about actually  
3 screening all these patients who have suspected CRE.  
4 And you saw the numbers that Ian put up there,  
5 essentially screening close to 600 patients to get to  
6 14. And the microlabs just looked at us and said,  
7 you're out of your mind. So we cannot -- we could not  
8 get at least the microlabs to want to take on that  
9 work to screen patients into the study. So we have  
10 the test. We have the patients. We have the machine  
11 to run the test. We just don't have the ability for  
12 the microlabs to do that.

13 DR. MARKS: Thanks. Kert?

14 DR. VIELE: I was going to mention that the  
15 notion of trial networks in this context with  
16 diagnostics, having a network and having multiple  
17 drugs, a lot of the newer platform trials that are  
18 being run in, say, oncology, they partition a patient  
19 stream on the basis of biomarkers, if you have a HER-  
20 2-positive breast cancer, you're eligible for certain  
21 drugs in the study and not others. Having a network  
22 and a central way to do that kind of screening -- you

1 know, if you imagine that you're running a trial and  
2 he's running a trial and you can't enroll the exact  
3 same patients, when you encounter a patient that you  
4 can't enroll but he can, having a way to take that  
5 full patient stream and just efficiently getting it to  
6 the drugs that are still in the running for that  
7 patient population would be valuable.

8 DR. DUDLEY: Yeah. I would agree. I think  
9 the interesting question here for Sam -- I'll get  
10 there in a second. But the elephant in the room right  
11 now though is that what we're hearing is that  
12 developing these tests for clinical trials from a  
13 diagnostic industry standpoint, okay, maybe. But a  
14 diagnostic test for use in clinical use for doing  
15 exactly what Jeff just described in clinical practice,  
16 not enough of a market there. So maybe you could help  
17 us understand if that's -- you know, is that something  
18 the way that you see the universe or because I think,  
19 yes, having a diagnostic to help us get a clinical  
20 trial done is great. But I think what clinicians'  
21 expectations are is that they'd really love these  
22 direct specimen tests to be able to make those

1 decisions at the bedside, to be able to put patients  
2 on the appropriate drug.

3 DR. BOZZETTE: Okay. Let me -- let me one  
4 quick comment on the microlabs. One of the barriers  
5 to rapid diagnostics is the tradition of microbiology.  
6 There are expert systems that will release  
7 identifications from automatic machines automatically.  
8 They are essentially always right. And at least  
9 they're as right as a human would be.

10 But people are reluctant to turn them on  
11 because microbiologists are used to looking at the  
12 results and releasing the ones that they think are  
13 most appropriate. In addition, microlabs tend to run  
14 only during the day or at least into the evening. So  
15 if you have a diagnostic that takes two or three  
16 hours, you run the test at 8 o'clock at night, no  
17 one's going to know anyway. And so, we face this when  
18 you shorten, say, times to positivity in blood  
19 cultures. You know, if a result falls in the forest  
20 at 3:00 in the morning and there's no one there, does  
21 it make a sound? And the answer is no, it doesn't.

22 So I think part of the clinical trials

1 infrastructure should involve buffing up laboratories  
2 and increasing laboratory capability. Now, in respect  
3 to developing tests, we have two problems. One is  
4 that we face commodity pricing. We don't have value-  
5 based pricing. When a test comes on, they'll look at  
6 the cost of a similar test and say, okay, that's what  
7 you get. So we get -- I don't know, we'll get \$80 to  
8 do -- to run a companion diagnostic test on an  
9 oncology drug that's costing \$60,000, \$80,000 a year.  
10 So we face commodity pricing.

11 And the second thing is cost of development.  
12 And so, when you look at the NPV for narrowly focused  
13 tests, it's just not there. So why are we willing to  
14 develop specific tests for specific trials and  
15 specific drugs? Frankly, because you guys are paying  
16 for it. And so, it lowers the development cost and  
17 our marginal costs, you know, our marginal cost to  
18 production will be hopefully not that high and we'll  
19 make some money back. So what's the answer? I think  
20 what we've heard in terms of decoupling for  
21 pharmaceuticals needs to be developed for diagnostics  
22 as well. So fixed amount of pharmaceuticals, paid for



1 in an upfront payment of some sort, market entry fee,  
2 whatever. And something similar needs to happen to  
3 the diagnostics that would go along with that  
4 indication.

5 Now, in microbiology, the diagnostics are  
6 not going to be true companion diagnostics for a lot  
7 of the reasons that John has pointed out in terms of  
8 the variety of alternatives and stuff. But when you  
9 get into tomorrow -- I'm sorry I won't be here -- you  
10 may get to the point where we're talking about  
11 something that really is a true companion diagnostic.  
12 And in that case, we're going to have to tweak the  
13 model because the oncology model frankly isn't working  
14 for us.

15 DR. MARKS: We have a colleague over at the  
16 microphone over there. Just your name and your  
17 affiliation, please.

18 DR. CONNELLY: Yeah, Lynn Connelly, with  
19 Achaogen. So I work with Ian on the CARE study. In  
20 addition to rapid diagnostics, we can look at patient  
21 characteristics or epidemiological factors that place  
22 them at high risk for infection by the target

1 pathogen. We found that very useful in the context of  
2 our study to allow patients to enroll on the basis of  
3 being known colonized with CRE or because they reside  
4 in an ICU where the rate is so high of CRE. So we can  
5 look at things that are less technologically  
6 challenging in order to help in all these studies.

7 DR. MARKS: David, your name and your  
8 leisurely retirement affiliation?

9 DR. SHLAES: Yeah, David Shlaes, retired.  
10 So after hearing today's presentations, it kind of  
11 brought me around to thinking about tomorrow. And I  
12 had a few thoughts and questions I'd like to share.  
13 One question is, Ian and Mike, and we just talked  
14 about this, but if you had a drug for which there  
15 wasn't the non-inferiority possibility -- so pathogen-  
16 specific -- given your experience with your CRE  
17 development programs and the kinds of patients you  
18 have to study, would you as a company be willing to  
19 take the risk to do it? And you know, I think that  
20 one of the jobs that we'll have to undertake in terms  
21 of thinking about feasibility for pathogen-specific  
22 drugs, which again I guess we'll talk about tomorrow,

1 is how do we de-risk these sorts of trials. And I  
2 think it'll be -- as we talked about earlier, it'll be  
3 important to think about external controls.

4 The other comment I'd like to make is given  
5 the importance of pharmacokinetics and PK/PD in the  
6 way we're going to be -- we're thinking about the  
7 drugs that we're talking about today and even more the  
8 ones we're going to be talking about tomorrow, from  
9 kind of a commercial perspective, when you think about  
10 how you're going to deal with this with physicians and  
11 hospitals treating patients, especially in the United  
12 States where 70 percent of hospitals are under a  
13 hundred beds or under 200 beds, this is going to  
14 require a huge -- I believe a huge educational effort  
15 to make people understand that PK/PD can actually  
16 contribute to their decision-making process for  
17 individual patients. So I think those kind of two  
18 things, along with external controls, they all kind of  
19 make a set of issues that we still have to grapple  
20 with. But I'd be interested in comments, especially  
21 from Mike and Ian, on that.

22 DR. FRIEDLAND: I'll go first on part one.

1 You know, this is the reason why we're having this  
2 workshop and why there's the whole discussion tomorrow  
3 is because I think we all recognize that there are  
4 therapies in development that are pathogen-specific.  
5 And I think without figuring out what are the pathways  
6 to get these developed is a major disincentive to  
7 continuing those programs. I am hopeful that we will  
8 come up with something because pathogens like  
9 Acinetobacter is far too much of a problem without us  
10 coming up with some sort of solution on how to treat  
11 these. But I think you are right in that we do have  
12 to have some assurance that there is a pathway before  
13 one will actually sort of undertake these clinical  
14 trials. We may develop them up to the point we get to  
15 Phase I and PK/PD. But without knowing the clinical  
16 pathway, it's not going to go much further than that.

17 DR. DUDLEY: Yeah. I'll just add a couple -  
18 - I may keep our powder dry until tomorrow on the  
19 single pathogen. But what I will tell you is that,  
20 you know, we have intravenous minocycline, which we  
21 recently had approved with a new formulation in the  
22 United States. And we'll be looking at a program for

1 Europe where Acinetobacter, as you well know, is, if  
2 anything, a bigger problem for multi-drug-resistant  
3 Acinetobacter. So that'll -- we'll talk a little bit  
4 more about what our thoughts are about that tomorrow  
5 and how that might -- how one might go through that,  
6 where clearly a non-inferiority trial is probably not  
7 going to be very feasible there.

8 What I would say about the PK/PD question, I  
9 think that a lot of us that have been working in this  
10 area have recognized that the educational component  
11 needs to come with better software and better ways of  
12 communicating what the PK/PD is telling us.

13 So I will -- and Paul may want to comment on  
14 this, and I -- because it's his program -- but I think  
15 that PK-PD Compass program, which is an iPhone/iPad-  
16 based program which I think really takes all of that  
17 information and sort of demystifies a lot of the  
18 mathematics and a lot of -- uses real-time information  
19 either from an individual hospital or from  
20 surveillance data, epidemiologic data and using the  
21 best available information that we have about clinical  
22 pharmacology of these drugs is going to help us I

1 think make better decisions as it relates to thinking  
2 about things as not sensitive or resistant, but  
3 thinking about -- I think, as one of our panelists  
4 stated here, is that it's a distribution of exposures  
5 and a distribution of MICs that will help us make  
6 better decisions at the bedside. And I don't know if  
7 you want to add anything more, Paul, to that, but --  
8 thank you.

9 DR. MARKS: Well, we might be interested in  
10 Helen's perspective on these in the clinical utility  
11 realm of this type of approach.

12 DR. BOUCHER: You know, I agree a hundred  
13 percent and I think that we see stewardship programs  
14 as a major vehicle for helping to do this. I mean, we  
15 have thankfully a few new drugs and all of those are  
16 being used in stewardship programs where they exist and  
17 we're really happy that CMS has its proposed rule to  
18 make stewardship a condition of participation in  
19 hospitals in the U.S. I think the form that  
20 stewardship takes is going to be different. You know,  
21 to the -- to Dr. Shlaes' comment about the 80-bed  
22 community hospital, it may be that a stewardship

1 program in that setting is like one that one of my  
2 former fellows is running now in North Carolina where  
3 she sits in Charlotte, but is in charge of stewardship  
4 for academic hospitals, community hospitals and indeed  
5 physician practices where the largest amount of  
6 antibiotic overuse takes place.

7 So you know, stewardship is not always going  
8 to be what we have at Tufts. You know, it's going to  
9 be different things. But thankfully, I think the era  
10 is coming where we'll have more and where tools like  
11 Dr. Ambrose's tool can be used. I would still  
12 advocate you need the experts who use it and interpret  
13 it and the doctors who we serve largely when we see  
14 their patients want what drug at what dose and for how  
15 long do I give it.

16 DR. MARKS: So we'll go to John, and then  
17 thanks for being patient, and then we'll come to the  
18 audience. Thank you.

19 DR. REX: So picking up on this PK question  
20 and unusual populations and sort of thinking about  
21 what I said earlier about, you know, pediatrics,  
22 you're often thinking about extrapolating based on

1 just getting the PK right in the neonate. One of the  
2 changes that has occurred for FDA labeling in the  
3 recent years has been that the information around  
4 pharmacology has been more and more limited to just  
5 the approved indications, and for reasons having to do  
6 with the way the Code of Federal Regulations talks  
7 about what you can put in the label. And I'm not  
8 quite sure for EMA where that is.

9 But I'd like to I guess ask our regulatory  
10 colleagues to think out loud about the question of  
11 providing the pharmacology data for other scenarios.  
12 And in the case of pediatrics, it's little people.  
13 And in the case of the rest -- you know, everybody,  
14 it's oddball body types or odd physiologic conditions,  
15 that sort of thing. So it's this notion -- in a  
16 sense, it's analogous to the second group of organisms  
17 in the microbiology section where the first group, we  
18 talk about the ones that actually have clinical data.  
19 The second group, we talk about ones where, well,  
20 we've never actually studied it, but it looks like it  
21 might be susceptible.

22 And so, I'm thinking about those themes and



1 wondering if that's something -- because we've heard a  
2 couple of calls for information in the label from  
3 these difficult trials. And it feels like sort of the  
4 minimum thing you could get at would be in the spirit  
5 of the way we did pediatrics and dosing, could we do  
6 that here.

7 DR. COX: All right. So let's see, maybe  
8 I'll start out -- I mean, you are right, John. I  
9 think it was -- I don't know if we used to do it. But  
10 I know -- I mean, even 15 years ago, we -- you know,  
11 the attention to the information provided with regards  
12 to drug levels, you know, in various different tissues  
13 is, you know, one where the labeling would include  
14 information for sites that were relevant, you know, to  
15 the approved indication.

16 So if you had a skin indication and you had  
17 a blister fluid study, the information would be in  
18 there. If you also had, you know, information about  
19 ELF levels, but it didn't have any sort of pneumonia  
20 indication, then that indication would not go in the  
21 label. So I think this stems from sort of a balancing  
22 of providing information, you know, that's consistent

1 with the approved indications and then some concern  
2 about providing information that might in essence sort  
3 of enable off-label use in the setting of not having  
4 an indication that was relevant to the particular  
5 tissue fluid level.

6           You know, this is something that we've been  
7 looking at a little bit more over, you know, the last,  
8 oh, couple of years, I'd say, you know, because it's  
9 coming, you know, more apparent that there are  
10 situations where such information, you know, could be  
11 helpful to folks. It is information too that is, you  
12 know, essentially straight factual, if you will. It  
13 doesn't tell you that the drug is going to work. It  
14 does provide you some information about the level in a  
15 particular tissue fluid. So I would say, you know,  
16 this is something that we're still looking at and  
17 trying to figure out, you know, how do we balance, you  
18 know, providing this information. What's the  
19 implications for the approved indications, for  
20 indications that are essentially not approved or,  
21 quote, unquote, "off-label"?

22           And then, the other thing too that we always

1 have to be mindful of is that we generally try and  
2 take approaches that, you know, are the same. And so,  
3 you know, we think about these things a lot of times  
4 from the standpoint of the particular therapeutic  
5 areas that we look at in, you know, our groups. But  
6 there's also implications too for other areas. So  
7 there's you know, a fair degree of, you know, trying  
8 to navigate through all of the implications of doing  
9 something about including information about tissue  
10 sites that might be, you know, related to indications  
11 that are not approved. So but yeah, no, I understand.  
12 And this is something -- we've talked about it at  
13 meetings before over time. This has come up, so --

14 DR. MARKS: Marco?

15 MR. CAVALERI: Yeah, I think we are  
16 completely in line with what Ed just said about sort  
17 of being careful, not promoting off-label use. But of  
18 course in the context of the potential of granting an  
19 indication per pathogen, it may come up the issue on  
20 how to provide information to the prescriber about  
21 different set of infections that we did not study,  
22 which could be don't do that because the PK is not

1 supporting you. But it might be that the PK is good  
2 enough. So you may consider that. So I think here,  
3 in that context only, it would be important to try to  
4 reflect about how best we could include this kind of  
5 information in the SmPC.

6 DR. MARKS: Thank you, Marco. So we'll  
7 bounce to our audience. Name and affiliation, please?

8 DR. KINDRICK: Sure. Amy Kindrick, from  
9 Genentech Roche. I'd like to go back to something  
10 that was touched on briefly earlier today and that is  
11 the issue of excluding patients with prior antibiotic  
12 exposure. The interval I think is 72 hours within  
13 which only one dose could have been given. And I  
14 think Mike Dudley or Ian Friedland -- I can't remember  
15 which -- pointed out that it's one of the major  
16 reasons for screen failures. And it's a bit of a  
17 conundrum because one of the things we know for sure  
18 is that prior antibiotic exposure is one of the  
19 biggest predictors of antibiotic-resistant infections.  
20 So it's really an effort to try to balance scientific  
21 rigor with the reality, which is that, at least in our  
22 experience, large numbers of ICU patients violate that

1 prior antibiotic exposure. So does the panel have any  
2 thoughts about ways that potentially we could address  
3 that when we're looking at drug-resistant infections?

4 DR. COX: So maybe just a few comments on  
5 the issue. So -- and Dan and Sumathi are going to  
6 correct me if I stray here. But essentially, if  
7 you're doing a superiority trial, you can have prior  
8 therapy. It doesn't really -- I mean, it decreases  
9 your -- it may decrease your chance of showing  
10 superiority if it's effective therapy. But in the  
11 setting of a superiority trial, you could use prior  
12 therapy. Another situation -- but if you use too much  
13 of it, you may treat the infection and then the  
14 ability to show superiority may essentially evaporate.

15 There are situations too where patients get  
16 prior therapy and essentially they're failures.  
17 They're not responding to therapy and you continue to  
18 have positive cultures. So in that situation, the  
19 presumption is that you're really not affecting the  
20 course of treatment. So that patient could still be  
21 enrolled. You know, and we describe that in our  
22 guidance documents that talk about non-inferiority

1 trial designs and, you know, I've already said for  
2 superiority, you could give antibiotics. So you could  
3 obviously do it there too.

4 Now, the issue becomes if you're actually  
5 treating the infection. You know, and we've heard  
6 about the importance of those early doses and, you  
7 know, the literature bears that out too. The early  
8 doses in serious infections are so important and, you  
9 know, getting effective therapy on board within hours  
10 or less, you know, in order to be able to reduce  
11 mortality. You know, and if you've actually had a  
12 significant impact on the infection, it can be  
13 difficult to, you know, do a good test of the  
14 antibacterial drug. And no one wants an antibacterial  
15 drug out there that we really don't know if it works  
16 when it's being used for patients with serious  
17 infections.

18 So you know, so now, to get to what do we do  
19 about this, so the CTTI folks are tackling at least  
20 one approach to this. And the way Vance Fowler  
21 describes this is that, you know, if there's only so  
22 far that we can go with prior therapy on this end of

1 the equation because we'll be treating the infection,  
2 what can we do over here. So the CTTI folks are  
3 working on a study in HAP/VAP with the first  
4 observational phase to understand, you know, who are  
5 the patients who are developing HAP/VAP. Can we  
6 identify risk factors? Can we pre-consent patients?  
7 You know, are there other mechanistic things that can  
8 be put in place to minimize, you know, the need for,  
9 the pressure for, you know, longer courses of therapy  
10 before getting into a trial.

11 And I think, you know, those sorts of  
12 efforts -- I'm very optimistic about this -- I'm  
13 hoping it will help. I'm hoping that it will allow  
14 for patients to be, you know, more routinely enrolled  
15 into the trial with shorter durations of prior  
16 antibacterial therapy. And if you look at our  
17 guidance documents, we do allow some prior  
18 antibacterial therapy just because if we didn't, it  
19 would be probably impossible to run a trial.

20 And in particular, we think it would be  
21 difficult to have sites in the U.S. So we are trying  
22 to balance these two issues. And it's a difficult

1 situation. I think this underscores really, you know,  
2 one of the very difficult challenges in studying an  
3 antibacterial drug -- the urgent need to start  
4 therapy, you know. This can happen anywhere at any  
5 point in time to any one patient. You know, and you  
6 don't really know exactly what you're treating when  
7 you start this first course of therapy out.

8           So I think there are efforts being made.  
9 But it is a tough problem. And you know, it's not  
10 just prior therapy too. But we'll be talking more  
11 about this too tomorrow. But it's concomitant therapy  
12 also. And you know, to get drugs that don't overlap  
13 with the spectrum of your investigational drug,  
14 particularly at the point in time when you're  
15 initiating empiric therapy, can be really difficult.

16           But at the same time too, you know, if the  
17 concomitant therapy is all you really need, then, you  
18 know, the quality of the test for assessing the test  
19 drug is, you know, really pretty limited. So yeah, so  
20 maybe my final comment on this is that I think we all  
21 -- you know, we're all trying to do some things to try  
22 and make this better. But it is a -- it is a



1 difficult problem, so --

2 DR. MARKS: But you certainly don't want to  
3 delay starting therapy while you're trying to get  
4 informed consent for an investigational agent. So  
5 that ability to at least start something makes a big  
6 difference. Marco, any other add-ons?

7 DR. CAVALERI: No. I think I fully agree  
8 with Ed. This is a very difficult topic. We are  
9 putting efforts in trying to allow as much as  
10 possible. But we have to be careful in not  
11 contaminating the data. So we are open to discuss  
12 evidence that is emerging and whether we can allow  
13 more. But at this stage, it's difficult to go beyond  
14 what we are recommending.

15 DR. MARKS: Thanks. And over to the  
16 microphone again? Name and affiliation, please? And  
17 then we'll come back to you, Aaron.

18 DR. HILLAN: Ken Hillan, Achaogen. At the  
19 recent ASM, I had an opportunity to talk to someone  
20 presenting data on Avycaz and I was asking about  
21 susceptibility testing and what they had seen. And  
22 they said they didn't know because they actually

1 didn't have susceptibility testing available in the  
2 U.S. at their institution. I also went to a seminar  
3 at ASM and had an opportunity to learn that it can  
4 take three to four years sometime to have broad  
5 availability of antimicrobial susceptibility testing.  
6 And it seems for these new drugs, we've made amazing  
7 progress in getting rapid regulatory pathways to  
8 approval.

9           But some relatively basic things, like broad  
10 availability of automated susceptibility testing takes  
11 so long. And it seemed, at least if you were trying  
12 to organize this a priori, you would want the  
13 availability of the testing to be available exactly  
14 the same time as the availability of the drug. And I  
15 wondered could people comment on what we should be  
16 striving for moving forwards and what we can do to  
17 streamline the process to make both the drug and the  
18 susceptibility testing available at the same time.

19           DR. COX: Go ahead. You do it.

20           DR. NAMBIAR: Yeah. So thanks for that  
21 comment. I think we're acutely aware of the issue and  
22 we've heard it from many different stakeholders, be it

1 sponsors, drug companies like you or clinicians who  
2 are trying to use the drug because I think the point  
3 you make is very valid. Having that drug approved  
4 just doesn't make it, you know, easy for the clinician  
5 to use it and use it appropriately. It was very  
6 important that these products be used appropriately in  
7 the right patient.

8           So having said that, we know it's a problem.  
9 We've heard this in other fora and we are in close  
10 conversations with our colleagues at CDRH and  
11 hopefully in the coming few months we plan to have a  
12 public discussion. So I think that would be very  
13 good, where we can facilitate the process and the  
14 interaction between the various stakeholders to be  
15 able to find the solution forward. So I think we  
16 recognize that this is important and need to address  
17 it. Thank you.

18           Oh, yeah, and Ed reminded me, I think  
19 there's also work ongoing -- I don't know if anyone  
20 from CDRH is here or not. But there is ongoing work  
21 on a draft guidance being published on co-development  
22 of diagnostics and that touches upon AST devices as

1 well with drugs. So that's forthcoming. I don't have  
2 an exact timeline. But I think your comment is very  
3 timely and we are aware of it and we should hopefully  
4 start the conversation soon.

5 DR. MARKS: Aaron? Oh, David?

6 DR. SHLAES: I was just going to add --

7 DR. MARKS: You've got a follow-up?

8 DR. SHLAES: A lot of this is not really a  
9 regulatory problem. It's a diagnostic company issue.  
10 So what we used to do in the old days is we would give  
11 laboratories discs because the disc criteria are  
12 available immediately on approval. And they would use  
13 the discs and get an idea of what the susceptibilities  
14 were in their hospitals and that was a reasonable  
15 interim step. These days it's harder because  
16 microlabs are more constrained. But I think it's an  
17 important problem. But there may be ways to deal with  
18 it.

19 DR. MARKS: Thanks, David. Aaron?

20 MR. DANE: Yes. It's kind of a question for  
21 Mike actually. But, so Mike, you were talking about  
22 the idea of like a CRE network rather than a broader

1 network. And I just wondered how that would work, you  
2 know, because if you had a much narrower population  
3 you were going after, is how you would set up the  
4 network in terms of where you go and also getting more  
5 cross-sponsor commitment to do that when not  
6 everybody's going to be going off to CRE, for example.  
7 So I didn't know how you saw that. That maybe --

8 DR. DUDLEY: Yeah. Can I have my first  
9 slide -- no. That's a tall -- that's a tall order.  
10 What I -- what I guess I would say is that what I  
11 believe I've heard here is that there is somewhat of a  
12 -- I won't say consensus, but I think a recognition  
13 that this type of information is important. And I  
14 think that we want to I think take a balanced approach  
15 towards looking at this and saying, well, look, there  
16 are a number of sponsors that are interested in  
17 conducting these types of trials. There are a number  
18 of sites and investigators that are interested in  
19 developing these trials. We heard from Helen that a  
20 lot of them would like to participate, but not having  
21 some sort of base support to build infrastructure  
22 within their institutions would be helpful.

1           So this to me sort of sounds like we're  
2 asking the right questions when we're asking -- when  
3 we're trying to establish trial networks. I think  
4 that we would just say that it may be useful for us to  
5 think about it in the context, and at least from our  
6 perspective, that need is more to try to create the  
7 infrastructure to get these sicker patients into the  
8 trials and to get the proper GCP training and base  
9 support in those laboratories. Look, we're not going  
10 to solve -- what we want is a network of engaged  
11 clinical investigators that are in infectious  
12 diseases.

13           And that isn't necessarily what happens in a  
14 cUTI network. Those are urologists and people are  
15 treating patients in the outpatient. So I think if we  
16 want to, you know, address this problem head-on with  
17 the best minds, I think I would advocate that let's  
18 try to figure out how to crack this problem of getting  
19 the sicker patients with CRE into a network.

20           MR. DANE: Yeah, and maybe that's what I was  
21 thinking, is you could do both at the same time in  
22 some sense.

1 DR. DUDLEY: Yeah.

2 MR. DANE: So if we have a network that  
3 isn't too narrow, we can -- we'll get some resistant  
4 pathogen data. I mean, we talked about the  
5 operational efficiencies. The other factor that's  
6 incredibly important is it can be a much more  
7 efficient use of data and patient data because we can  
8 share control on. So we could do all of that and try  
9 to address some of these resistant pathogen questions  
10 at the same time I think.

11 DR. DUDLEY: Yeah. I think clinicians would  
12 like to know, out of those 69 regimens that we  
13 identified in our natural history, which of the few of  
14 those look pretty good. And so, I think strategy  
15 trials and, you know, Sam mentioned ACTG and I'm from  
16 that era as well where the clinical trial networks  
17 with AIDS clinical trials was instrumental. And not  
18 so much in actually developing new drugs. It did do  
19 that, but it actually was understanding strategies of  
20 how to use them. Do I start with two drugs or do I  
21 start with three drugs? When do I add the third drug?  
22 What patient populations benefit by that?

1           Those were enormously important questions  
2 that served as the basis for HIV treatment guidelines  
3 for decades and they were based on those. So yes,  
4 let's go ahead and create a network now and answer the  
5 question what is the best available therapy. So, and  
6 then set that framework so that we can start rotating  
7 these new therapies in, much like what others have  
8 proposed.

9           MR. DANE: I think the other aspect to that  
10 -- we were talking about over lunch, which is if you  
11 got to a point where that network and the data were  
12 broad enough, you might even be able to have a new  
13 product coming through and you can somehow try and  
14 match the patients to the appropriate ones that you've  
15 got. And that might give you a more meaningful  
16 comparison than what we try to do at the moment.

17           DR. COX: Yeah, maybe just to follow up, and  
18 Aaron, you may have been hinting at this, if you've  
19 already said it. But I'm trying to figure out -- so  
20 if, you know, resistant phenotype is not really a  
21 determining factor per se, but it's more patient  
22 comorbidities and patient factors, I mean, surely



1 there must be other patients out there with similar  
2 comorbidities, similar factors who don't necessarily  
3 have the resistant phenotype. I think that may be  
4 what you were getting at.

5 MR. DANE: Yeah, last point, that's exactly  
6 it. Yeah, so it might be that you can try and match  
7 people up a bit more and you'll have a richer data set  
8 to do that with.

9 DR. COX: If the particular resistant  
10 phenotype is really so rare that it's hard to  
11 constitute the trial. But if there's a lot of other  
12 similar people with regards to other patient factors  
13 but, you know, they may have the organism, they may  
14 have -- you know, they may not have the particular  
15 resistant phenotype. It seems like that may be the  
16 sort of information that could be helpful and then you  
17 wouldn't necessarily be so restricted by the  
18 prevalence of a phenotype -- resistant phenotype  
19 that's exceedingly difficult to identify.

20 MR. DANE: Yeah, and you're more likely to  
21 get that in a network than just your single narrow  
22 trial where you may get a couple of patients like

1 that.

2 DR. MARKS: Sam?

3 DR. BOZZETTE: Can I say something about why  
4 development diagnostics is low --

5 DR. LOUIS: Just one more quick promotion of  
6 networks and that is for patients who may not be  
7 available for any of these trials and are in what  
8 would hope to be an observational database, you'd  
9 still want to have it be observational and not passive  
10 with standardized data collection. And that really  
11 won't happen I think without some kind of a network  
12 wrapper on the whole thing.

13 DR. BOZZETTE: I think that to accelerate  
14 the development of automated diagnostics, what's going  
15 to have to happen is to have -- for these purposes is  
16 to have sort of a stable pipeline of customers,  
17 meaning pharmaceutical companies. And we need to  
18 start collaborating much earlier than we do now. It  
19 is not so easy -- it's not the same thing as  
20 developing a disc or an e-test where you can just say  
21 one drug because there are only a limited number of  
22 slots in these cards. And every time we change one,

1 we have to make an essentially new application because  
2 it's a new card. So it's complicated, but doable.  
3 And I think that, as I said, what we really need is to  
4 upstream the collaboration so that this just works  
5 better for everybody.

6 DR. COX: I might ask -- I mean, we're  
7 almost at 2 o'clock. But before we, you know, leave  
8 this little section -- and we can come back to it  
9 later if there's a whole bunch more thoughts -- but a  
10 difficult problem. You know, we've heard some about,  
11 you know, the patients that we might see in a non-  
12 inferiority trial. We've seen data about who actually  
13 gets in to, quote, unquote, the "resistant", you know,  
14 pathogen studies that have been out there. Some of  
15 the PK differences. We've heard some of the ideas  
16 about how we might approach, you know, the PK being  
17 one of the things we can measure. You know, Aaron was  
18 mentioning the idea of, you know, maybe you can enroll  
19 patients with similar comorbidities who didn't  
20 necessarily have the resistance phenotype of interest.

21 I'm wondering are there any more thoughts on  
22 potential ways to address, you know, the issue of, you

1 know, the differences in the patient populations to  
2 get at, you know, how you could generalize information  
3 beyond these two ideas, both of which are good ideas,  
4 because it seems like this is an important issue.  
5 Other thoughts or other ways we might tackle that?  
6 And if there's nothing, maybe -- you know, we can  
7 always come back to it later on if people come up with  
8 good solutions because it's a difficult problem. And  
9 that's why I'm asking the question. I think, you  
10 know, we've got two good ideas about things that could  
11 be done. I'm just wondering if folks have any other  
12 thoughts.

13 MR. DANE: Well, I guess if you were  
14 confident enough about the characteristics you had or  
15 are there other external sources of information you  
16 could draw upon. I mean, I can't think of any  
17 straightaway. But that might be another potential as  
18 a way of providing some context for what you see in  
19 some of these smaller studies, particularly in areas  
20 where we anticipate the responses to be pretty low.  
21 So then you can say, well, if we have got a relatively  
22 small number and the responses are much better, that

1 gives us a lot of confidence about what we're doing.

2 DR. MARKS: One final question before we go  
3 back to the presentation. Name and affiliation,  
4 please?

5 MR. MOORE: Sure. John Moore, unemployed.  
6 I have a -- I have a -- regarding the automated  
7 susceptibility testing, I understand that by adding  
8 one drug, you've got to take another drug off. Has  
9 there been discussions around trying to develop a  
10 panel, whether it be Vitek or MicroScan, of drugs in  
11 which -- are used for unmet medical need. For  
12 example, when you run your primary panel, if you get a  
13 certain resistant phenotype, a resistance to this,  
14 this and this, then run your secondary panel that has  
15 all the other drugs on it. That way, you don't have  
16 to worry about taking a drug off and adding another  
17 one on. Has that been discussed at any length  
18 somewhere?

19 DR. BOZZETTE: Sure.

20 MR. MOORE: Yes, it has? And is there any -  
21 - is there opposition to something --

22 DR. BOZZETTE: Well, you --

1 MR. MOORE: I can see how a company would  
2 not want their drug to be on a secondary panel. But  
3 reality is that's how they're utilized.

4 DR. BOZZETTE: The real issue is the one at  
5 a time thing. You know, so do you make a card that  
6 has two drugs, three drugs, you know, when in fact  
7 we're looking at, you know, 64 and soon to be a  
8 hundred well cards. So you know, the trouble is that  
9 the economics of the N + 1 drug is not good. But I  
10 agree with you that, you know, secondary cards -- and  
11 we do do that actually, secondary cards or cards for  
12 specific markets, like Japan where they have a  
13 different profile of drugs that are used and that sort  
14 of thing is something that we do, and we could do more  
15 of, I suppose.

16 SESSION 3: STATISTICAL CONSIDERATIONS

17 DR. COX: All right. Well, thanks. We're  
18 at the 2 o'clock hour. So I thought we'd move on to  
19 our next section to talk about statistical  
20 considerations for studying drugs that are being  
21 developed for treating patients with unmet medical  
22 need. And our first speaker of the session is Dan

1 Rubin. Dan's a statistician with us here at FDA. And  
2 he's worked with us on a number of different  
3 antibacterial drug applications and also with some  
4 antiviral drugs. And we appreciate Dan's willingness  
5 to give the talk with us here today. He's always a  
6 source of very interesting ideas, as he not only tries  
7 to understand the statistical issues but some of the  
8 other practical and, you know, clinical issues faced  
9 with studying these drugs. So Dan, the podium is  
10 yours.

11 EVALUATING ANTIBACTERIAL DRUGS IN UNMET NEED  
12 SETTINGS

13 DR. RUBIN: Well, thank you very much for  
14 the opportunity to present today. I'll first discuss  
15 randomized trials in the resistant pathogen setting,  
16 focusing on several examples, the potential for  
17 platform trials and trials that combine subjects with  
18 infections at different body sites. I'll then discuss  
19 challenges and options when it's very difficult to  
20 enroll large numbers of subjects with resistant  
21 pathogens, including differences between inferential  
22 and descriptive statistics and differences between

1 Bayesian and frequentist statistics.

2           The table on this slide is showing four  
3 recently published randomized clinical trials that  
4 compared colistin monotherapy to colistin combination  
5 therapy with either rifampicin, fosfomycin or  
6 meropenem for treating life-threatening carbapenem  
7 Acinetobacter baumannii infections. The fourth trial  
8 is still ongoing and Acinetobacter is the dominant,  
9 but not exclusive pathogens. And you can see that the  
10 trials together have enrolled about 600 total  
11 subjects. And they're addressing an important  
12 question, because if combination therapy is improving  
13 survival, then that's a major benefit. If it's not  
14 improving survival, then the benefit-to-risk profile  
15 would be unfavorable because rifampicin, for instance,  
16 would lead to a lot of drug-drug interactions.

17           The table on this slide is showing the  
18 mortality results in the three completed trials. You  
19 can see from the pooled results that we don't actually  
20 have an answer yet for whether combination therapy  
21 should be given to these patients. There was  
22 approximately 50 percent mortality in both subjects



1 randomized to colistin monotherapy or combination  
2 therapy. But the confidence interval for the  
3 treatment difference can't rule out a mortality  
4 benefit from combination therapy of as high as 15  
5 percent.

6 Now, fully powered randomized trials would  
7 provide the most statistically reliable answers to the  
8 most important questions, such as this question with  
9 combination therapy. For complicated patients with  
10 many comorbidities, randomization ensures that  
11 treatment effect estimation is not confounded by  
12 baseline differences between treatment and control  
13 groups.

14 The most natural questions in this setting  
15 are superiority questions because patients with  
16 effective therapeutic options could be folded into  
17 more traditional non-inferiority trials. However, as  
18 shown in the previous example, to obtain definitive  
19 answers, it must be possible to enroll a relatively  
20 large number of subjects with infections due to multi-  
21 drug-resistant pathogens. So discussion topics for  
22 today have been what other strategies are there to

1 increase enrollment and then what can be done if it  
2 simply is not possible to enroll large numbers of  
3 subjects.

4 One method to make trials in this setting  
5 more achievable, as we've discussed today, are  
6 platform trials and a platform trial using a common  
7 master protocol could potentially allow for a study of  
8 multiple antibacterial drugs, studies of multiple  
9 indications or a study using a shared control group.

10 Just from sharing a control group, the potential gains  
11 are if two sponsors run separate trials of drug A  
12 versus control and drug B versus control with 100  
13 subjects per arm, the sponsors together must enroll a  
14 total of 400 subjects and compete for study sites.

15 But if instead there's a three-arm trial with drug A,  
16 drug B and control with 100 subjects per arm, the  
17 trial only enrolls a total of 300 subjects rather than  
18 400 subjects. And separate statistical comparisons  
19 could be made for drug A versus control and drug B  
20 versus control.

21 In a straightforward platform trial design,  
22 drugs would enter/exit the study in a staggered

1 manner. The study would attempt to answer multiple  
2 questions of interest. There would be advantages in  
3 shared clinical trial infrastructure, study sites and  
4 IRBs. The study would be able to prospectively plan  
5 for how comparisons would change if the standard of  
6 care regimen had to be updated due to ongoing trial  
7 results. And the comparisons of interest would be  
8 between subjects concurrently randomized to tested  
9 control drugs.

10 The slide here is showing the abstract from  
11 a prostate cancer MAMS trial, standing for multi-  
12 arm/multi-stage trial, which along these lines was a  
13 seamless Phase II/III design that uses shared  
14 continuously updated control group to evaluate  
15 multiple interventions for prostate cancer. It's  
16 important to note that many statistical design  
17 features could potentially be part of a platform  
18 trial, but are separate issues that would need to be  
19 considered independently of whether to evaluate  
20 antibacterial drugs using a common protocol. Such  
21 issues include response-adaptive randomization,  
22 Bayesian adaptations for efficacy and futility,

1 stopping criteria or use of statistical modeling with  
2 non-randomized comparisons such as comparisons between  
3 subjects in the trial assigned to drug A or drug B who  
4 are not concurrently randomized.

5 Now, beyond platform trials, another method  
6 that may make studies in this setting more achievable  
7 would be to combine subjects with infections at  
8 different body sites. To illustrate the potential  
9 utility, the CDC says about carbapenem-resistant  
10 Enterobacteriaceae that patients whose care requires  
11 devices like ventilators, urinary catheters or  
12 intravenous catheters and patients who are taking long  
13 courses of certain antibiotics are most at risk for  
14 CRE infections. And some CRE bacteria have become  
15 resistant to most available antibiotics.

16 So then, the question becomes should one  
17 conduct a single trial, combining subjects with, say,  
18 nosocomial pneumonia, bloodstream infections and  
19 complicated urinary tract infections, despite possible  
20 differences in endpoints, comparators, durations and  
21 patient characteristics and recent examples of  
22 Antibacterials that may have had discordant efficacy

1 results across body sites.

2 In principle, we can use body site-specific  
3 endpoints or responder indices, comparators and  
4 treatment durations. And statistical methods can use  
5 smoothing or shrinkage to form more accurate body  
6 site-specific estimates of treatment effects by  
7 borrowing information across subgroups. However,  
8 whether to do this is not only a statistical  
9 heterogeneity issue, but also a clinical heterogeneity  
10 issue regarding whether patients with infections at  
11 different body sites constitute a reasonable combined  
12 target population because we may have very low  
13 statistical power to detect differences in treatment  
14 effects between different body sites. And with small  
15 sample sizes, statistical methods also can't guarantee  
16 accurate estimation for every body site subgroup in  
17 terms of having both low bias and low variance.

18 The table on this slide is showing the  
19 percentages of subjects with different body site  
20 infections from the three completed Acinetobacter  
21 trials that I mentioned earlier. You can see from the  
22 first column that pneumonia was the predominant

1 infection. In one of the trials, about a fifth of the  
2 subjects had bacteremia and there was a scattering of  
3 other types of infections, like intra-abdominal  
4 infections and urinary tract infections. So these  
5 were in some cases multiple body site trials.

6 For the remainder of the presentation, I'll  
7 discuss statistical considerations when it's simply  
8 very difficult or not possible to enroll a large  
9 number of subjects with resistant pathogens in a  
10 clinical trial. The sample size table in this slide  
11 is showing that to statistically demonstrate  
12 superiority with a reasonable number of subjects or  
13 even with a few hundred subjects per arm with the  
14 resistance marker, the new antibacterial drug would  
15 need to provide relatively large benefits compared to  
16 current standards of care.

17 Now, given the sample size calculations from  
18 the previous slide, a natural question is whether it's  
19 possible to move from studies that use inferential  
20 statistics to studies that use descriptive statistics.  
21 FDA has traditionally interpreted trials that use  
22 inferential statistics and formal tested hypotheses as

1 providing reliable evidence. Descriptive analysis of  
2 a clinical trial would present success rates for drug  
3 A and drug B, but would not necessarily formally test  
4 a hypothesis. And descriptive analysis is useful for  
5 assessing patterns and examples of descriptive  
6 statistical analyses of antibacterial drugs include  
7 many Phase II studies, pediatric studies and safety  
8 studies, including the Phase II studies factoring into  
9 the FDA approval of ceftazidime-avibactam in 2015 and  
10 also FDA approvals of antibacterial drugs in earlier  
11 decades in clinical data used to set susceptibility  
12 breakpoints.

13           So then, a really important question becomes  
14 can trials pre-specify decision criteria somewhere  
15 between P less than 05 at each body site and post hoc  
16 descriptive analysis that would give reasonable  
17 operating characteristics in the unmet need setting.

18           I'll next discuss differences between  
19 frequentist inferential statistics and Bayesian  
20 inferential statistics. Frequentist methods such as P  
21 values and confidence intervals have been the default  
22 paradigm for clinical trials. By a type 1 error rate

1 control, the usual statistical significance level, we  
2 mean that approximately only one out of every 40  
3 clinical trials have ineffective treatments, will  
4 falsely conclude efficacy. And we have the coverage  
5 guarantee that in approximately 95 out of every 100  
6 clinical trials, the confidence interval for the  
7 treatment effect will contain the true effect. The  
8 nice thing about these methods is that statistical  
9 theory provides type 1 error rate control and coverage  
10 guarantees under essentially minimal conditions  
11 without need for a lot of modeling assumptions or data  
12 external to the clinical trial of interest.

13 Now, Bayesian methods are a different class  
14 of statistical methods from frequentist methods and I  
15 won't be able in this talk to go through the machinery  
16 of how the Bayesian analysis would work or some of the  
17 more conceptual differences, other than to say that in  
18 practice, this isn't necessarily how the difference  
19 between the two types of methods are defined, but in  
20 practice, the main difference between using Bayesian  
21 methods and using frequentist methods is in how the  
22 Bayesian methods attempt to integrate the data from



1 the trial itself with data or evidence from other  
2 sources.

3 For antibacterial drugs, the prior evidence  
4 may come from previous randomized or observational  
5 studies of the new drug, comparator or related drugs,  
6 previous studies at different body sites of infection,  
7 PK/PD data, animal data, in vitro data or expert  
8 elicitation. And an advantage of Bayesian methods is  
9 that they can attempt to incorporate more of this  
10 information into the analysis and formalize for  
11 different sources of uncertainty. A disadvantage is  
12 that this can lead to erroneous answers if the prior  
13 beliefs are incorrect and are debatable or too  
14 strongly held. And I'll give examples of Bayesian and  
15 frequentist methods in the next few slides.

16 So we saw earlier in the Acinetobacter  
17 studies that in the pooled randomized trials, there  
18 were mortality rates of 51 percent for subjects  
19 treated with colistin monotherapy and 47 percent for  
20 subjects treated with combination therapy. If you  
21 pool the studies -- and this is just illustrative, not  
22 necessarily to endorse raw pooling as the way that

1 these studies should be meta-analyzed -- but if you  
2 pool the studies, you would estimate a difference in  
3 mortality rates to be 4 percent, with a confidence  
4 interval from -6 percent to 15 percent. And because  
5 the lower confidence limit does not exceed zero and  
6 because the upper confidence limit can't rule out a  
7 mortality benefit of as high as 15 percent, the usual  
8 interpretation is that this confidence interval is too  
9 wide to tell us whether combination therapy improves  
10 survival.

11           With the same data, the Bayesian analysis  
12 can actually depend on prior information. If we use a  
13 so-called uninformative prior that attempts to handle  
14 the treatment and control as neutrally as possible,  
15 which would imply that before the trial we thought  
16 that there was a 50/50 chance that monotherapy or  
17 combination therapy had better survival, then the  
18 frequentist and Bayesian decisions would tend to be  
19 very similar after the trial results came in.  
20 however, if we used an informative prior, say that  
21 before the trials we model from the available evidence  
22 that there's an 80 percent chance that the mortality

1 rate for subjects treated with colistin monotherapy is  
2 between 0.6 and 0.7, then after the trials, we would  
3 find from a beta binomial model that there's a 99  
4 percent chance that colistin combination therapy  
5 actually improves survival.

6 So the next few slides illustrate this. The  
7 top histogram in this slide is showing the  
8 uninformative prior for the chance of death with  
9 colistin monotherapy before the trial results. And  
10 you can see that it's essentially placing any  
11 mortality rate between zero and one for the  
12 monotherapy group on equal footing. If you use this  
13 uninformative prior, then after the trial results,  
14 you'll get the histogram on the bottom of this slide,  
15 which is called a posterior distribution. And you can  
16 see that the chance of death with colistin monotherapy  
17 is centered around the 50 percent rate that was  
18 actually observed in the trial.

19 Conversely, the top histogram in this slide  
20 is showing a very informative prior for the chance of  
21 death with colistin monotherapy, and which we have  
22 modeled based on whatever evidence is available before

1 the trial results that the chance of death with  
2 colistin monotherapy is fairly concentrated at around  
3 about 65 percent. In this case, because the Bayesian  
4 analysis would depend both on the trial results where  
5 we saw a 50 percent mortality rate for this group and  
6 the prior evidence, the result of the analysis would  
7 be to say after the trial results that there's still a  
8 fairly high chance that subjects treated with colistin  
9 monotherapy would have a death rate exceeding 50  
10 percent.

11 In summary, there are opportunities for  
12 conducting randomized trials in the resistant pathogen  
13 setting using platform trials. A trial combining  
14 subjects with different body site infections can be  
15 statistically analyzed. But then, the important  
16 question becomes how should heterogeneity be  
17 addressed. Conducting powered superiority trials in  
18 the unmet need setting requires either a large  
19 treatment effect or a large sample size. So the  
20 important question here is what pre-specified decision  
21 criteria are reasonable beyond descriptive analysis.  
22 And Bayesian and frequentist methods are both valid

1 statistical tools. But in the anti-infective setting,  
2 the most important consideration is how much weight to  
3 give modeling of nonrandomized evidence. And here are  
4 my references. So, I thank you.

5 [Applause.]

6 DR. MARKS: Thank you, Dan. And building on  
7 this construct in terms of innovative trial designs,  
8 Kert Viele, director and senior statistical scientist  
9 at Berry Consultants, is going to share his thoughts  
10 as well. Thank you, Kert.

11 INNOVATIVE TRIAL DESIGNS

12 DR. VIELE: There we go. So thank you for  
13 having me. The work presented here is funded by ARLG.  
14 It's a project directed by Roger Lewis and Brad  
15 Spellberg. This discussion has involved a lot of  
16 academics, pharmaceutical companies, the FDA, BARDA  
17 have been involved in this. One of my goals is really  
18 to talk about several different innovations that have  
19 all been talked about today, but provide a few more  
20 numbers on what kind of savings might actually be  
21 encountered.

22 So we're talking about a trial -- I'm going

1 to focus on the resistant pathogens. But this is  
2 particularly relevant to a network that might enroll  
3 UDR and resistant pathogens within the context of the  
4 trial. Of course, lots has been said today. It's  
5 hard to do inferences on resistant pathogens. So I'm  
6 going to be talking a lot on how far can you get in  
7 order to bridge this divide between the sample sizes  
8 are too small versus we'd really like formal kinds of  
9 statistical methods.

10 Standard trials, we see a lot of trials that  
11 focus on one drug versus one control at one body site.  
12 And this gets repeated. Lots of trials happen. We've  
13 enrolled the control arm in multiple studies. We've  
14 got UTI in this study. We've got intra-abdominal in  
15 that study. What do we do? So I'm going to talk  
16 about three innovations: platform trials -- and all  
17 of this is building off of what Dan talked about --  
18 early stopping and sharing information across the body  
19 sites. Each of these has the potential to decrease  
20 the required sample sizes for trials.

21 I'll start with platforms. This has been  
22 mentioned a lot. It's been mentioned in the sense of

1 trial networks. But this could also be used simply  
2 for three companies getting together and putting their  
3 drugs all in one trial at the same time. So this is a  
4 scalable enterprise. Some examples, platform trials  
5 are being used in lots of areas. One of the oldest  
6 running platform trials is something called I-SPY 2,  
7 which is a breast cancer study.

8 Nice things about I-SPY, you can see lots of  
9 articles -- not the most recent, but a recent New  
10 England Journal of Medicine had four articles on I-SPY  
11 2. I-SPY 2 is interesting from the standpoint of it  
12 tries to match drugs to particular patient  
13 populations, which may be relevant for resistant  
14 versus UDR kinds of mechanisms. There's different  
15 types of allocation for HER2-positive breast cancer.  
16 Drugs can graduate with certain signatures. We think  
17 this drug works in people with triple-negative breast  
18 cancer. That's one of the outcomes of that study  
19 which may be relevant for antibiotics.

20 Other examples, so again, just trying to  
21 emphasize this isn't new and radical. This is  
22 happening in a lot of places. The IMI EPAD initiative

1 is an Alzheimer's study that's intended to test  
2 combinations. If you have a trial network, you have a  
3 patient stream that's big enough that you can start  
4 thinking about combining drugs in different ways.  
5 There's a PREPARE initiative in Europe which is  
6 intended to be ready for epidemics. The influenza  
7 study of that I think is what Mike Dudley was talking  
8 about in terms of a learning health system.

9 We know lots of things that we think will  
10 work. But physicians differ. They make decisions on  
11 what they've seen before. The notion of using this  
12 health system and having all the data come in.  
13 Patients are randomized and in real-time having access  
14 to these are the things that are working and these are  
15 the things that aren't -- that's the kind of thing  
16 that you can do within a trial network and it is an  
17 example of a platform trial. GBM AGILE, this is  
18 getting a lot of press. If you want to see some  
19 really slick videos on YouTube, whoever their PR  
20 person is, they're really good. There's also an Ebola  
21 trial which, as an example of trying to put together a  
22 platform trial that works incredibly quickly of



1 getting drugs in combinations to patients as quickly  
2 as possible. So this is something that we're getting  
3 a lot of experience about in the broader realm.

4 The sharing of control information is the  
5 key place that we gain efficiency in these kind of  
6 trials. I've talked about 40 drugs here, the notion  
7 of doing this for 10, 12 years. But the efficiency  
8 gains on the order of 25, 30 percent, even three or  
9 four companies getting together, just the mere fact  
10 that you've saved a control arm is worth that kind of  
11 advantages. So you could really do some good things  
12 here.

13 There are some synergies in a platform. I  
14 haven't even talked about early stopping yet. But if  
15 you have a platform trial where drugs can go in and  
16 out and stop, when one drug stops, another one can  
17 come in. Being able to do that, it doesn't work quite  
18 like compound interest. You know, you don't double  
19 every month or whatever. But this notion of investing  
20 savings forward certainly does exist and it's very  
21 valuable to combine early stopping with a platform  
22 kind of idea.

1           Platforms in general, if you can run lots of  
2 drugs at the same time, savings can be 35 percent.  
3 This is a paper that -- the clinical trials paper  
4 that's coming out. It may be in print now, but it  
5 will be shortly if not. This shows savings up to 50  
6 percent just from the ability of sharing a control arm  
7 and being able to stop drugs. I think this paper has  
8 response-adaptive randomization in addition to try to  
9 tailor drugs to particular patient groups. Early  
10 stopping of body sites. We're talking about a trial  
11 that enrolls in multiple body sites.

12           If you have a drug like daptomycin and  
13 you're able to see this is failing in HAP/VAP, you can  
14 stop that and enroll the HAP/VAP patients in other  
15 things. I'm not going to spend a lot of time on this.  
16 This early stopping I think is more well understood.  
17 But the sample size savings there can often be 15 to  
18 20 percent compared to running a standard trial. One  
19 thing to keep in mind, when we talk about formal  
20 inferential statistics, if you're trying to get 80 or  
21 90 percent power, you're designing a study with the  
22 intent that even if I get unlucky, I still win. That

1 50 percent power is aimed at if I get exactly what I'm  
2 expecting.

3 To get 80 or 90 percent power, you're saying  
4 even if I get unlucky and I get less than what I'm  
5 expecting, I still want to get conclusive evidence.  
6 If you're talking about a platform and you're going to  
7 have 30 or 40 drugs, you're not going to get unlucky  
8 all the time. If you're one company, you don't want  
9 your one product to die on the vine or one of your key  
10 products to die on the vine. But if we're running,  
11 you know, 20, 30, 40 drugs over the course of many  
12 years, we're lucky half the time. We're unlucky half  
13 the time. We may as well make sure we get the  
14 savings. We don't need to protect ourselves against -  
15 - we don't need to buy an insurance policy for every  
16 single drug and early stopping lets us do that.

17 As I said, early stopping has synergies with  
18 platform trials. If you're talking about getting 40  
19 drugs over the course of a decade or more, saving 20  
20 percent, you can evaluate 48 drugs. So again, this  
21 notion of paying forward. And I've tried to save time  
22 for this one thing that hasn't been talked about much

1 today which is sharing information across body sites.  
2 In a lot of cases, trials are run in, say, UTI or run  
3 in intra-abdominal and maybe you're not -- you don't  
4 want to run a trial in HAP/VAP because of the expense.  
5 The ability to run potentially smaller trials across  
6 multiple body sites and sharing the information across  
7 those body sites -- excuse me -- has a lot of value in  
8 terms of you can get more statistical efficiency and  
9 of course it also allows us to see exactly how a drug  
10 does perform in those settings rather than having to  
11 rely on extrapolation.

12 I'm not going to get into the details of the  
13 modeling here, for the same reasons Dan didn't. It's  
14 difficult within the time allotment. But a notion of  
15 the kind of fear that you have in running small trials  
16 in several body sites. Suppose we ran a trial and we  
17 had HAP/VAP, UTI and intra-abdominal together in the  
18 trial. And I'm focused on just these are the  
19 resistance that come out of this.

20 So you can imagine a larger trial. I may  
21 have several hundred usually. I'm trying to answer  
22 the question what about the resistant populations

1 here. So in HAP/VAP, my control data -- I got 5 out  
2 of 12 successes, 42 percent. In the treatment, I'm  
3 doing great, 10 out of 13, huge advantage. The  
4 problem is if I'm looking for a P value of 0.025, I am  
5 a Bayesian, but -- so I've termed this in terms of  
6 posterior probabilities and 97.2 percent chance of the  
7 treatment is better. That corresponds to about a  
8 0.028. I just missed. Yuck. Now, I'm going to have  
9 to go in and ask for, well, was I close enough.

10 But I didn't just run the HAP/VAP study.  
11 I've got the UTI data next to it. I've got 9 out of  
12 25, 36 percent on control, 23 out of 25, 92 percent on  
13 treatment. This is fantastic results. This is a slam  
14 dunk win. No one's going to question the UTI results  
15 here. And then, in intra-abdominal, remember one  
16 thing that happens in intra-abdominal, a lot of times  
17 you get successes on the basis of surgery. So the  
18 control rates are often higher. So I got 14 out of  
19 22, 64 percent for the control and 87 out of the  
20 treatment. That's a Bayesian probability of 94.5  
21 percent. It's a P value of 0.055. I missed again.  
22 This is not unusual at all in underpowered trials.

1 When we talk about the notion of I can't achieve  
2 statistical, formal inferential statistics in small  
3 trials, I'm not saying I can't get trends. I'm saying  
4 I can't get 80 or 90 percent power. And this is the  
5 type of setting that you're in. This is where you're  
6 missing, lots of trials that give you indications, but  
7 they're not conclusive.

8 A key point here though is that none of  
9 these data -- while only the UTI is convincing in and  
10 of itself, the context here is very important. I just  
11 missed in HAP/VAP and I have a promising trend in  
12 intra-abdominal. I may not be willing to say for  
13 intra-abdominal this is conclusive evidence. But  
14 doesn't it matter that it's paired with the other  
15 things that are going on? Seeing the intra-abdominal  
16 results in a vacuum, this is my only study is one  
17 thing. Seeing the intra-abdominal results combined  
18 with the fact this is a slam dunk win in UTI, combined  
19 with the fact that the HAP/VAP data is strong, this is  
20 more evidence in favor.

21 What the more -- the methods that Dan was  
22 talking about for borrowing information across sites,

1 what they aim to do is essentially partition the  
2 variation that you're seeing in the data. They're  
3 partitioning it into what kind -- what's the true  
4 differences between the sites and what's just result  
5 of noise, sampling variability. Here, what we're  
6 seeing is general effects. So the differences that we  
7 see among these drugs, it's more likely to be sampling  
8 variability. These are small trials. We just  
9 couldn't recruit enough patients. But the overall  
10 trend is consistent. We attribute the variation here  
11 to sampling variability and that the true differences  
12 are small.

13           When we fit these models, generally what  
14 happens is the effective sample size is increased  
15 through this analysis. And good models do this  
16 dynamically. So this isn't a situation -- I'm not  
17 pooling the data together. Pooling's a very dangerous  
18 thing. There's been -- Sumathi was talking about the  
19 dangers inherent in this. You never want to put  
20 together unlike things. Good models do this  
21 dynamically these days whereas if they see common  
22 trends, they borrow information between the groups.

1 But if they see very disparate trends, they borrow a  
2 lot less. And that's a protection against the kind of  
3 dangers that you'd see when you pool data together.

4 Back to our sample data set, if you see the  
5 bottom numbers in red, what's happened is because  
6 these data don't appear in a vacuum, we see each of  
7 them combined with strong results. The HAP/VAP data  
8 that just missed at 97.2 goes up to 99.7. The UTI is  
9 still a slam dunk. The intra-abdominal also went up.  
10 The consistent picture has allowed us to increase the  
11 effective sample size in each group. And I think this  
12 is intuitively what clinicians would do. I know this  
13 drug works in UTI. I've got data that says it works  
14 reasonably well in others.

15 What are you going to do? If you can't  
16 enroll the big study, you're going to basically do the  
17 intuitive conclusion here, which is this probably  
18 works. That's what this is trying to formalize and  
19 trying to put some statistical teeth on it and  
20 statistical teeth in a way that allows us to test the  
21 operating characteristics. We can go to the FDA and  
22 say here is our design in advance. Here are the error



1 rates attached to it. This isn't ad hoc, oh, we know  
2 we missed, but can't you just give us the benefit of  
3 the doubt. This is a way where we know what the error  
4 rates are for this procedure.

5 Here is another data set. This is a  
6 situation where intra-abdominal appears to have a  
7 significant problem. You can see again HAP/VAP, the  
8 treatment is doing better than the control data. UTI,  
9 again, the treatment's doing much better than the  
10 control better. We actually seem to be doing harm to  
11 the intra-abdominal subjects. So they're going the  
12 wrong way and I picked this to be an extreme example  
13 for a number of reasons. One reason I picked this is  
14 to illustrate the dangers of pooling. If you said in  
15 advance, I was going to pool the data, what in effect  
16 you would do is the good HAP/VAP and UTI sites and the  
17 very bad intra-abdominal, you'd pool those together  
18 and you'd end up saying my essential conclusion is  
19 that nothing is going on, which isn't what the data  
20 seem to be telling you at all. It tells you something  
21 horrible is going on in intra-abdominal.

22 This is also intended to be a data set that

1 shows you the dynamic part of these kind of models.  
2 The probability the treatment is better, you can see  
3 if I analyze the intra-abdominal separately, that  
4 probability is 1.4 percent. That's very low. So  
5 again, separate analyses recognize there's a problem.  
6 If you do -- if you did pooling, you would pull that  
7 up dramatically. You would say, well, I'm just going  
8 to average out the HAP/VAP and UTI and you'd say,  
9 well, maybe it works in intra-abdominal.

10 Here, what happens is the model recognizes  
11 that the difference between HAP/VAP and UTI, it's more  
12 than can be accounted for by sampling and variability  
13 and it doesn't pull up the intra-abdominal. So I  
14 think there's a lot of hope here to be able to get  
15 data in multiple body sites and be able to still make  
16 inferences potentially with smaller sample sizes than  
17 doing one body site and having a big study and  
18 effectively having zero in other sites.

19 Sharing information, this can save sample  
20 sizes 30 to 45 percent. It's substantial. So to give  
21 a notion about this is more aimed at a trial network  
22 kind of arrangement, but a standard design -- say

1 you're doing a UTI trial, non-inferiority. You're  
2 going to add these features, potentially look at  
3 resistant pathogens. A standard design may require  
4 400 to 425 per arm. If you borrow -- and that's  
5 across sites, 400, 425 across all three sites.

6 Borrowing alone can reduce those sample  
7 sizes to 300 per arm. If you add early stopping to  
8 that, you can get to 230, 275 per arm. There are  
9 assumptions attached on this. I haven't gone through  
10 all of them. So these are scalable kinds of savings.  
11 And then, finally, putting those kinds of drugs in a  
12 platform and sharing the control information, it  
13 becomes more relevant to talk about this as a per drug  
14 kind of issue because you'll have a shared control  
15 arm. But that gets down to something like 325 per  
16 drug, which is not arms. So these are substantial  
17 kinds of savings. And it depends on the assumptions  
18 and the treatment effects. But there's a lot of  
19 potential here that we can start making more efficient  
20 designs and trying to expedite this process.

21 So in summary, I talked about platform  
22 trials, early stopping sharing of information. Main

1 thing I want to emphasize is there's just a lot of  
2 synergies here, the ability to put drugs together.  
3 You can start playing with a lot of interesting levers  
4 to try to make things work more efficiently. And  
5 certainly I again want to emphasize these aren't novel  
6 or crazy ideas. These are things that are being done  
7 in a variety of areas and hope we can do them in  
8 antibiotics. Thank you.

9 [Applause.]

10 CLARIFYING QUESTIONS (PANELISTS AND  
11 AUDIENCE)

12 DR. COX: Thanks to both Kert and Dan for  
13 your excellent presentations. I just sort of wanted  
14 to open it up now for questions about the  
15 presentations. Aaron?

16 MR. DANE: Yeah. I suppose my first comment  
17 would be, you know, with Bayesian methods, all the  
18 information borrowing, the critical element is the  
19 assumptions and an explicit discussion of the  
20 assumptions going in. So these are approaches that  
21 are quite reasonable. But you need to be able to  
22 assume, for example, that the responses are going to

1 perform similarly across body sites because although  
2 it does deal with that to some degree, as Kert showed,  
3 you know, you do increase your chance of making the  
4 wrong decision, if that's not true. But it feels that  
5 should be just a discussion we have up front and  
6 decide whether it's a reasonable thing to do and not a  
7 reason not to do it. So it's just to state that  
8 really, that that's one of the key things here.  
9 There's probably additional assumptions that we make  
10 when we do this that we just have to be mindful of.

11 DR. COX: Ian?

12 DR. FRIEDLAND: I have a comment and then I  
13 have a question. So the examples that were given of  
14 the platform-type protocols, there are actually --  
15 well, I know at least one example in the antibacterial  
16 space. Sivextro and Cubist got together and with the  
17 FDA came up with a joint protocol for osteomyelitis in  
18 pediatrics. They had a common protocol with a shared  
19 control group. Unfortunately, that study wasn't  
20 conducted for reasons other than the study itself. It  
21 was a financial disagreement.

22 But I think there are those kinds of

1 examples. I think pediatrics definitely lends itself  
2 to that kind of opportunity. And one would imagine in  
3 even in the unmet need space, if two drug developers  
4 had drugs for the same target, that there could be a  
5 potential for coming up with a common protocol with a  
6 shared control group. I just think we don't always  
7 think about this in industry that much. That was the  
8 comment.

9           And the question I had is -- and as I said,  
10 the statisticians on the panel -- what they think  
11 about the DOOR and RADAR analyses that Scott Evans  
12 described because those kind of analyses do tend to  
13 lend themselves to smaller studies.

14           DR. RUBIN: Yes. I can comment on that  
15 since I was a co-author on one of the RADAR papers.  
16 So the idea behind here is to use sort of an ordinal  
17 outcome, meaning that instead of someone being a  
18 success/failure, you have to be able to rank patients.  
19 So if you have two patients, you have to say which one  
20 of them had the better outcome in terms of maybe, you  
21 know, efficacy, safety or some combination. They're  
22 actually used in stewardship trials, where if there's

1 a tie, the patient who's on antibiotics for the least  
2 length of time is the winner. And then, what you do  
3 is average all of the subjects and try to determine  
4 whether subjects randomized to one arm or the other  
5 would, on average, have the higher ranking or be the  
6 winner. It's been used in some stewardship trials.

7 So I think it is an innovation that has some  
8 utility. It's mainly for superiority analyses. So  
9 you'd have to have some type of benefit over what  
10 you're trying to compare against. It may not  
11 necessarily have to be in terms of an efficacy  
12 benefit. It could be a safety benefit that RADAR  
13 would also try to take into account.

14 Now, it's not a -- there's no free lunch  
15 here. There are disadvantages of it that have to be  
16 worked through. Like any composite, it can be driven  
17 by its weakest link, in that a major -- a negative  
18 treatment effect on one component of the composite can  
19 be outweighed by a positive effect on less components  
20 in the stewardship trials if there's a danger that you  
21 could approve a less effective drug using this method  
22 if it just simply leads to -- the intervention leads

1 to less antibiotic use. So that has to be taken into  
2 account, that it is a different method of given some  
3 kind of introduction to it that could potentially be  
4 applied in some of these settings.

5 MR. DANE: Yeah, and I would -- so it's  
6 clearly helpful in that compared to our traditional  
7 response yes and no, it gives you more granularity  
8 than that. So it can give you a bit more information.  
9 I guess the challenge often in designing the studies,  
10 that you get into some quite complicated assumptions  
11 you have to make around if you have five different  
12 groupings, for example, you know, if you're moving  
13 from efficacy with no toxicity, efficacy with toxicity  
14 and then you often end up with five categories.

15 You've got to make assumptions on how many  
16 patients are in each of those different groups to be  
17 able to figure out how many patients you need to  
18 demonstrate superiority. So that can be a challenge  
19 in terms of investing in that study and knowing how  
20 likely you are to succeed. And I guess something else  
21 Dan just touched on is that the way that works is  
22 you're assuming each of those different categories has



1 equal weight as well. So you're assuming it's equally  
2 as important as you go through each of those. So I  
3 can see some use.

4 But at the moment, it feels like it would be  
5 a useful tool as a sensitivity or additional  
6 information rather than the method you would use to  
7 interpret a study because the other thing that I  
8 forgot to mention was that you end up with a figure  
9 and some evidence of effect. But you don't know quite  
10 how to interpret it because it's a number you don't  
11 really know what it means. So you'd still have to use  
12 it with some of your more traditional methods I think  
13 and it just may give you a view of the evidence.

14 DR. COX: John?

15 DR. REX: First, thanks for those two really  
16 good presentations. And I'd like to ask Dan a  
17 question to test my understanding and then that may  
18 lead to a comment. So are Dan's slides something that  
19 can be brought back up? Because my question will make  
20 more sense. Can you go to slide 18? All right. So  
21 in this slide, there was a slide before -- actually,  
22 back up one, slide 17.

1           So you analyzed the same data twice, right?  
2       And so, the first time you look at it, you say, okay,  
3       51 percent versus 47 percent. So a difference of 4  
4       percent, broad confidence interval. Those look like  
5       they could be about the same, or can't tell. It's  
6       kind of wide, wide? Next slide. Now, you look at it  
7       again and the first time you look at it, you say, I  
8       don't know -- the 0.5, the prior 0.5 means I have no  
9       opinion. That's the way I should put that into  
10      English, is I have no opinion. And so, when I get  
11      those data back, I don't know. I'm not much smarter  
12      one way or another.

13           The second time, you say, I have an opinion  
14      and I believe that the combination is better. I  
15      believe that pretty strongly. So now, when you do the  
16      math, would it be correct to say that you've concluded  
17      that the combination is better, largely because you  
18      believed it before you went in, and the only thing  
19      that would have turned you back would have been really  
20      a grossly negative result. So as long as it was sort  
21      of consistent with your belief, you're happy and you  
22      declare victory. Am I saying it correctly in English?

1 DR. RUBIN: I think you are saying it  
2 correctly, that with a Bayesian analysis, if you have  
3 an extremely strong prior for what's going to happen,  
4 you're going to stay with that opinion unless there's  
5 really a lot of evidence to move you in the other  
6 direction. This is meant to be illustrative of that.  
7 It's probably a stronger prior than anyone would use  
8 in a practical analysis with this type of data.

9 DR. REX: Because I've always wanted to be a  
10 Bayesian and yet you've made me not so happy with what  
11 that did there because it actually sort of twisted  
12 that.

13 MR. DANE: But John, slide 19, the next  
14 slide is actually quite useful for your question.

15 DR. REX: Well, okay. But I wanted to ask  
16 why is this -- but so now my question then spins off  
17 of Kert's presentation where, in effect, he showed us  
18 data in here little experiments -- intra-ab, UTI and  
19 nosocomial pneumonia -- and said, look, you know,  
20 they're all kind of the same, you know. Actually,  
21 both -- all three of them look like something better  
22 than a sharp stick in the eye was happening. So why

1 shouldn't we buy into that? And he did that without  
2 showing us any more math than that other than, you  
3 know, these three numbers are all pointing in the same  
4 direction. And I'm just -- it feels to me like  
5 something about writing these numbers down made me  
6 less happy with it, yet I looked at his three examples  
7 and I thought, well, that looks not too bad if I just  
8 eyeball it. That's not much of a question. I'm  
9 sorry. I'm just kind of bothered by what's going on.

10 DR. RUBIN: That's okay. Well, there were a  
11 lot of intricacies in exactly what to model, what the  
12 prior is and how the different sources of evidence are  
13 combined. And I think that the two examples from mine  
14 and Kert are illustrating that, you know, those  
15 assumptions and the specific statistical analyses can  
16 really change the results. But there are a few other  
17 people more familiar with Bayesian methods than me in  
18 the room. So --

19 DR. COX: So why don't we go -- we'll go to  
20 Kert, if you're set, Dan. Okay. We'll go to Kert.  
21 Then we'll go to Thomas. And then, we'll come over to  
22 Mike. Sure. Tom, you willing to take him up on that?

1 DR. LOUIS: I'll start by saying I'm known  
2 as a Bayesian, but what I really am is a statistician  
3 who uses the Bayesian strategy for most things, as a  
4 kind of guide to navigation. And I think Dan's  
5 example -- I'm just going to respond to one or two  
6 things and leave the rest for later in the afternoon.  
7 But I think whether you're a frequentist or a  
8 Bayesian, the only place that beliefs have a role --  
9 and they really have a role in whether you're a  
10 frequentist or a Bayesian -- is, for example, in what  
11 data are relevant to the current study, whether it be  
12 for designing or analyzing.

13 In Dan's example, if he had used the word  
14 that investigators had the belief that the following  
15 five studies were relevant to the current study and  
16 used those to develop a prior and it was the prior  
17 that he put down, there's still belief floating  
18 around. But really, the prior subject to at least  
19 which studies are relevant is an empirically based  
20 thing. And I think in the realm of public policy,  
21 clinical policy, put whatever word you want with  
22 policy as the last word, that has to be what's going

1 on in the Bayesian formulism and that we have to  
2 always understand the objective properties. And Berry  
3 Associates learned a lot of CPU, a lot of this CPU and  
4 a lot of that CPU understanding the objective  
5 properties of a protocol-driven analysis that is  
6 embedded in Bayesian formulism.

7 And so, I want to push for there being a  
8 little less separation of maybe 40 years ago when I  
9 would sit around and say, you know, frequentists are  
10 idiots -- I no longer say that. I'm sort of a  
11 frequentist. The world has gone beyond that, at least  
12 for most people, and that we're trying to design and  
13 analyze studies doing a good job and that the Bayesian  
14 stuff, now with computing available, is not a panacea.  
15 In fact, the obligations are greater. But there's no  
16 free lunch. But there are a lot of reduced price  
17 lunches and we should be going for them. I'll save  
18 other comments until later.

19 DR. COX: Kert, do you want to add?

20 DR. VIELE: I was hoping you'd say that and  
21 figured you'd say it better than me. So I let you go  
22 ahead and go. So to piggyback off of that, when we

1 design trials, one thing that we spend a lot of time  
2 on is going through individual data sets and the  
3 conclusions that would be drawn from them. This  
4 particular example I think is a good one. I think Dan  
5 was saying it's a fairly extreme assumption. And it's  
6 interesting to see this data set. I think this is  
7 almost a treasure trove example. We're making an  
8 assumption, 80 percent chance that the mortality rate  
9 for colistin monotherapy is between 60 and 70 percent.

10 That's a strong assumption in there. If  
11 it's true, this is the right conclusion to draw from  
12 this and that's what the Bayesian machinery is doing.  
13 If you're uncomfortable with this -- and I sense that  
14 you are -- I think what you're aiming at is not the  
15 methodology itself, but that you don't buy the 80  
16 percent chance is between 0.6 and 0.7. And when we  
17 design trials, I think that's one thing we like to  
18 show to people. Here are the conclusions that it  
19 would draw if this data set doesn't make you  
20 uncomfortable and basically tease out what are the  
21 comfortable assumptions. And the assumption that you  
22 may be willing to make here is that not this one, so I

1 don't want to draw that.

2           Related to this -- I'm going to talk for a  
3 little while, I guess. I might be more inclined in  
4 this example. If you look at the -- you've got 88 out  
5 of 174 for colistin. There are multiple ways to  
6 incorporate the prior. A lot of methods these days  
7 include what I'm going to call an off-ramp. It  
8 essentially says we've got control data in my current  
9 study and I've got this control data from the past  
10 that was the basis of this 80 percent belief. A lot  
11 of methods these days -- and I think Dan did a  
12 simplified example to illustrate things, so not  
13 picking on your example at all.

14           Having that kind of off-ramp I think would  
15 do a better analysis here because it would let you see  
16 the 88 out of 174. The data that you have in front of  
17 you isn't consistent with the assumption. So maybe I  
18 should borrow from it less and that would weaken this  
19 conclusion that you have now. So this notion of  
20 continually having models that check their own  
21 assumptions I think are viable and that's what this  
22 notion of dynamic borrowing, being able to decide



1 based on data is it valuable or not is big. And as a  
2 final point to this, I think it shows a dichotomy  
3 here.

4 We've talked about historical controls in  
5 the past. There's two notions of historical or  
6 external controls. There's fully external controls,  
7 where there's no controls in the study whatsoever and  
8 then there is running a 3:1, 2:1, 4:1 study where you  
9 enroll some controls in. And those are night and day.  
10 They tend to be lumped under historical controls when  
11 we talk about them. But the ability to see control  
12 data here is so valuable in testing those assumptions  
13 that having some in, I'd always recommend that we have  
14 some control data in any of the especially later phase  
15 studies that we do.

16 DR. COX: Thanks, Kert. And Mike still?  
17 Yeah?

18 DR. DUDLEY: Yeah. I think so. Thank you  
19 to both of you actually for both the presentations.  
20 So let me try this because I think, Dan, you brought  
21 this out about the Bayesian priors can come from a  
22 variety of different sources. So if we think about

1 earlier this morning, Dr. Ambrose's presentation  
2 taught us that a lot of things that we call failure  
3 are just simply because we're too low on the dose-  
4 response curve and we've become pretty good about  
5 modeling and attaining high probabilities of getting  
6 what we consider to be therapeutic exposures.

7           How would you use that type of information  
8 then to come up with a prior that would help you then  
9 to sort of become more confident in your small trial  
10 observation? So in other words, if we carried into  
11 that trial a prior belief that a dosage regimen is  
12 going to provide a certain level of exposure that's  
13 going to be attaining a pre-specified target, would we  
14 be able to use that to sort of strengthen our  
15 conclusion, sort of, to use Kert's term, borrow from  
16 that to help us understand?

17           DR. RUBIN: Right. That's a great question.  
18 And at this point, you've kind of put me on the spot.  
19 But I don't think FDA can necessarily endorse or not  
20 endorse that type of analysis. In the past, that type  
21 of data has been more hypothesis generating data, used  
22 for dose selection and used to set up candidate drugs

1 to see if they'll work really in the full standalone  
2 test of a Phase III trial. In terms of using an  
3 analysis that formalizes the borrowing PK/PD data and  
4 integrates that with the trial data, I mean, it's  
5 something that we'd have to think about in terms of  
6 what the details would be. I guess the concern would  
7 be, you know, how well do we -- how strongly do we  
8 believe that these data can predict how the results  
9 will translate to clinical -- to treatment effects on  
10 clinical outcomes and how suspect are we of the  
11 modeling assumptions. Those would really be the  
12 issues to address.

13 DR. DUDLEY: And just to follow up, if I  
14 can. So I suspect that that's all in sort of the  
15 secret sauce of the weighting exercise here about how  
16 much do you weight. Is that correct? You can sort of  
17 control -- I think, Kert, you said you can control how  
18 much you're going to borrow I think from these things.  
19 Is that what will happen, is that we'll sort of  
20 throttle that a little bit by deciding how much we  
21 want to borrow from that?

22 DR. RUBIN: Exactly. That was the last

1 point in my last slide, was that it's not so much  
2 Bayesian versus frequentist. It's how much weight do  
3 you want to give when making a decision to modeling of  
4 data other than the randomized --

5 DR. DUDLEY: So let me try this one more,  
6 just if I can -- and I'm not looking for any -- you  
7 know, I'm just -- this is just sort of idea sharing.  
8 So one might say then that based upon an a priori --  
9 when we're designing a small trial, we might be able  
10 to come to an agreement and say here's my PK -- here's  
11 my nonclinical PK/PD data or here's what I've learned  
12 from Phase I and nonclinical.

13 I'm going to propose that I borrow some of  
14 this information for my prospective, smallish trial  
15 that we're going to do and we might come to an  
16 agreement prospectively that says how much weight or  
17 how much borrowing we're going to be able to do, sort  
18 of in a prospective way so everybody kind of gets  
19 comfortable that we're not going to put our thumb on  
20 the scale at the end of something like that. Is that  
21 one possible way of doing this or --

22 DR. RUBIN: Pre-specification is always good

1 and would be needed for this type of analysis. I just  
2 can't give you an answer yet on --

3 DR. DUDLEY: But that might be some way of  
4 kind of thinking through how you can pre-specify.  
5 Maybe --

6 DR. COX: Okay. Either Aaron, are you on  
7 the same topic, because Tom, I'm guessing yours is a  
8 follow-up.

9 MR. DANE: You go first, yeah.

10 DR. COX: Go ahead, yeah.

11 DR. LOUIS: I just want to make sure -- I  
12 don't think we should be pre-specifying the weight. I  
13 think we need to -- and Kert emphasized this. We  
14 should be pre-specifying a model that includes a  
15 between study or a between body site or a between  
16 whatever it might be variance component that the data  
17 help estimate and not automatically, but with pre-  
18 specification of the structure, allow the data to say  
19 should it be given a lot of weight or not much weight.  
20 I think pre-specifying the actual weight is a  
21 dangerous idea. Pre-specifying a model that will  
22 adapt the weights is the right idea.

1 DR. RUBIN: Sorry. I misspoke. I concur,  
2 pre-specify the model.

3 DR. VIELE: Can I -- one to quickly add to  
4 this -- we've designed studies where we have specified  
5 in advance if the data matched up your prior  
6 expectation exactly, we'll weight your prior  
7 expectation 25 percent. But if they don't, then they  
8 weight at zero and it's dynamically -- you know, once  
9 you've programmed the airplane, it goes on autopilot  
10 and it decides the weight based on the results. So  
11 you've pre-specified exactly how you're going to  
12 determine the weight. But the weight is not fixed.

13 DR. COX: Okay. So I've got Aaron, Paul and  
14 John. Is it a direct follow-up or --

15 MR. DANE: Yeah. So mine was to that  
16 question --

17 DR. COX: Okay. Aaron, you've been patient.  
18 So, please.

19 MR. DANE: It was something that I've looked  
20 at before about can we use the PK/PD as a prior. And  
21 I guess to this point that it should be data-driven in  
22 some way, and although it's data, it's not the same

1 endpoint. It's not even patients necessarily. So  
2 it's more challenging. So does that say you ignore  
3 it? Maybe not. But it's probably the strength of it  
4 that you actually alter in some way.

5 And then, that does get to this idea of  
6 rather than pre-specifying the weight, but what you  
7 probably want to do is say, well, okay, we have an  
8 approach we're going to take and then we look at  
9 various scenarios under simulation or something where  
10 we say, well, what would it look like at the end so  
11 that we could all be comfortable that it makes sense.  
12 But I guess in summary it just felt like it was more  
13 challenging here because you've got to make that leap  
14 from the PK/PD data to the clinical data to construct  
15 a trial that just makes it more challenging generally.

16 DR. COX: And then, Paul?

17 DR. LOUIS: I'll let the speakers -- yeah,  
18 it's challenging and yet I think the benefits, in at  
19 least most cases, are worth it. But there may be  
20 situations where it's so complex at the moment,  
21 without understanding of the science, the biology and  
22 so on, that it's not ready for that, but maybe it's

1 not yet ready for any other analysis either. It's not  
2 clear.

3 MR. DANE: But one thing you could do is --  
4 you could -- yeah, even if it's not -- yeah, this  
5 concern here that this probably is too strong, you  
6 could even limit the less feasible type responses from  
7 the PK/PD which gives you a bit more information, even  
8 if it doesn't take you to somewhere like this. So it  
9 at least makes it more feasible than it is otherwise.

10 DR. COX: We'll go to Paul, and if there are  
11 folks in the audience that have questions, please  
12 start working your way up to the microphone. Paul?

13 DR. AMBROSE: Hi. Maybe it'd be easier to  
14 work the preclinical data in if we think of it in  
15 terms of exposure-response in the animal system and an  
16 exposure-response analysis of the human data.  
17 Oftentimes we can drive dose really low in the animals  
18 and get tons of failure of course and very high --  
19 higher than we would in people and we can begin to see  
20 a plateau of relationship.

21 But I think if we were able to take a  
22 clinical data set, maybe one from a program or two



1 that had a problem, and get a good Bayesian exposure-  
2 response analysis incorporating the animal data and it  
3 gives you a y-intercept so it tells you something  
4 about the no treatment effect, right, as drug exposure  
5 goes to zero and the plateau of that effect and  
6 magnitude of factor and some confidence bounds around  
7 that, it'll give you that. That'll help you decide  
8 how power -- or how many patients should be enrolled  
9 in the study.

10 And also, for a given regimen or for a given  
11 drug regimen, it will tell you how much efficacy is  
12 being left on the table, right? The dose worked or it  
13 barely worked or it kind of didn't work. But how much  
14 -- how much room do I have to bring it up and get more  
15 effect out of that regimen. So I think maybe  
16 incorporating into -- all into an exposure-response  
17 type analysis might be something to think about.

18 DR. COX: And John?

19 DR. REX: So I want to be sure I heard  
20 something clearly because Mike asked a question that I  
21 think caused Tom and Kert to talk about different  
22 ideas. So Mike's question was before I do my Phase

1 III trial, I have some PK/PD or other information that  
2 tells me that I believe that I think that this  
3 exposure is going to work. And Mike said could we  
4 agree how we're going to weight that. And then, the  
5 debate that went back and forth here was is that Kert  
6 said, well, yes, you could. Tom said I wouldn't pre-  
7 specify the weights. But I think you may have been  
8 thinking about if I did three different body sites and  
9 I don't want to pre-specify the weight across those.

10 Go back to the case of I'm going to do --  
11 it's like this one right here. I'm only going to do  
12 one site. Ignore the fact there isn't a site here.  
13 But I'm only going to study nosocomial pneumonia.  
14 It's the only -- one indication. I get one result.  
15 So the only thing I have before I do that is my prior  
16 belief from PK/PD and anything I've generated at Phase  
17 I and Phase II that there's exposure, everything that  
18 I can figure out that tells me I think I could work in  
19 the long -- and then, I get one clinical trial result.

20 So would we agree -- so because I think  
21 we're talking about two different things and I --  
22 because there's something potentially very valuable in

1 here in using some of this weighting in advance if we  
2 could really agree to do that because it's actually  
3 potentially a way to buffer against heterogeneity in  
4 small populations. And I'm sorry that's a complicated  
5 question. So I can either draw it out. But that --  
6 were you guys talking about different things? Does  
7 this make sense, that you were talking about weights  
8 across individuals --

9 DR. LOUIS: Let me start first by saying I'm  
10 still suffering a little bit from jet ears plugged.  
11 So I don't think -- I clearly didn't hear his question  
12 accurately because I think for the PK/PD, importing  
13 whatever you know for the current study --

14 DR. REX: Once.

15 DR. LOUIS: -- I would probably give it, if  
16 not 100 percent weight, unless there's some competitor  
17 that I could use, I would give it 100 percent weight.  
18 I was answering a question about in the outcome  
19 endpoint side of things, priors for the treatment  
20 effect or whatever it might be. And so, I think I  
21 answered correctly, but the wrong question.

22 DR. REX: Okay.

1 DR. LOUIS: But take my point as being a  
2 point that's valid but not necessarily for the  
3 question that he asked.

4 DR. REX: Well, so one of the things that  
5 comes up in tomorrow's discussion is the problem in  
6 smaller data sets when movement of a single patient  
7 from one category to another causes you to go crazy  
8 because all of a sudden you've drifted over some magic  
9 margin or confidence interval limit. And it could be  
10 that a Bayesian prior would allow you a little more  
11 buffer in a really small program. The problem in  
12 small programs, how do you get enough buffer against  
13 the stuff happens problem.

14 MR. DANE: So I think it's probably  
15 important that Ed suggests -- you know, there are  
16 different ways we can apply this. So one is the way  
17 Kert was talking where you're borrowing information  
18 across body sites, all in patients, all at the same  
19 time and that might be quite different from what we do  
20 when we're using preclinical PK/PD information and  
21 have to make this leap to a different endpoint.

22 But I guess the common principle is this

1 idea of dynamic borrowing means that to some degree  
2 it's driven by the amount of similarity you have in  
3 the historical data or the prior data and what you  
4 have. But what you can do is then try and understand  
5 how that's going to look. So you can -- to some  
6 degree, you can limit how strong that prior is going  
7 to be, you know, by the uncertainty you impose on it.

8 But also, then that's when you can start to  
9 look at different scenarios at the design stage and  
10 then make sure you're happy with what you end up with.  
11 You know, since it's to ensure that the prior doesn't  
12 overrule the data or something like that. So a lot of  
13 this is possible. It's just being clear when you're  
14 setting it up that you have to know how it's going to  
15 look and then it's not going to undermine all the  
16 conclusions at the end.

17 DR. VIELE: At the risk of perhaps saying  
18 something different again, you're talking about tiny,  
19 tiny, tiny sample sizes with your last question. So I  
20 think that becomes a qualitatively different problem.  
21 If you're talking an example like Dan was giving,  
22 there's a lot of control data that can bring to bear

1 on your --

2 DR. REX: [Inaudible, off mic.]

3 DR. VIELE: Right, yeah. So we're talking  
4 if you're smaller than that, the nice thing about any  
5 kind of dynamic borrowing is the ability of the model  
6 to make an assessment over are the assumptions valid  
7 and adjust to that. When you get down into the sample  
8 sizes as small as you're talking about, you know,  
9 three, four, six patients, there's not enough data to  
10 assess that.

11 And I think -- I'll let you weigh in as well  
12 -- I think at some point if you're going to weight  
13 prior information at all, you have to come up with  
14 some weight in advance. And you need to understand  
15 your study well enough to understand the risks. But I  
16 don't think you have enough information to dynamically  
17 assess that during your study. And then, it's a  
18 question of the Bayesian methodology that's intended  
19 to bring in all the information. But if you've made  
20 an assumption that's wrong, it's going to lead you in  
21 the wrong direction.

22 DR. COX: And then, over to the microphone,

1 if we can. Thomas, did you want to follow up  
2 immediately or --

3 AUDIENCE MEMBER: Yes, I --

4 DR. COX: Okay. To the microphone?

5 AUDIENCE MEMBER: Flick Gabray [ph]  
6 transcript. I have a question in that really what we  
7 seem to be doing here is we are going from a  
8 homogenous group into a heterogeneous group  
9 potentially even when we're looking at very small  
10 sample sizes. And I would like to go back to what  
11 Aaron said earlier on about matching and case controls  
12 because a lot of the data we have from PK/PD and from  
13 our early data is from very homogenous patient sets  
14 and our biggest challenge, even with the modeling,  
15 when we come to Phase III data is however much we  
16 drill down in our multiple logistic regression, we  
17 often end up with very small numbers of patients.

18 And we did a study back in the '90s in  
19 SmithKline looking at the impact of some of those  
20 confounding variables on the outcome of infection.  
21 And it was much greater than the impact of the  
22 antibiotic. And Helen will identify with this,

1 relating to the endocarditis study, and we go back to  
2 Ed's issue right at the beginning around how in  
3 serious bacterial infections the confounding variables  
4 become more of a challenge and the much more difficult  
5 to identify into putting them into our prior analyses.

6 So I wonder whether you have in small data  
7 sets a way of dealing with this. I work a lot in drug  
8 safety and in very large data sets we have means of  
9 dealing with it. But in these kind of small data  
10 sets, how do we deal with these very big confounding  
11 variables like patients who have COPD in HAP compared  
12 to those who are relatively -- have relatively fit  
13 lungs?

14 DR. COX: Any takers on that one? Aaron?

15 MR. DANE: Only to say my suggestion of  
16 matching relies on there being a data set to match to,  
17 which we haven't got at the moment. So that's  
18 probably a much longer term aim that would have to  
19 come from a network in many years' time because at the  
20 moment we are struggling to find external data to try  
21 and put what we're finding into context.

22 AUDIENCE MEMBER: Well, with the -- just to



1 come back to that, with -- there are programs in HAP  
2 and so on that we've already entered many patients  
3 into who have HAP. We could go back and look at those  
4 data sets. The agencies could go back and look at  
5 those data sets and we could understand the impact  
6 much better. And I think we haven't been good at  
7 looking in those data sets to understand the impact of  
8 comorbidities which might help us to be able to  
9 analyze much smaller data sets more effectively.

10 DR. COX: Thomas, did you want to follow up?

11 DR. LOUIS: Just a partial answer and that  
12 is that you have -- for all of these, I think we have  
13 to think of it in the context of as compared to what.  
14 And what I mean by that is the Bayesian approach isn't  
15 going to be magically solving these problems. But the  
16 non-Bayesian approach or set aside Bayes isn't going  
17 to solve them either if you have lots of complications  
18 of heterogeneity of patient attributes but essentially  
19 no data, then you have to do something.

20 And at least for me, a strategy of having a  
21 discussion about if there are any data that are  
22 relevant, build a model with those and build in it the

1 opportunity for people to be individualized as data or  
2 as a group of people to be individualized as  
3 information builds up so that early on -- and what I  
4 mean by that is early on either in a set of studies  
5 for one individual or as data accrue for individuals -  
6 - you'll be using as your curve or whatever it might  
7 be the -- whatever your best guess was a priori.

8 But you will then, as time goes on, be  
9 giving more weight to the direct evidence as the  
10 direct evidence needs less help. And this is part of  
11 that dynamic weighting where the model gives the  
12 opportunity for the direct evidence as it becomes more  
13 stable to be given more weight. And I'm not saying in  
14 this case you described this is going to be magical  
15 because if there's no information, there's no  
16 information. But it's no worse than having no  
17 Bayesian formulation and it may be a little better if  
18 you can even just have expert opinion give you a good  
19 start if that's all you've got.

20 DR. COX: Okay. I was going to go to John.

21 DR. TOMAYKO: Yeah. Thanks, Ed.

22 DR. COX: Yeah.

1 DR. TOMAYKO: John Tomayko, Spero  
2 Therapeutics. I have two comments, kind of related.  
3 First, as a former sepsis researcher, I just sort of -  
4 - I like this idea of matching that Aaron brings up.  
5 But I think about what happened in the last 10 or so  
6 years with sepsis, which is pretty amazing actually.  
7 You know, Xigris comes on the market for a short  
8 period of time and they start surviving sepsis with  
9 this mandate of reducing mortality in severe sepsis by  
10 25 percent over five years. And I was sitting there  
11 when that first came out thinking, wow, that's a  
12 pretty tall order. I guess they really think this  
13 Xigris stuff is going to be great.

14 But it wasn't necessarily the Xigris because  
15 it came off the market and they achieved it just by  
16 getting us to pay quicker attention and more diligence  
17 to starting antibiotics and doing source control,  
18 managing the ventilator appropriately -- even though  
19 that's been somewhat controversial -- and a number of  
20 other kind of standard of care-type approaches. So  
21 that's a pretty hard endpoint and a really important  
22 to me lesson of how much we could really predict, how

1 much heterogeneity is out there and how much could we  
2 really control.

3           But then, the other thing I wanted to maybe  
4 ask because I agree, Dan and Kert's talks were really  
5 great, what's the kind of -- how do we judge -- you  
6 know, what's the measure that we're going to judge on  
7 or agree that this is the right prior weighting we  
8 should give. I mean, there has to be some sort of  
9 formula, and I'm going to stick my neck out and say,  
10 you know, we're always concerned about type one error.  
11 But I don't understand how you're going to handle it,  
12 what does the context of one type of error mean, means  
13 change somehow when you weight things differently or  
14 what's -- so could somebody help me understand that  
15 point?

16           DR. VIELE: I'll definitely take that one.  
17 So I think that's an incredibly important question and  
18 a key thing that happens when we design trials in this  
19 way, we don't want to change the definition of what  
20 makes a good trial. The goal -- I mean, so issues  
21 like type one error, power, to the extent that they  
22 were valuable yesterday, if you switched the design,

1 you can evaluate it. I certainly didn't show them.

2 But we have -- we have type one error rates  
3 for this design. You can see situations where it  
4 reduces type one error and situations where it raises  
5 it. And you can weigh how often that happens. But we  
6 would assess these kinds of trials the same way we  
7 would assess any others, which is given a certain  
8 treatment effect, what is the probability that you  
9 make the right decision. We may, as we go forward,  
10 want to adopt an approach where we are maybe a little  
11 more utility patient-centered, you know, what  
12 proportion of the population do we treat well. That  
13 may be possible.

14 But we could assess a frequentist trial or a  
15 Bayesian trial by that same way. So in effect, we  
16 perform the same calculations. And so, I mean, one --  
17 I didn't show it, but largely this sample size savings  
18 comes about by being able to get the equivalent type  
19 one error and getting more power out of the design and  
20 then being able to reduce the sample size. So  
21 definitely don't want to change the definition of what  
22 makes a good trial.

1 DR. COX: Okay. Well, why don't we do this?  
2 I know there's one person over here at the microphone  
3 and there was another person there and if your  
4 questions have been answered, that's fine. But let's  
5 go ahead and take a break. We're at 3:16. We were  
6 supposed to go 3:10 to 3:30. So why don't we go  
7 until 3:35 and then we'll come back and the person at  
8 the microphone over here, we'll start with you at the  
9 next session. You'll help kick us off with the next  
10 portion of the program. Thank you very much. See you  
11 at 3:35.

12 [WHEREUPON, the foregoing went off the  
13 record at 3:17 p.m., and went back on the record  
14 at 3:43 p.m.]

15 DR. COX: All right. I'll ask that folks  
16 move towards your seats. We'll get going here in just  
17 a minute. And maybe while folks are moving towards  
18 your seats, out at the registration table, you'll find  
19 a copy of a case that we'll discuss tomorrow as part  
20 of the workshop tomorrow. So you may want to grab a  
21 copy of that and read it tonight. It's fairly  
22 complex. And thanks to John Rex and a group of others

1 that contributed to putting that together. It's meant  
2 to be a challenging example to help illustrate some of  
3 the issues that need to be worked through if you have  
4 a drug that targets a single species and that species  
5 occurs relatively infrequently.

6 And just so folks know too, the slides from  
7 today -- and I believe the case that we'll talk about  
8 tomorrow -- are posted on the Web and on the back of  
9 your agenda, you'll see the Web address if you want to  
10 find those materials. I'm not sure if things -- I  
11 don't think things are up for tomorrow yet. But --

12 DR. NAMBIAR: For tomorrow they are.

13 DR. COX: For the slides?

14 DR. NAMBIAR: The slides are --

15 DR. COX: Okay.

16 DR. MARKS: A fair bit of tomorrow's stuff -

17 -

18 DR. COX: Well, I think everybody's slides  
19 except my own are up for tomorrow.

20 DR. MARKS: The intro material is up.

21 DR. COX: But you'll also find slides there  
22 at that same website and after I get mine, I'm sure

1 they'll be up there too. And I think that's it for  
2 the announcements. And folks are back, so that's  
3 good. And I think at the microphone over here just  
4 before we broke, I think Todd Black, from Merck, had a  
5 question for the group. So, Todd, go ahead.

6 DR. BLACK: Yeah, so earlier today we were  
7 talking about how best available therapy can evolve  
8 very rapidly. So I'm just trying to understand in the  
9 context of a platform-type study, if we're going to be  
10 doing this, you know, longitudinally over time, how do  
11 we account for then those potential differences in the  
12 control group, and I think also in the context of what  
13 we just talked about in the colistin example, it was  
14 really about trying to modify our understanding of the  
15 control response rather than the treatment response in  
16 that case. So you know, how do we bring a Bayesian  
17 component into that when it really could be truly due  
18 to an evolution in the population in the control set?

19 DR. COX: Does anyone want to try and grab  
20 hold of that one? Kert?

21 DR. VIELE: I'll start. It's a little bit  
22 traumatic to a trial when the control arm changes.



1 This certainly has happened to I-SPY recently with I  
2 think pertuzumab, which it's going through that kind  
3 of change. If you're talking about a trial network,  
4 there are some advantages, especially if the new drug  
5 -- if your network is large enough that the reason  
6 you're changing control arms is because of a drug that  
7 was in your network, you have the particularly nice  
8 setup where you already have data on that drug within  
9 your network.

10 So you can do it a little more seamlessly.  
11 But there's absolutely going to be challenges. I'm  
12 not sure they're any more challenging than starting  
13 new trials with that. But certainly you'd have to  
14 make adjustments and you'd have to update -- you know,  
15 update forms and everything else that goes with it.  
16 It's an uprooting experience, but it can be -- it can  
17 be accomplished.

18 DR. RUBIN: I would say that -- oh, sorry --  
19 that the ability of a platform trial to anticipate and  
20 plan ahead from when one of the arms may become the  
21 standard of care and change the control group is  
22 actually a big advantage of studying drugs in a master

1 protocol and being able to prospectively plan for  
2 those whereas if separate sponsors are conducting  
3 individual trials and not knowing when a different  
4 sponsor may win or when the standard of care may  
5 change, that that would be something that would be  
6 harder to implement.

7 DR. COX: Okay. And Aaron?

8 MR. DANE: Yeah, and I would just add the  
9 Bayesian component to that is probably less of the  
10 issue because this is true whatever analysis you're  
11 doing. If that happens, you've still got to handle  
12 that same problem that, you know, halfway through  
13 certain comparisons. But as Kert said, you know, you  
14 can handle that with the data you're generating as an  
15 externality in that study.

16 DR. COX: Okay. And then, over here at the  
17 microphone -- and just so folks are aware, at 3:30,  
18 we're supposed to have public comments. So after this  
19 question at the microphone, if there's anybody who  
20 wants to make public comments, we have a little  
21 session then and then we'll go back to the discussion  
22 after we've completed that. So please introduce

1 yourself at the microphone on my right.

2 MR. WEBBER: Yeah. My name is Frank Webber.  
3 I'm an independent consultant from Europe. I want to  
4 come back to Dan's wonderful case. What I saw on the  
5 chart is a mortality rate of 50 percent -- what I saw  
6 on the chart was a 50 percent mortality rate in that  
7 infection. And given the statistics he gave us, to  
8 bring it down to 40 percent, you would need 385  
9 patients for a superiority trial. And I think  
10 everybody admits that 385 patients in such an  
11 infection, to show that mortality is a no-go because  
12 it's not recruitable. It's an 800-patient study. And  
13 everybody I think would admit that going to 40 percent  
14 mortality in that infection would be an advancement of  
15 care. And the question then is how much more are this  
16 panel or the FDA willing to accommodate Bayesian  
17 borrowing to the control group to allow an  
18 augmentation treatment to get down to 40 percent and  
19 have an approval of being an effective augmentation of  
20 colistin or whatever.

21 So in other words, colistin, having 50  
22 percent, the erratic add-ons not being much better,

1 but a new drug would give you 40 percent. How would  
2 you try to develop that drug and what type of  
3 statistics would you allow being borrowed from  
4 historical control groups, matched control groups and  
5 perhaps from the active arm through a Bayesian  
6 approach.

7 DR. COX: You want to do that one Aaron?

8 MR. DANE: Well, I won't speak -- I mean,  
9 Kert's done a lot more on this than me. But this  
10 comes down to this question of whether you can use  
11 external controls, I think, could help to some degree.  
12 So if you're in a situation where you've got some  
13 recent trials that are conducted in a similar way,  
14 then you could borrow some of that information and, I  
15 mean, I know Kert's done some work on augmenting  
16 control designs which do borrow that information in  
17 some way and reduce the burden of the study. I don't  
18 think that's going to help us when we're talking about  
19 40 or 50 patients. But it may do when we're talking  
20 in the 100 or 200 patients.

21 DR. RUBIN: Yes. An intervention that  
22 reduces the mortality rate from 50 percent to 40

1 percent is kind of an interesting example because, on  
2 the one hand, it would be a very major benefit in  
3 terms of saving the life of 1 out of every 10 subjects  
4 in terms of number needed to treat. But on the other  
5 hand, the sample size tables show that the randomized  
6 trial would become very difficult, but also the  
7 treatment effect of 50 to 40 isn't so large that in a  
8 nonrandomized comparison you wouldn't be worried about  
9 confounding and whether selection effects outweigh  
10 treatment effects. So I think that's kind of why  
11 we're talking about this today.

12 DR. COX: And John Rex?

13 DR. REX: So the generalized question, as I  
14 heard it, was if the mortality for your best therapy  
15 is 50, 60, 70 -- sorry, excuse me, if the survival --  
16 if the mortality is 50, 40 or 30 and you want to show  
17 a reduction by from 40 to 30 or from 40 to 20, right -  
18 - so that's the question -- by adding something on.  
19 And your question was not about a different therapy  
20 but about an add-on. Is that correct? It was about a  
21 --

22 MR. WEBBER: [Off mic] -- replace what you

1 have with colistin, you have already to go to this --  
2 [off mic] -- leave out colistin, take my new drug and  
3 the --

4 DR. REX: Okay.

5 MR. WEBBER: [Off mic] -- it doesn't address  
6 unmet medical need. If the patient is dying -- how  
7 about when the patients are dying and I think the  
8 unmet medical need is getting down.

9 DR. REX: Right, so --

10 MR. WEBBER: [Off mic] -- you do it in heart  
11 failure. You do it in oncology. You do it -- I know  
12 you augment as long as it's tolerable and then you'll  
13 have incremental benefits, whether you're --

14 DR. REX: Right. So it's really important  
15 to separate the case of augmentation, as you're  
16 saying, standard of care versus standard of care-plus  
17 as opposed to new drug versus old drug. So the case  
18 of standard versus standard-plus, you phrased it as if  
19 the question was what will the FDA accept. I'm going  
20 to argue that that question is incorrect and that it's  
21 not -- you know, what the FDA accepts or not is, in a  
22 sense, irrelevant. If you can't -- if FDA approves

1 it, if it's available on the market, you still have to  
2 go to a payer and say, all right, you should pay me  
3 \$10,000 for this and they're going to say why, show me  
4 why.

5 And if your answer is sort of a collection  
6 of sort of stray bits of data that you assemble into  
7 an argument, you're not going to get your \$10,000.  
8 You're going to have to show on something that's  
9 really, really clear why you should pay on top of.  
10 It's different from instead of, A versus B. It's  
11 different from A added onto B.

12 And I think it's really important to be  
13 aware of that. You know, we're doing pricing and  
14 payer arguments around the world right now and I can  
15 just tell you flat out that you're not going to get  
16 anybody to reimburse for an add-on unless you have  
17 some very strong data to say why you need to do the  
18 add-on. And in cardiology, they do that. You know,  
19 you generate large data sets. So you know, I'm just  
20 telling you the reality as I have faced it in, you  
21 know, recent days, weeks and months.

22 DR. COX: Yeah, and maybe just to follow up

1 on it, I think, you know, people, patients, everybody  
2 in general would be interested in a drug therapy that  
3 can reduce mortality by, you know, 10 percent. I  
4 mean, there's no question about that. And I think  
5 really what this workshop is about is how do you work  
6 through some of the challenges that are faced in  
7 demonstrating such a finding.

8           And you know, we talked some about this at  
9 the break. You know, this point in time where  
10 colistin might be best available therapy for some  
11 patients we hope is time-limited. And you heard, you  
12 know, some experiences with trying to show  
13 superiority. It's not easy. So I think that's why  
14 we're talking about some of the options which you  
15 might utilize here, whether it be, you know, trying to  
16 study the drug in non-inferiority setting where you  
17 can understand its safety and efficacy, the trial's  
18 feasible. You can gather some PK data. Maybe you can  
19 enrich for some sicker patients and that might be a  
20 pathway to study for a drug. When you've also heard  
21 some of the discussions about, you know, Bayesian  
22 approaches, how you might use them.



1           So I don't know that we can specifically  
2 answer your question. But I think that's what we're  
3 trying to get at here today, which is, you know, what  
4 are some of the feasible approaches. How can you  
5 actually, you know, develop this drug, study it in a  
6 way so that it can be available to patients.

7           Other questions, thoughts on this particular  
8 issue? And then, we'll open it up for the public  
9 comment period. And maybe I'll just move towards  
10 that. Is there anyone who does want to make a  
11 specific public comment at today's workshop? If you  
12 do, I will pause for a minute as you start making your  
13 way towards the microphones. Everybody can just take  
14 a deep breath for a moment.

15           PANEL DISCUSSION 3 (COVERING ALL TOPICS)

16           DR. COX: Seeing no takers, I guess we will  
17 move on. Any questions that folks want to pose,  
18 either on the panel, topics for discussion? Lynn,  
19 you've got a question. But I -- at the -- nope,  
20 you're just working your way towards the seat or did  
21 you have a question at the microphone?

22           MS. KEANE: No, I was ambivalent about

1 whether I wanted to ask it or not. Anne Keane from  
2 Achaogen --

3 DR. COX: Just please get a little closer to  
4 the microphone so we can all hear you.

5 MS. KEANE: Okay. Anne Keane, from  
6 Achaogen. Dr. Cox, in the beginning of June, you were  
7 at BIO and you had made a comment that if the LPAD  
8 legislation passed, the division would feel that that  
9 would give you greater flexibility to approve drugs  
10 for rare, very serious pathogen studies, that it would  
11 give you more flexibility because you'd be able to  
12 take into consideration the risk-benefit of the drug.  
13 And unfortunately, as of today, from what I've heard,  
14 the LPAD legislation is stuck, made it all the way  
15 through the House, made it all the way through the  
16 Senate subcommittee and now it's attached to an  
17 innovations bill that Patty Murray is holding up  
18 unless she gets a guarantee of \$8 billion a year for  
19 NIH. So it may go nowhere.

20 So what I'm wondering is given everything  
21 that we've heard today and kind of acknowledgement I  
22 think from most people that there is an unmet need,

1 that these patients have a very high mortality rate  
2 and there are lots of creative ideas about things that  
3 we can do moving forward, but those ideas are all  
4 going to take years probably to come to fruition, and  
5 there is subpart E regulations which talks about using  
6 the broadest regulatory flexibility when you're  
7 reviewing NDAs for drugs, for patients with severe,  
8 life-threatening infections, instructs FDA to consider  
9 risk-benefit to allow greater uncertainty and also  
10 gives or suggests at least that FDA work with sponsors  
11 to agree on post-marketing commitments that could  
12 collect additional data to increase the knowledge  
13 about the drug and the risk-benefit.

14 I'm wondering if in the absence of a  
15 functional Congress if FDA can rely on the existing  
16 regulations that give you that flexibility and in  
17 particular in settings where you have a pathogen-  
18 focused study in the setting of a separate randomized  
19 control study in another indication.

20 MS. BORIO: [Off mic.]

21 [Laughter.]

22 DR. COX: All right. So maybe I'll just

1 tell you a story. So -- yeah, so without, you know,  
2 commenting on any particular, you know, pending  
3 legislation and that sort of stuff in any sort of  
4 direct way, so the question that Anne asked me when I  
5 was out at Bio was, you know, if LPAD doesn't change  
6 the standard, then what does it do for you. And you  
7 know, we talked about some of the tools that LPAD has  
8 within it where, you know, there'd be premarket review  
9 of promotional materials, a designation of, you know,  
10 a product as an LPAD product so that people would  
11 understand there was a greater degree of risk or, you  
12 know, greater degree of uncertainty and/or risk  
13 associated with a product and that that, you know,  
14 probably would impact upon, you know, how folks  
15 utilize the product out there.

16 So it gives us maybe a little more -- it  
17 gives us some tools to give us some of the potential  
18 risks and/or uncertainty associated with a product.  
19 So I think now you're asking me, you know, how do we  
20 deal with this, you know, situation where, you know,  
21 we're dealing with unmet medical needs and, you know,  
22 there may be products out there where there may be

1 greater degrees of risk and uncertainty. And I think,  
2 you know, what you're seeing and hearing today is  
3 we're really trying to work the best we can within the  
4 tools and situations that we have, you know, to be  
5 able to gather the evidence to understand how these  
6 products worked, how these products work as best as  
7 possible, you know, will -- I think you've heard some  
8 ideas here.

9           And you know, clearly when we think about  
10 product development -- and you'll hear this also  
11 tomorrow too, and that is that there really do need to  
12 be, you know, achievable pathways so that the drugs  
13 that are out there can be developed. You know,  
14 patients, you know, need new options now. We know  
15 they'll need new options in the future. And you know,  
16 we'll continue to try and take, you know, a science-  
17 based approach and do the best that we can with the  
18 tools that we have available to us. So maybe I'll  
19 stop there and hope that that's given you some  
20 insights into your question. David?

21           DR. SHLAES: Yeah. I actually want to go  
22 back to the discussion, if I can, and leave LPAD,

1 between -- with Mike and pharmacometrics a little bit,  
2 just to try and expand on this and maybe, Paul, you  
3 can help with this. But this is something we actually  
4 talked about I think back in 2012 or so, where the  
5 idea was, for example, with meropenem, to take a  
6 practical example, you have a target attainment of 90  
7 percent or something in most patients. Is there -- if  
8 you could then reduce that to what happens in patients  
9 with Pseudomonas infections, in patients with VAP and  
10 you could look at what happens with a Pseudomonas MIC  
11 goes up to eight, you would get then a predicted  
12 control response level which would -- which -- and the  
13 question is how robust could one make that in terms of  
14 using it to establish or contribute to a dataset of  
15 external controls for the kinds of things we're going  
16 to be talking about tomorrow. So I guess that's --

17 DR. AMBROSE: Sure. Most of the clinical  
18 data sets, since many of the drugs don't -- are not  
19 frank disasters, right, there's not lots of exposures  
20 that approach zero -- our confidence bounds on those  
21 relationships get quite wide as we go from the upper  
22 asymptote down, the exposure-response function. And

1 that's the -- that's the main problem with those  
2 relationships. And that's why we've, you know, done  
3 things like bring in the preclinical data to help  
4 inform that slope. But that's been the problem with  
5 them.

6 DR. SHLAES: Yeah. Okay, so the answer is  
7 that the existing data, including the PK -- sparse PK  
8 from the Phase III trials does not provide enough -- a  
9 robust enough dataset to really use that way. Is that  
10 right?

11 DR. AMBROSE: At least in individual trial.  
12 I don't know. Maybe you could do something by looking  
13 at a bunch of different trials.

14 DR. SHLAES: Multiple trials. Yeah, that's  
15 -- so something I've asked the Agency. I mean, have  
16 you guys ever tried to look back at those data in the  
17 -- because, I mean, you have access to all the data.

18 DR. COX: Yeah, so we have. I don't know if  
19 any of our clin pharm folks are here. But they have  
20 looked back. I mean, it's come up in the area of  
21 pediatrics in particular, where, you know, we've tried  
22 to go back and look at the data. And I think that

1 sometimes the data that we have is not what people  
2 think we have. And it hasn't been quite as rich a  
3 resource as we might have hoped that it would have  
4 been. But we have tried to do that, particularly in  
5 the area of biothreat agents. So you know, we may not  
6 have quite as much as you think we have. So, but we  
7 have tried. We have tried to do it in some areas.

8 DR. MARKS: I think John wanted to go next.

9 DR. REX: So that question made me ask --  
10 made we wonder about the question of is there a  
11 generalized framework under which you approach the  
12 question of constructing a Bayesian prior. And you  
13 know, like in benefit-risk, there's these semi-  
14 quantitative benefit-risk analysis tools that are  
15 supposed to help you at least document your reasoning  
16 as to how you get to, you know, conclusion X. And it  
17 feels to me like one of the issues with the Bayesian  
18 thing, or Bayesian prior is that at some point it  
19 involved making a choice. You know, is the number 65?  
20 Is it 62? Is it -- you know, what's the shape of the  
21 prior.

22 And I'm just -- is there a general approach



1 to that that has ever been developed? You know, how  
2 is it done such that everybody, you know, understands  
3 the tradeoffs that went into it and the documentation  
4 of same and sort of does it the same way the next time  
5 for a case that's got some of the same features? How  
6 do you do it?

7 DR. LOUIS: Good question. The answer, I  
8 think, is both yes and no. The yes part is that  
9 there's a fairly developed literature on eliciting  
10 prior opinions, not necessarily based on empirical  
11 evidence; possibly so, but a process to have a group -  
12 - either an individual or a group or individuals come  
13 up with their individual priors and then decide  
14 whether you're going to simply do a mixture of those  
15 or take each of them on their own and do a sensitivity  
16 analysis. But the process for doing that is pretty  
17 well developed, not that there isn't work that can be  
18 done.

19 For empirically based priors where the  
20 information -- excuse me, the opinion part may be  
21 mostly on what data are relevant, Dan and Kert may  
22 have something different to say. I don't think it's

1 very well formalized, any more formalized than our  
2 using those same data sources to decide on the design  
3 of a study in terms of baseline rates, this, that and  
4 the other thing. So there may be some general  
5 principles. But I don't know of anything that could  
6 be approximating an algorithmic approach. But I'll  
7 turn it over to the other side there.

8 DR. VIELE: I think the answer for us is  
9 largely no. What we tend to do in practice when we  
10 design trials is we may elicit. But more than likely,  
11 we look at the available stuff and we do custom priors  
12 for each individual project. So I know of no piece of  
13 software that -- I mean, there are pieces of software  
14 that will elicit priors, but will not design a  
15 clinical trial for you. What we tend to do is to try  
16 to stress test our designs in a lot of detail. And  
17 essentially we go back to operating characteristics.  
18 If we use this prior, here is how well it works under  
19 a variety of assumptions.

20 So if your prior belief accurately reflects  
21 the world, here's the advantage that you get from  
22 using the prior because it's giving you good

1 information. If your prior doesn't match the world,  
2 here is the risk that you are taking by incorporating  
3 that prior if in fact it is wrong and it becomes a  
4 risk-benefit to the sponsor of I know under what  
5 situations I'm going to get a benefit from using this  
6 prior and I know under what situations I'm going to  
7 take a risk. And then, it's a question of how much do  
8 you believe it.

9 DR. REX: Are they using expert elicitation  
10 in any of the I-SPY, lung map, any of these platforms?  
11 Do they put that in place up front or is that a  
12 strength or a weakness of platform trials to be able  
13 to do that?

14 DR. VIELE: I-SPY -- I should be careful. I  
15 don't know every detail of I-SPY. But by in large, I-  
16 SPY uses non-informative priors. And it is Bayesian  
17 from the standpoint that the accumulating data within  
18 the trial is used to update those priors. But there's  
19 not expert opinion going in up front. It's the fact  
20 that after you've enrolled a couple hundred patients,  
21 that data is used to update.

22 DR. LOUIS: If I could, I'd like to use that

1 to segue to another benefit of the Bayesian formalism,  
2 setting aside the issue of priors and in fact sticking  
3 with let's say uninformative priors. For both basic  
4 and complicated settings, you get to use the laws of  
5 probability to make your inferences, and especially  
6 for a nonlinear model and so on. You're no longer  
7 doing Taylor series and plugging things in. You're  
8 letting the full uncertainty percolate its way through  
9 the system and frequently ending up with more  
10 uncertainty than you would as a frequentist. It's not  
11 always an uncertainty win. It's always, or almost  
12 always a validity win. And it also is very effective  
13 at addressing nonstandard goals. And I'll just  
14 mention one.

15           If you're ranking things, whether it be  
16 drugs or small area disease rates, it actually isn't  
17 best to simply take your point estimates however you  
18 produce them and rank those. One of the nice things  
19 about the Bayesian structuring is you say if I only  
20 knew those underlying parameters, if I had them in my  
21 hand, how would I rank them? Well, I'd put them in a  
22 line, small to largest. I don't get to see them, but

1 what I do get to see is the posterior distribution of  
2 them. And I can do what is a nonstandard computation  
3 to get the best ranks and the associated  
4 uncertainties. It's just one example where it's very  
5 hard to even know how to think about that without the  
6 Bayesian formalism, not necessarily the Bayesian  
7 philosophy, if you'd like, you know.

8 DR. COX: Yeah, Kert?

9 DR. VIELE: Yeah, very quick follow-up. In  
10 terms of when we say Bayesian methods, we design, you  
11 know, a hundred trials a year. By in large, almost  
12 all of ours are non-informative priors. We use  
13 Bayesian in terms of how to use the data that's coming  
14 into the trial as it accumulates more than in the  
15 sense of incorporating these extra pieces of  
16 information prior to the trial. So there's just  
17 another way to use Bayesian methods.

18 DR. REX: Because I think that in this  
19 particular area, what we're faced with -- if you look  
20 at the handout for tomorrow, you're going to see  
21 there's this hypothetical drug that we've, you know --  
22 it's actually pretty close to some real cases. But

1 the sense you have going into Phase III is that it  
2 does what all other antibiotics do. It seems to kill  
3 bacteria and it works in a variety of models in  
4 animals and even in a little version of a human being,  
5 or sorry, version of a human illness.

6 And so, you have this belief going into  
7 Phase III that, you know, it probably will do  
8 something. And so, I guess what you're saying is that  
9 there's not a standard way of taking that, the  
10 observation that you'll see in the handout and turning  
11 it into some sort of an informative prior as opposed  
12 to an uninformative prior.

13 DR. VIELE: I think that in general would be  
14 very hard.

15 DR. REX: Yeah.

16 DR. VIELE: I think this gets back to what  
17 Ed was saying. You know, if there was a long history  
18 of here is the data that I had prior to a number of  
19 trials and here is how this evidence translated into  
20 my clinical endpoint, you could do a lot with that.  
21 But I'm not sure -- I'm not sure we're there.

22 DR. REX: Well, but in fact, those data do

1 exist because that's the domain of Paul Ambrose. You  
2 know, all of that still -- like the little picture you  
3 showed just this morning, Paul, of the likelihood of  
4 Phase III efficacy success based on where you were in  
5 your preclinical PK -- where your actual pharmacology  
6 came out on the doses on the exposure-response curve.  
7 So in effect, that exists. One of the -- maybe one of  
8 the stepping stones.

9 DR. COX: I think Aaron?

10 MR. DANE: Yeah. I mean, that starts to  
11 inform I guess what we would have to look at is the  
12 uncertainty around that and what the prior  
13 distribution would look like because the numbers are  
14 small, just because there haven't been that many  
15 development programs. And it gives some comfort, but  
16 I'm not sure how much it would help in terms of an  
17 informative prior.

18 DR. MARKS: Sam?

19 DR. BOZZETTE: Well, I think it is an  
20 informative prior because I think that's what  
21 Ambrose's presentation showed us. I mean, it showed  
22 us we have some failed programs and when we went back

1 and looked, there was an informative prior that either  
2 people chose to ignore or that we discovered  
3 afterwards. So I do think that there are informative  
4 priors. I don't think we have a lot of examples --  
5 and we can come to those -- of clinical trials that  
6 failed because of sunspots or some unexplained  
7 phenomenon in the universe.

8 I think that's been the lesson over the last  
9 few decades is that we've had -- we've learned a lot  
10 about doses and we've learned a lot about exposure-  
11 response relationships that a lot of these sort of  
12 failed trials are rooted in that area where I believe  
13 those priors are going to be extremely important in  
14 terms of structuring our priors for clinical trials.

15 MR. DANE: I think the point is, Mike, that  
16 it depends whether you want your prior to be elicited  
17 or data-driven or empirical because if you elicit it,  
18 you can make that comment. But if it's more data-  
19 driven or you're using the numbers you've got, that's  
20 where there's a lot more uncertainty, because the  
21 numbers are small. You know, we haven't got many.  
22 We've only got -- I can't remember the numbers now,



1 but a relatively small number of approvals or failed  
2 studies. So yeah, normally we'd ideally want the  
3 prior to be driven by the data rather than  
4 elicitation, if we can. And there's still uncertainty  
5 there just because there's not a lot of data there to  
6 do that with in terms of drugs that have been approved  
7 or haven't.

8 DR. MARKS: Sam, we'll bounce back to you,  
9 then --

10 DR. LOUIS: I think the very act of going  
11 into Phase III means somebody thinks something good  
12 has a reasonable chance of happening. Otherwise, I  
13 can't imagine going into Phase III. And it might be  
14 the prior. But it might also be the industries' or  
15 the government's or somebody's utility that even with  
16 a relatively broad uninformative prior, the win would  
17 be so big if we got it that it's worth doing. So I  
18 think we need to -- can't unlink priors from utilities  
19 basically. And some combination of those makes it a  
20 good bet I guess is the way to put it.

21 DR. MARK: One more time, Sam.

22 DR. BOZZETTE: My prior is that there's a

1 lot of information about priors out there. And even  
2 in -- even in failed trials, you know, there's  
3 information in the control arm and especially in the  
4 context of a platform trial looking at, you know,  
5 informing estimates of the effect in the control arm.  
6 It seems to me that there are a lot of studies out  
7 there that could be used to do that. So I don't think  
8 -- I mean, it's certainly PK but I think clinical data  
9 is there.

10 It's just going to take a specific effort to  
11 pull that stuff together. And I don't know if you do  
12 that through agency, you do that through -- well, it  
13 was mentioned at lunch a big data effort from clinical  
14 databases, you know, the large clinical databases or  
15 of it's done by a consortium of companies looking at  
16 their own trials. But there's an awful lot of  
17 information out there on what happens in standard  
18 therapy.

19 MR. DANE: I don't think that needs to be  
20 Bayesian. I think we should just do that anyway,  
21 irrespective of the analysis approach you're going to  
22 take. You know, there's an element of this, well, we

1 should try and pull together the information we have.  
2 And then, we'd get into discussions of what's the most  
3 appropriate analysis. But all of that's going to  
4 inform whatever we do and however we do it, I would  
5 say.

6 DR. MARKS: John?

7 AUDIENCE MEMBER: Yeah, I thought that was a  
8 nice comment that Sam made, that there's a lot of  
9 prior out there. But I also think there's a lot of  
10 heterogeneity out there that I worry about. And you  
11 know, maybe my memory doesn't serve me correctly. But  
12 I think when doripenem came to an ad com, the first  
13 time around, it was like a 500 mg three time a day  
14 dose and they did what I thought was the first study  
15 in VAP patients, the DORI-10 study. And if I recall,  
16 they met the endpoint. But there were some issues and  
17 we were changing endpoints. It was a clinical cure  
18 endpoint. But there were some issues.

19 And then, they went out and, probably for  
20 good reason that wasn't disclosed that I know, doubled  
21 that dose and failed to even complete a study because  
22 it stopped for futility. So I mean, I don't know. I

1 know that getting the dose right is important. But  
2 Paul talked about augmented renal clearance and I  
3 heard about that. You know, that's a hard thing to  
4 study ahead of time. Yeah, you could go to an ICU  
5 population and maybe do some BALs and whatever. But  
6 there's just a lot of variability in exposure that  
7 you're going to see in your patients. It's hard to --

8 DR. BOZZETTE: Yeah, but there are millions  
9 -- let me just say there are millions of cases out  
10 there, not only -- I mean, if one wants to -- you can  
11 look beyond the clinical trials even and look at the  
12 large EMR datasets to get some sense of what happens  
13 with these patients. And they have things like  
14 creatinine clearance and some other things. It's  
15 certainly not PK data. But it's things that you can  
16 make inferences from, you know, and comorbidity  
17 information, labs, et cetera, et cetera. So I think  
18 both within clinical trials and in large, you know,  
19 EMRs, that there might be some potential. Sorry to  
20 interrupt.

21 DR. AMBROSE: So even with the doripenem  
22 higher dose study, right, it was a gram every eight

1 hours and it was over a four-hour infusion. So the  
2 steady-state drug concentration for a four-hour  
3 infusion on average for doripenem would be 16 µg/mL.  
4 It penetrates about 25 percent of the epithelial  
5 lining fluids, so let's just make the math. Should we  
6 drop it to µg/mL? And then you throw on 60, 70  
7 percent variability on clearance and volume. You end  
8 up with people approaching drug exposures of zero  
9 again. I don't -- you know, the dose wasn't high  
10 enough. It's just -- it's the variability. It's what  
11 gets you.

12 AUDIENCE MEMBER: But the first time the  
13 dose did not -- [off mic].

14 DR. AMBROSE: No, it wasn't good enough. It  
15 didn't get approved.

16 AUDIENCE MEMBER: It didn't get approved --  
17 [off mic].

18 DR. AMBROSE: No, it had more mortality. I  
19 believe it was with seven deaths in the doripenem arm  
20 and one versus the control or some number like that.  
21 But --

22 DR. MARKS: We'll go to the microphone.

1 DR. BLACK: Yeah, Todd Black, with Merck.  
2 So I think just to point out, all the new drugs we're  
3 talking about today are  $\beta$ -lactams,  $\beta$ -lactamase  
4 inhibitors, aminoglycosides. Having done drug  
5 discovery now for many, many years, you know, what we  
6 would really want, that new agent, new mechanism is  
7 really, really hard to come by. It's not for lack of  
8 trying. So our only solution in the future may be  
9 this adjunctive therapy. So to John's point, that may  
10 be where these priors and understanding or how you're  
11 modeling I guess the add-on on top of an effective  
12 therapy. Does it open up a door for us there to help  
13 us do these developments with an adjunctive therapy as  
14 a primary, as we, you know, get around all these  
15 concerns and questions about combination therapies.

16 DR. MARKS: And I was going to ask a  
17 question about sort of the borrowing piece, to go back  
18 a little bit, borrowing across body sites, how  
19 comfortable we are with, let's say, if we have good  
20 success in intra-abdominal infections, does that help  
21 with HAP/VAP? You might say not very much. But if  
22 you had success with HAP/VAP, would you weight that

1 more heavily in terms of trying to support an intra-  
2 abdominal infection and how people feel about the  
3 different body sites influencing the data more or  
4 less.

5 DR. AMBROSE: I'll take a whack at it.  
6 Yeah, I'd feel more comfortable going backwards from  
7 HAP/VAP. Why would that be? I think when we've  
8 looked at, from a PK/PD perspective, clinical trial  
9 datasets, an intra-abdominal infection requires  
10 something like net bacterial stasis in the animals.  
11 It's a relatively low, low threshold and, generally  
12 speaking, those studies are done at relatively modest  
13 bacterially dense inoculums, right? The pneumonia  
14 studies are done at high bacterial inoculums and,  
15 generally speaking, require more drug.

16 So I do feel that generally speaking, if you  
17 can treat a pneumonia, you probably are going to be  
18 okay in an intra-abdominal infection, assuming, you  
19 know, you're not inactivated in a more acidic  
20 environment or something like that. I'd feel more  
21 comfortable in that direction than the other.

22 DR. MARKS: And how about UTI when it comes

1 to intra-abdominal infections? Because intra-  
2 abdominal infections, I don't know, one-and-a-half,  
3 maybe two times slower to enroll, a little bit less  
4 influence in the antibiotic, more related to the  
5 surgical intervention. If you had a lot more urinary  
6 tract infections, would you be more comfortable  
7 propping up the difficult intra-abdominal infections?

8 DR. AMBROSE: I think a urinary tract  
9 infection, relative to pneumonia, again, is a little  
10 bit easier to deal with, most of them anyways than a  
11 pneumonia. But are you asking me to rank it versus  
12 intra-abdominal infection? You know, we don't have  
13 many exposure-response analyses at all in the urinary  
14 tract infections. It hasn't been a place that we've  
15 done those analyses. My gut instinct is that some --  
16 you know, generally speaking, it's not as high a  
17 threshold as ventilator-associated pneumonia.

18 DR. REX: I'll just add an observation that  
19 we had out of the Avycaz program, which was that if  
20 you take nosocomial pneumonia, intra-ab and UTI and  
21 look at actual physiologic derangements, which one of  
22 the three is the hardest on average in that population



1 to hit the exposure you want, and it turned out that,  
2 at least for that combination, intra-ab was actually  
3 the hardest. You know, and nosocomial pneumonia was a  
4 close second. But intra-ab was really tough.

5 And I think the logic, the best we could  
6 tease it out, was you've got people going to surgery,  
7 you've got deranged volumes of distribution in the  
8 belly. So all kinds of whacky things are happening  
9 with your blood volume. So you know, I guess to  
10 answer your question, I think one of the things I got  
11 out of that was that intra-ab is -- surgery is a  
12 confounding variable. But on the other hand,  
13 pharmacokinetically, it's a very demanding setting. I  
14 just thought that was an interesting observation.  
15 That will be in some one of our papers somewhere, that  
16 that fact was observed.

17 DR. MARKS: Helen, any thoughts?

18 DR. BOUCHER: Yeah, I would just add that  
19 clinically it sort of comes back to something we  
20 talked about this morning. I think the inclusion of  
21 any group of patients certainly with pneumonia, but  
22 also with bloodstream infection, is incredibly

1 meaningful to the clinician. And that's also in this  
2 group where there's a predictable high mortality.

3           So if we see that the new drug works, that's  
4 incredibly useful, especially if the main study is a  
5 UTI study, where I know we get the bacteria. We have  
6 the potential for statistical testing. But  
7 clinically, we're not always comfortable with just UTI  
8 data to take it into that much sicker population.

9           And so, if there's any way to learn that  
10 information in a high quality type of study, like a  
11 registration type of study, even if it's not the whole  
12 study, that's a lot better than relying on a random  
13 publication. And I think in the real world, we're  
14 often -- that's what we get and we get it two years  
15 later, you know, after the approval is publication of  
16 cases -- and again, don't get me wrong. That's my  
17 business. But the high quality data, the patients  
18 enrolled and monitored and studied for safety as well  
19 as efficacy in this kind of setting really does have  
20 power that's important.

21           DR. MARKS: Well, let me draw on that a  
22 little bit more because some sponsors are going with

1 the complicated urinary tract infection studies and  
2 then jumping to a multi-body site, more drug resistant  
3 population. But what's missing in that equation for  
4 you and what -- how could they supplement that package  
5 to get you more interested?

6 DR. BOUCHER: I think that, you know, in  
7 doing that kind of a thing, really important is going  
8 to be the enabling work that enables them to go into  
9 those other body sites and, coming back to Paul's work  
10 and others, to make sure the dose is correct or is as  
11 good as we can estimate. And again, you know, in a  
12 perfect world, we'd have the perfect. But this is not  
13 the kind of thing that's going to lend itself to  
14 perfect. So really good enabling data, really good  
15 ability to describe the patients that are treated in  
16 terms of diagnosis and in terms of outcome, really,  
17 really important. And we didn't get into this today.  
18 But again, from Nick and my earlier life with  
19 aspergillosis, you know, drugs have been approved on  
20 historical controls and that's all about the ability  
21 to describe the population in each individual patient  
22 to ascertain that they really had the infection, to

1 the best of our knowledge, that they had a good  
2 treatment effect.

3 DR. MARKS: So on Sumathi's slide earlier  
4 this morning, she had cUTI, stroke, cIAI or whatever  
5 acronym you used on that slide, as sort of  
6 interchangeable, one or the other. Would you prefer  
7 one or the other in terms of a sponsor coming to you  
8 for running clinical trials? You'd rather have an  
9 intra-abdominal infection program rather than a UTI?  
10 You want both? You want --

11 DR. BOUCHER: I mean, again, I think in a  
12 perfect world, we'd want it all, right? And so,  
13 treating the kind of patients that I treat, I would  
14 always prefer to see some experience in the more ill  
15 patients. But I could see very reasonable approaches  
16 using either. And I think a lot of the pros and cons  
17 have been articulated. You know, UTI, you get the  
18 bugs. It's a more homogenous population.

19 So that's a good thing in some ways. And on  
20 the other hand, in the complicated intra-abdominal  
21 infection, it's a little harder to treat. The  
22 patients are more ill. There's more probably sepsis

1 in that study and things that might, you know, make us  
2 feel more comfortable in a population. But that could  
3 be addressed in other ways if you did the small  
4 pathogen -- the small group study. So I think both  
5 could work.

6 DR. MARKS: So it would be a review point,  
7 just to use the FDA language. Sorry. Ian?

8 DR. FRIEDLAND: So I have a question. I'd  
9 be interested in what Helen has to say and what the  
10 regulatory folks have to say. And this is also again  
11 about prior knowledge. So if you're dealing with a  
12 known class, let's say  $\beta$ -lactams, we know a lot about  
13  $\beta$ -lactams. We know a lot about the PK/PD, versus a  
14 completely new class that has a new PK/PD. Would you  
15 be more comfortable with uncertainty when there's like  
16 a known class of drug, even if it's a new drug versus  
17 like it's a completely new class or are you totally  
18 agnostic of the drug class?

19 DR. COX: So if you think about it, I mean,  
20 the question is at least two-dimensional. And so,  
21 you're asking suppose somebody else comes in with, you  
22 know, another member of the same class. So the level

1 of innovation there may not be huge. It may offer  
2 something that existing drugs don't offer. But it  
3 probably, on the benefit side, is not going to be sort  
4 of something completely different. So I mean, we  
5 would take that level of benefit into consideration.  
6 Is it addressing some unmet medical need? What do we  
7 know about the safety? And weigh those two things.

8 Now, the thing that you are contrasting that  
9 is a wholly new class, something that operates via a  
10 completely different mechanism. I can make good  
11 arguments to accept a fair degree of uncertainty  
12 around that drug because I'm presuming that it may be  
13 able -- you know, it operates via a wholly new class.  
14 So it may, you know, provide benefit in certain patient  
15 populations that, you know, may go beyond what you  
16 could do with a class modification. So you know,  
17 those benefits may be for a particular subset of the  
18 population, not for the population at large. But I  
19 mean, you can argue these situations both ways.

20 So I don't know that there's an answer one  
21 way or another, specifically what's easier, you know,  
22 this way or that way. I think there's -- you know,

1 each of those two molecules -- and these are  
2 hypotheticals, so we don't know exactly what they do -  
3 - you know, has the potential to bring, you know,  
4 either, you know, different levels of benefit, you  
5 know, based on the type of molecule. And then, you  
6 know, the other question is what do we know about  
7 risk. Sometimes you come into your clinical program  
8 with, you know, completely clean animal studies and it  
9 doesn't look like it's provoking much of anything.  
10 And you know, then it looks clean even in the limited  
11 safety database. That doesn't give you guarantees,  
12 but it sure, you know, looks like it's not a big  
13 problem.

14 The flipside is suppose that preclinical  
15 data -- you know, you're starting to see significant  
16 toxicities already and you've seen some of that being  
17 reflected in the patients that you see. So it's very  
18 hard to answer those hypotheticals. But I've outlined  
19 at least some of the things that you might think about  
20 as you're looking at these two different types of  
21 prototypical agents, something from a new class and  
22 something from a wholly new -- or something from a new

1 class versus a class modification. So hopefully that  
2 makes sense.

3 DR. KARTSONIS: So to kind of segue a little  
4 bit more to the safety question, we talked a lot  
5 obviously today about efficacy. But -- and I know the  
6 original streamline guidance spoke to a sort of  
7 specific safety database of at least 300. Has any of  
8 that thinking changed or is it still the assumption  
9 that it's 300 and is there a modification on that at  
10 this point? Just curious on that.

11 DR. COX: Yeah. So the derivation of the  
12 300 number. So if you do 300 patients and you don't  
13 see anything terrible within the 300, the upper bound  
14 of the 95 percent confidence interval I think is 1  
15 percent for that zero number. So that's where the 300  
16 comes from. And, you know, I mean, at some point,  
17 it's just trying to figure out, you know, how much do  
18 you want to know about a drug before it's out there on  
19 the market. You know, the 300 number is one that, you  
20 know, we've sort of turned to and, you know, I don't  
21 know that there's anything magical about it. But it  
22 gets you to a certain level of certainty with regards



1 to bounding risk, you know, before a drug gets out on  
2 the market. Are you suggesting we go higher or are  
3 you suggesting we go lower?

4 DR. KARTSONIS: I was just wondering if  
5 there's been -- because we didn't touch on it today --  
6 I just --

7 DR. COX: Yeah.

8 DR. KARTSONIS: I mean, I particularly think  
9 it's going to be relevant as we speak tomorrow about,  
10 you know, single pathogen because you may be in  
11 situations where you may not be able to get to 300  
12 without --

13 DR. COX: Right. So you're right. We will  
14 talk about it some more tomorrow too. And you know,  
15 while it may be difficult to get that number of  
16 patients with a particular target pathogen of  
17 interest, in the course of, you know, doing what  
18 you're doing in your trial, unless you have a really,  
19 really good diagnostic, you may be able to gather some  
20 safety data from other patients that don't necessarily  
21 have the target pathogen of interest. Their course of  
22 therapy may not be as long, unless you find out they

1 have something else, you might stop the therapy. But  
2 you may be able to gather some additional safety data.

3 So you know, it may -- you know, it may be a  
4 number that still is achievable within the development  
5 program. And you know, if you think about it, you'll  
6 have some, you know, multiple dose studies and, you  
7 know, studies in patients. So you know, I think it  
8 probably is still achievable, even though -- even  
9 though, you know, because you're going to be getting  
10 data beyond just the patient population with the  
11 single species of interest. That's my impression.  
12 I'd welcome thoughts from other people on that too,  
13 from the experiences you may have.

14 DR. LOUIS: So I need to do a methodological  
15 moment. If you see N events in trials, as long as N  
16 is greater than about 15, the upper 95 percent limit  
17 is three over N, no matter what N is. Pretty cool.

18 DR. COX: So did I get the math right?

19 DR. LOUIS: Absolutely.

20 DR. COX: Okay. That's good.

21 DR. LOUIS: N was greater than 15 and three  
22 was -- [off mic].

1 DR. MARKS: Just going back and reflecting  
2 on -- I think John mentioned it earlier in terms of  
3 trying to work through all the pricing and  
4 reimbursement, which I know we don't directly deal  
5 with here, but when you think of statistics and how to  
6 have these kinds of conversations with payers and we  
7 start adding in things like we're borrowing from here,  
8 there and yon, I was on a call recently with some  
9 other pharmaceutical companies talking to a European  
10 pricing reimbursement group, which said essentially  
11 you're telling me that this drug is essentially the  
12 same as what's already approved. How am I supposed to  
13 pay you a premium for that? Now, we're going to have  
14 another complicated situation of trying to describe,  
15 well, we borrowed from here, we borrowed from there.  
16 So I think that'll be interesting times.

17 MR. DANE: Although some of those payer  
18 groups have been doing the Bayesian analysis more than  
19 we have in the regulatory setting. So I'm not sure --  
20 there's still to be worked through the assumptions and  
21 everything like that. But I'm not sure it necessarily  
22 is a huge problem in that some of that's brought in

1 for some of the indirect comparisons that happen and  
2 all sort of other things that tend to happen in that  
3 reimbursement setting.

4 DR. REX: So it wasn't a huge news release.  
5 But about 10 days ago, Sweden announced that it was  
6 going to engage in a two-year pilot program to test a  
7 novel way of buying antibiotics. And the Swedish  
8 model is one of simply paying an access fee on an  
9 annual basis to ensure that the drug is available.  
10 And then, there's -- and they estimate that they will  
11 use a tiny number of courses of the drug. But they  
12 simply want to know that it's available and that it  
13 will be available to them. And there are a couple of  
14 drugs that look like they would be appropriate  
15 candidates for that pilot. And they've said they're  
16 going to figure out how to do that this fall.

17 And I'm close enough to that to know that,  
18 you know, really part of what tips it over there is  
19 that the agents have a very clear-cut -- each one of  
20 them has a very clear-cut thing that it offers and so,  
21 you can articulate it. It's a very clear science-  
22 based story. It's an organism that is otherwise

1 difficult or treats a form of resistance that is  
2 otherwise difficult and the data are really reasonably  
3 good. And that's why I come around to Mike -- there's  
4 another conversation going on in the U.K. about a  
5 model that has a somewhat different structure. It's  
6 an annual fee that includes a number of courses of  
7 therapy. But it's essentially the same thing. It's a  
8 market entry reward. And the same things are tipping  
9 the balance there is that you've got to be very clear  
10 about what you're buying for your money.

11           And it was -- it's been those conversations  
12 that led me to the fire extinguisher analogy to saying  
13 that there's just not going to be a lot of interest in  
14 the same old fire extinguisher. And that's just a way  
15 to articulate what you need to get reimbursed. And  
16 so, you know, it's just kind of part of what you've  
17 got to deal with. It isn't -- because it's inherent  
18 in all of this.

19           You don't buy a new iPod or a new iPad or a  
20 new I-anything unless there's some feature you want  
21 that's not in the one you've got, right? And so, I  
22 just -- I think it's important to keep that in mind.

1 And you know, it's also that bit about statistics,  
2 only show you what you can already kind of see. You  
3 know, that's the -- you know, stats, if you can't  
4 already sort of see it with your eye, you're probably  
5 not going to believe the stats. So I think that's  
6 something else to remember in all of this. We can  
7 buff it up a little bit with statistical calculations.  
8 But fundamentally, it better be something that you can  
9 sort of see in the dataset.

10 DR. BOZZETTE: I guess I would just say that  
11 I'm not sure how diagnostics would fit into the  
12 schemes that John has discussed. But we have to  
13 figure that out or there won't be the kind of  
14 supportive diagnostics that are needed.

15 DR. REX: I a hundred percent agree and I  
16 mention the DRIVE A/B project going on in Europe right  
17 now about the value of antibiotics. There is a DRIVE  
18 D/X that is just now forming up that is meant to  
19 tackle the same problem because I think the  
20 reimbursement issue for diagnostics is at least an  
21 order of magnitude harder than it is for  
22 antimicrobials. And yet, we desperately need you to

1 make good tests.

2 DR. MARKS: And the other thing I've figured  
3 out is my next career, I'm going to offer a non-  
4 informative priors as an expertise. So I learned  
5 that.

6 [Laughter.]

7 DR. REX: So -- so before we close, could I  
8 say something about tomorrow, just real quick?

9 DR. MARKS: Please do.

10 DR. REX: There is -- if you didn't get one  
11 already, there's a handout on the table outside. And  
12 if you didn't -- if you don't want that, you can also  
13 download it. If you'll go to the webpage for the  
14 meeting, you'll find it with FDA unmet need workshop  
15 2016. That's how I'm finding it on my browser.  
16 There's a hypothetical case of a drug called X1 that  
17 is a narrow spectrum anti-pseudomonal and a number of  
18 us have collaborated on pulling together a story.  
19 What you'll be able to download is the preclinical  
20 database and a little bit of Phase I and Phase II data  
21 and your homework for tonight while you're having your  
22 glass of wine with dinner is how would you develop

1 this. And there's some useful tables provided.  
2 What's the frequency of Pseudomonas? But you've got  
3 to design a real program. And my target upper limit  
4 suggestion for you is within 1,000 patients get this  
5 study -- do the Phase III program because that's, you  
6 know, somewhere between \$60 and \$100 million,  
7 depending on how you do it, and you might be able to  
8 get that much money together to do this. So that's --  
9 I just want to say that that challenge is there. And  
10 a fair number of people at the table right now have  
11 been involved in kind of turning that into what we  
12 hope is a very realistic story. So don't miss your  
13 homework. So tomorrow will be more interesting to you  
14 if you've done that.

15 DR. COX: All right. Well, it seems like  
16 we've arrived for today. So I want to thank everybody  
17 for joining us here today and participating in the  
18 discussions. And I think it was, you know -- at least  
19 from my standpoint, it was an excellent day with lots  
20 of important information imparted and a good chance to  
21 talk through a number of issues. Tomorrow, we'll  
22 start at 8:30. So get some rest. John's giving you -



1 - has given you your homework. And believe me, it is  
2 quite an assignment and we'll spend some time  
3 discussing that tomorrow. So we look forward to  
4 seeing you tomorrow. Have a good night.

5

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7 [WHEREUPON, the foregoing adjourned at 4:41

8 p.m.]

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CERTIFICATE OF NOTARY PUBLIC

I, IRENE GRAY, the officer before whom the foregoing proceeding was taken, do hereby certify that the proceedings were recorded by me and thereafter reduced to typewriting under my direction; that said proceedings are a true and accurate record to the best of my knowledge, skills, and ability; that I am neither counsel for, related to, nor employed by any of the parties to the action in which this was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.



IRENE GRAY

Notary Public in and for the  
District of Columbia

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CERTIFICATE OF TRANSCRIPTION

I, BENJAMIN GRAHAM, hereby certify that I am not the Court Reporter who reported the following proceeding and that I have typed the transcript of this proceeding using the Court Reporter's notes and recordings. The foregoing/attached transcript is a true, correct, and complete transcription of said proceeding.

07/27/2016

Date



BENJAMIN GRAHAM

Transcriptionist

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