



U.S. Food and Drug Administration

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ISSUES IN THE DESIGN AND CONDUCT OF  
CLINICAL TRIALS FOR  
ANTIBACTERIAL DRUG TREATMENT

Monday, August 2, 2010

Crowne Plaza Hotel

Silver Spring, Maryland

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

2 JOHN FARLEY: First I want to apologize for  
3 the delayed start. For those of you who are from the  
4 Washington area, most of you are aware of what happens  
5 when it rains here in terms of the roads and they got  
6 bad at around 6 a.m.. We still have some folks on the  
7 panel who haven't quite made it yet but they're on  
8 their way. But we are going to go ahead and get  
9 started.

10 I'm John Farley; I'm the Deputy Director of  
11 the Office of Antimicrobial Products. On behalf of  
12 myself and Ed Cox, the Director of the office was well  
13 as the staff of the FDA, we want to welcome you to this  
14 workshop today.

15 I want to thank all of you for taking time  
16 out of your schedule and journeying to Washington in  
17 August which can be a hardship, but fortunately we have  
18 fairly good weather for you, at least for the next  
19 couple of days in terms of the heat at least.

20 Also, I particularly want to thank our  
21 speakers and panel members over the next two days who  
22 have put a lot of effort into preparing this workshop.

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1           As many of you know, last week we had a very  
2 productive workshop jointly sponsored by the IDSA and  
3 our colleagues at NIAID focusing on antibiotic  
4 resistance. This workshop should compliment that very  
5 nicely in terms of a rather thorough discussion of the  
6 challenges confronting the pipeline today for  
7 antibacterial drugs.

8           Today's workshop will focus on design issues  
9 and tomorrow will focus on trial conduct. And the  
10 emphasis of the workshop these two days is Phase III  
11 clinical trials which are intended to be submitted as  
12 substantial evidence of efficacy to the Food and Drug  
13 Administration in anticipation of approval for  
14 marketing in the United States.

15           This is a very informal workshop as you can  
16 tell by the absence of the chain, et cetera for those  
17 of you who are familiar with advisory committee  
18 configuration. So, audience members are welcome to  
19 participate and join the panel in terms of questions  
20 for speakers as well as discussion when you are  
21 recognized by the moderators for each session and there  
22 are a couple of microphones you'll notice scattered

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1 around the room.

2 For those of you who wish to ask anonymous  
3 questions and that actually may be more germane  
4 tomorrow when we talk about trial conduct and GCP  
5 issues, there actually are cards in the back which the  
6 staff will be keeping track of for the panel discussion  
7 phase.

8 There is a formal public comment section in  
9 the program. If you do wish to make a formal public  
10 comment, we ask you to limit your comments to five  
11 minutes, and Chris Moser who's -- Christine Moser who's  
12 standing in the back or will be at the table outside --  
13 what you want to do if you're going to be doing public  
14 -- wish to make a public comment formally is to present  
15 yourself to the folks outside by lunchtime and we'll  
16 want to load your slides over the lunch period.

17 So, we're going to begin with self-  
18 introductions and disclosures by today's panel members  
19 and we hopefully are ready to go with the slides for  
20 that. Yeah. So, we're going to start with Joe Turner  
21 to my immediate right and move to his right to start  
22 with.

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1               JOE TOERNER: Good morning. I'm Joe Toerner;  
2 I'm the Associate Director of Medical Affairs in the  
3 Office of Antimicrobial Products at FDA.

4               ED COX: Good morning, Ed Cox, Director of  
5 the Office of Antimicrobial Products, FDA.

6               JOHN FARLEY: And I'm John Farley. I've  
7 already introduced myself.

8               BOB TEMPLE: I'm Bob Temple. I'm Deputy  
9 Director of CDER for Clinical Science and Director of  
10 the Office of Drug Evaluation I.

11              BARRY EISENSTEIN: Barry Eisenstein, Senior  
12 Vice President Scientific Affairs Cubist  
13 Pharmaceuticals. My conflicts are that I work for  
14 Cubist. I also hold stock in Eli Lilly.

15              JOHN FARLEY: Katherine Laessig will be  
16 joining us shortly. She is the Deputy Director of the  
17 Division of Anti-Infectives and Ophthalmology Products  
18 within our office.

19              SUMATI NAMBIAR: I'm Sumati Nambiar, Deputy  
20 Director for Safety, Division of Anti-Infective and  
21 Ophthalmology Products.

22              JOHN FARLEY: Leslie Ball will be joining us

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1   shortly.  She is the Director of the Division of  
2   Scientific Investigations at the FDA within the Office  
3   of Compliance.

4               KAREN HIGGINS:  Hi, I'm Karen Higgins, I'm a  
5   statistics team leader in the Office of Biostatistics  
6   at FDA and I support the Division of Special Pathogen  
7   and Transplant Products.

8               CHERYL DIXON:  I'm Cheryl Dixon; I'm a  
9   statistical reviewer at the Division of Biometrics for  
10  Office of Biostatistics CDER, FDA.

11              JOHN FARLEY:  Leslie -- excuse me, Laurie  
12  Burke will be joining us shortly from the study  
13  endpoints and labeling development team as will Elektra  
14  Papadopoulos.

15              HELEN BOUCHER:  Hi, I'm Helen Boucher from  
16  Tufts University School of Medicine and Tufts Medical  
17  Center in Boston.  And I'm here on behalf of the IDSA  
18  today.  And as shown on the slide, I've provided advice  
19  and consultation to a number of anti-infective  
20  companies, sit on a DSMB and adjudication committee as  
21  part of my work.

22              SCOTT HOPKINS:  Hello, I'm Scott Hopkins.

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1 I'm the Chief Medical Officer at Rib-X and I'm fully  
2 conflicted also.

3 JOHN FARLEY: We're now going to start with  
4 Shy and move to his left.

5 SHY SHORER: Good morning. I'm Shy Shorer.  
6 I'm the Director of Office of Clinical Research Affairs  
7 at  
8 DMID/NIAID/NIH.

9 JUDY SIUCIAK: Good morning. I'm Judy  
10 Siuciak. I'm the Scientific Program Manager for the  
11 Biomarkers Consortium at the Foundation for the NIH.

12 FELIX GYI: Good morning. I'm Felix Gyi.  
13 I'm the Chief Executive Officer of Chesapeake IRB. And  
14 I don't have any conflicts other than how to review the  
15 research. Thank you.

16 PETER SCHIEMANN: Good morning. My name is  
17 Peter Schiemann. I'm with Hoffmann-La Roche out of  
18 Switzerland. I head the global group concerning  
19 quality risk management and clinical QA.

20 EILEEN NAVARRO: I'm Eileen Navarro. I'm the  
21 acting Deputy Director Special Pathogen and Transplant  
22 Products and I have no conflicts other than I'm a



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1 public health official and that might be considered a  
2 conflict by others.

3 JOHN FARLEY: Great. Thank you very.

4 So, session one which will continue until the  
5 lunch break, is going to focus on clinical trial  
6 designs for antibacterial drugs with a particular focus  
7 on the non-inferiority trial design. For those of you  
8 who've never heard of a non-inferiority trial, that  
9 won't be the case by the time you -- or we arrive at  
10 our lunch break.

11 That session will be moderated by Bob Temple  
12 and Barry Eisenstein and I'm going to turn the program  
13 over to them.

14 BARRY EISENSTEIN: As the co-chair of the  
15 morning session I have the great honor and privilege to  
16 introduce our first speaker, Dr. Robert Temple. There  
17 was an article published in the July 4th issue of the

18 Washington Post that starts off: "Robert  
19 Temple doesn't look obscenely rich, he's got big  
20 glasses and a thick walrus mustache. He doesn't wear  
21 bling. The fact of the matter is that Robert Temple is  
22 not obscenely rich, but he could have been. Temple is

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1 a professional regulator, to be specific, Director of  
2 the Office of Medical Policy at the FDA. He's been  
3 called an FDA icon."

4 And it ends: "When I reached Temple at his  
5 FDA office and asked him why he's remained at the  
6 Agency since 1972, and he just received a 40-year  
7 federal award for his service, his answer was less  
8 abstract, 'because it's a hoot.'"

9 And with that, we look forward to your  
10 presentation.

11 ROBERT TEMPLE: Okay. I'm going to see if  
12 it's a hoot for everybody else.

13 Well, good morning, good morning.

14 One of my anxieties was that there would be  
15 too much overlap. You're going to hear in a lot of  
16 detail from Karen Higgins about non-inferiority studies  
17 and probably everybody else is going to touch on this.  
18 But I'm going to start with something of an overview.

19 So, just to touch on some of the critical  
20 regulations and guidance we've provided on this matter  
21 and a little bit of history, but not much.

22 For people not in the business, the

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1 effectiveness requirement is written this way in the  
2 law since 1962. A drug -- an NDA can be rejected if  
3 there isn't substantial evidence that the drug will  
4 have the effect it's represented to have under the  
5 proposed conditions of use.

6           People who are lawyers know that substantial  
7 evidence is actually a very low standard, well below  
8 preponderant, well below beyond a reasonable doubt.  
9 But in 1962, the wise people who wrote the law took the  
10 substantial evidence requirement and strengthened it by  
11 saying what the source of that substantial evidence has  
12 to be.

13           Substantial evidence must consist and can  
14 consist only of adequate and well controlled  
15 investigations on the basis of which it could be  
16 concluded the drug will have the effect it's supposed  
17 to have. And then it goes on to say what an adequate  
18 and well-controlled study is.

19           An adequate and well-controlled study is one  
20 that uses the design that permits a valid comparison  
21 with a control allowing a quantitative assessment of  
22 drug effects. The protocol and results should describe

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1 it in detail, including various things like the  
2 duration of treatments.

3           You might wonder why anybody would even  
4 bother to say that. But if you go back and read the  
5 literature of the 1950s, you just can't tell what --  
6 who was in a trial or how long they were in it or what  
7 the treatments were. It's sort of amazing. You  
8 certainly can't tell what they did with all the  
9 patients.

10           Anyway, the trial should say whether the  
11 sample size is predetermined based on an interim  
12 analysis, et cetera, et cetera.

13           And it gives -- the current regulations give  
14 five kinds of controls. One is a placebo-controlled or  
15 a no-treatment concurrent control, a dose response, an  
16 active control or a historical control.

17           When we first proposed these rules describing  
18 this in 1982, we actually had a hierarchy. We said  
19 placebos are best and if you can't do that then you can  
20 use these other things. But we got a lot of flack from  
21 PMA and others and now PHARMA and there is no longer a  
22 formal hierarchy. All of these kinds of control groups

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1 are used every year to approve new drugs. But they do  
2 have their advantages and disadvantages and one has to  
3 understand those.

4           A critical distinction is between trials that  
5 are designed and intended to show a difference between  
6 the two treatments. This includes placebo, no  
7 treatment, dose response, some active controls but not  
8 most and most historical controls. And trials that are  
9 intended to show that there is no difference or no  
10 difference beyond a certain size between the treatment  
11 and the control, those are now called -- they used to  
12 be called equivalence trials, but we don't really call  
13 them that anymore; we call them non-inferiority trials.  
14 And that includes most active controls including the  
15 ones we're going to be interested in today.

16           The law, as I said, used the term  
17 "substantial evidence," but it then went on -- not the  
18 law, the law said it has to be an adequate well-  
19 controlled study. In the regulation in 1985,  
20 describing adequate and well- controlled studies, a lot  
21 of time was spent on defining what the active control -  
22 - the active treatment concurrent control would consist

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1 of.

2           So, this -- I won't read all of this, but  
3 obviously, this is where the test drug is compared with  
4 the known effective therapy, usually because you can't  
5 leave people untreated on ethical grounds, and if the  
6 intent of the trial is to show similarity of the test  
7 and control groups, the study report should assess the  
8 ability of the study to have detected a difference  
9 between treatments, because similarity of tests and  
10 active control can mean either that both drugs were  
11 effective or that neither was effective and you won't  
12 know the difference just looking at the trials; you  
13 have to bring outside information to this.

14           So the analysis of the study has to explain  
15 why the drug should be considered effective in that  
16 study; for example, by reference to results in previous  
17 placebo control studies of the active control drug.

18           Now, this was in 1985. We've spent a lot of  
19 time since then elaborating on this concept. This is -  
20 - this all leads to the idea of a non-inferiority  
21 margin, to looking at the historical experience so that  
22 you know without measuring that the new drug was

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1 effective in the new trial and so on. So it was not  
2 quite fully described but was in some ways ahead of its  
3 time.

4           So we all know and everybody in the ID  
5 business knows that non-inferiority trials are a major  
6 regulatory ethical and international problem, they're  
7 aware of the fundamental distinction between trials  
8 that are trying to show a difference and trials  
9 intended to show similarity.

10           We all understand the desire to use  
11 equivalence and to leave no people untreated. It seems  
12 sensible but there are plenty of problems associated  
13 with it, so I'm going to run through those.

14           Once again, sorry, to repeat myself, but in a  
15 trial that's intended to show a difference between  
16 treatments, the question of whether the trial is well-  
17 designed, well-executed, well-powered, is to a degree  
18 answered by the fact that it does succeed in showing a  
19 difference. If a trial's no good, if the patients  
20 didn't have the disease, if the follow-up was sloppy,  
21 then the study will lose, it will not show that the  
22 drug was effective.

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1           So, if the trial lacks assay sensitivity,  
2   that is the ability to distinguish drugs that do work  
3   from drugs that don't, from a regulatory point of view,  
4   you don't make the mistake you really don't want to  
5   make, that is, you don't approve a drug as effective  
6   when it, in fact, is not.           Now, the world might  
7   lose a useful drug, that's not irrelevant, but you  
8   don't put something that doesn't work in the market.

9           The second major approach is showing  
10   equivalence or non-inferiority. In an active control  
11   study, what that trial shows is that the new drug isn't  
12   worse than the control drug by some defined amount and  
13   that amount cannot possibly be larger than the effect  
14   of the control drug in this study, and usually we don't  
15   want to lose almost all of the effect of the control  
16   drug so we -- we define a smaller amount that has to be  
17   excluded.

18           We call the largest possible difference  
19   between the trials, the non-inferiority margin,  $M_1$ , the  
20   largest possible difference between trials that you'd  
21   accept is a difference that it represents the whole  
22   effect of the control drug. I'll expand on this a



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1 little bit more.

2 And the amount of the effect that needs to be  
3 retained or the maximum amount of the control drug that  
4 you'd be willing to lose we usually call M2, the non-  
5 inferiority margin that's used in the study. Let me  
6 show you a little more.

7 Anyway, showing equivalence to a known active  
8 drug is perfectly sensible but, in fact, you can't  
9 really show equivalence in the sense that there's no  
10 possibility that any of the effect is lost except by  
11 showing that the new drug is better. So we seek what's  
12 called non- inferiority. This is actually a misnomer  
13 because it's really showing inferiority -- it's showing  
14 that the inferiority is no more than a certain margin  
15 so it's really a not-too-much inferiority trial.  
16 That's what they really are because they do not rule  
17 out inferiority.

18 And the test that you're looking at, the  
19 thing you're always concentrating on, is the difference  
20 between the control treatment and the new drug or C-T  
21 and that has to be smaller than M and M can be no  
22 larger, obviously, than the whole effect of the control

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1 drug.

2           If you go back into the literature, I have to  
3 say even well into the '70s and '80s, what you'll see  
4 is something different. You'll see that drug -- the  
5 new drug is compared with the control, no significant  
6 differences found so they say, ah-hah, I work. That is  
7 not true, that doesn't tell you anything. And those  
8 conclusions have been appearing in the literature  
9 probably not so much anymore but they certainly did ten  
10 years ago.

11           If we were thinking about a placebo or no  
12 treatment control trial, we have null hypothesis that  
13 the effect of the test drug, T, is less than or equal  
14 to zero. That's the null hypothesis, no effect. So,  
15 if the null hypothesis is -- the test drug is less than  
16 placebo, then the alternative is that the test drug is  
17 greater than the placebo and the whole point of the  
18 test is to show that the second of those is true by  
19 ruling out the first.

20           And you rule out the first usually by showing  
21 that the 97-1/2 percent one-sided lower bound of the  
22 confidence interval for test minus placebo is greater

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1 than zero. That's standard operating procedure;  
2 everybody knows that.

3 And a successful difference showing trial  
4 absolutely demonstrates an effect as long as the  
5 defeated control is not worse than zero which, of  
6 course, the placebo is not. So it -- the trial speaks  
7 for itself. You don't have to bring any external  
8 information to the game.

9 In the non-inferiority study, the null  
10 hypothesis is that the degree of inferiority of the new  
11 drug T to the control drug C, or C-T, is larger than  
12 the margin M that is larger than the whole effect of  
13 the control drug which would mean that there was no  
14 effect of the new drug at all. So the null hypothesis  
15 is that C-T is greater than M, the margin.

16 The alternative is that C-T is less than M.  
17 And that's what we do. We look at the 97-1/2 percent  
18 lower bound -- 97-1/2 percent confidence interval, in  
19 this case, the upper bound, and we try to reach the  
20 conclusion that C-T is not greater than M. And if you  
21 do that, then you've met your null hypothesis.

22 Obviously, the smaller M is, the harder it is

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1 to show that C-T is less than M. And it -- you should  
2 see immediately that you don't measure M in the trial,  
3 you bring your impression of what M is to the game from  
4 the past because you know what the drug used to do in  
5 other studies. You don't know what it does in this  
6 study because there's no placebo.

7           So everything, everything, depends on the  
8 validity of M. If M is larger than the actual effect  
9 of the control in the study, cause in the study,  
10 somehow there was something wrong with the study, you  
11 will make a mistake. This makes us inclined to choose  
12 the margin conservatively.

13           For example, if you say that the margin is  
14 10, that is the effect of the control drug is 10, and  
15 then if C-T, the 97-1/2 percent upper bound is less  
16 than 10, say 8, then T has an effect. Not really a big  
17 effect maybe but it has an effect.

18           But if in that study, the effect of the  
19 control is, in fact, only 5, T will not have an effect.  
20 So you'll be wrong. It will look like the drug has an  
21 effect but you'll be incorrect and you'll be approving  
22 a drug that doesn't work. So we need to be very, very

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1 sure of the margin and that tends to make us choose  
2 that margin conservatively.

3 And I said this already.

4 So, if the logic is okay, what's the problem?

5 And the problem, as I've been saying, is that unlike a  
6 finding of superiority which speaks for itself, a  
7 finding of non-inferiority depends absolutely on an  
8 assumption or a guess if you like rather than on actual  
9 measurement.

10 So what's that assumption? Well, the crucial  
11 assumption is that the trial could have detected a  
12 difference or a difference of some defined size if  
13 there had been one. And we call that assay  
14 sensitivity. And that depends in turn on the  
15 assumption that the control drug would have had an  
16 effect of some specified size in this study had there  
17 been a placebo group to compare it to. But the control  
18 drug effect is not, in fact, measured; there is no  
19 placebo group. So the assumption can be very hard to  
20 support in many situations.

21 Now, infectious disease it may be somewhat  
22 easier to support. In symptomatic conditions,

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1 depression or anxiety, it's really impossible to  
2 support that assumption because we know that something  
3 like half of all trials of active drugs can't tell drug  
4 from placebo. So there's no way you can ever think you  
5 know what the effect of a drug like that is in any  
6 given study, cause there often isn't an effect in the  
7 study for some reason or other.

8           It's worth remembering this is not a matter  
9 of power. Power just tells you what kind of difference  
10 you could have detected. But if the -- if the effect  
11 of the active control is not what you thought it was,  
12 you can make the studies as big as you want and it will  
13 never be able to give you the right answer.

14           The second problem is that given that the  
15 usual reason for using an active control trial is you  
16 don't want to leave people untreated. The idea that  
17 you would show that C-T is less than the whole effect  
18 of the drug is not quite satisfactory. You don't want  
19 to lose all but a teeny little bit of an effect of a  
20 major -- of a major benefit, so we tend to make the  
21 non-inferiority margin smaller, some fraction of the  
22 total effect of the control drug. In cardiovascular

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1 settings, we've tended to settle on being sure that  
2 you've preserved at least 50 percent of the effect.  
3 That's not very satisfactory when the effect is  
4 mortality, but if you want more retention than that,  
5 the trials get into the 20, 50 and 10,000 people so we  
6 settle for that.

7           In infectious disease, we haven't usually  
8 looked at a fraction of the effect. We've looked at an  
9 actual effect size so you try to -- you may think the  
10 effect of the control drug is 50, 60 percent, very  
11 large, but we'll try and -- we'll try to rule out a  
12 loss of say, 10 percent, because you don't want to  
13 leave people with bad infections poorly treated.

14           The third big problem for non-inferiority  
15 studies or indeed any study where you're trying not to  
16 show a difference is that sloppiness obscures  
17 differences. The best way to show that one drug is  
18 equal to another is to mix up the therapies, just  
19 completely randomly assign them. And I guarantee  
20 you'll see no difference between treatments.

21           So, you know, nobody's trying to be sloppy  
22 but the incentive to be perfect is diminished in this

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1 setting and that's a worry.

2           So, I've used the term "assay sensitivity" a  
3 few times. There's not a lot of really great  
4 definitions but what we mean by it is that it's a  
5 property of a clinical trial. It means that the trial  
6 had the ability to distinguish active from inactive  
7 drugs or in the specific cases we're worried about, the  
8 ability to show a difference of a specified size called  
9 M between treatments where M is the effective C that is  
10 presumed present in the new study.

11           So the trouble with assay sensitivity in the  
12 non-inferiority setting is you don't measure it, you  
13 have to assume it's there based on your keen analysis  
14 of the previously existing trials.

15           And, once again, if you don't know whether  
16 the trial had assay sensitivity, finding no difference  
17 between the control and test drug means that either  
18 both drugs were effective or that neither was  
19 effective. And you can't tell from the trial itself,  
20 you have to bring other information to the game.

21           I actually remember when I realized what this  
22 problem was. We'd been agonizing for years and were



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1 criticized severely for not giving beta blockers a  
2 claim of angina treatment. And the reason was that  
3 when you did trials using exercise testing and so on, a  
4 lot of them failed to show that there was any benefit  
5 to the drug. But, with a lot of agony, looking at the  
6 literature with the help of our then director, Dick  
7 Crout, we finally concluded that propranolol did, in  
8 fact, have an effect on angina.

9           So in came -- in came Squibb with a proposal  
10 to show that their drug, their beta blocker drug,  
11 Nadolol, also had had an effect in angina and they were  
12 going to compare it with propranolol. But we'd just  
13 been through fifty trials in which comparison with  
14 placebo of propranolol couldn't show a difference so we  
15 finally tumbled on this and said, what is this? How  
16 can we possibly reach a conclusion if all they can show  
17 is that Nadolol and propranolol aren't different when  
18 propranolol and placebo aren't different at least half  
19 the time?

20           That helped a lot and we began talking about  
21 this. We didn't apply it to infectious disease  
22 settings for a long time anyway.

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1           But we began to -- we began to notice it. So  
2 in 1982, we proposed the regulation I read for you -- I  
3 read to you before that said if you're going to do a  
4 non- inferiority study you better tell us how you know  
5 that the control drug worked in this trial.

6           Anyway, so for something like 25 years, we  
7 have figured out that the big problem with non-  
8 inferiority trials is that you have to make a crucial  
9 assumption which is that the control drug had the  
10 effecting the trial that you hoped it would and that,  
11 of course, gives non-inferiority studies an unsettling  
12 similarity to historically controlled trials. And as  
13 soon as you say historically controlled trials, people  
14 immediately and appropriately are nervous because how  
15 do you really know the conditions are the same, how do  
16 you really know anything?

17           All right. I've already touched on all this.

18           Although it took us a while into the early  
19 '80s to figure this out, others -- other smart people  
20 on the outside had figured this out long before us.

21           Lou Lasagna who -- whose -- most of whose  
22 studies involved pain and things like that and who was

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1 very conscious of depression was trying to explain what  
2 kind of trial design you could use; this was in a paper  
3 in 1989, and he said that in certain situations you can  
4 justify comparisons between a new drug and a standard  
5 drug even if a placebo group is out of the question,  
6 but such a trial is convincing only when the new remedy  
7 is superior to standard therapy. That's a very  
8 demanding standard.

9           If it's inferior or indistinguishable the  
10 results are hard to interpret because in the absence of  
11 placebo controls you don't know if the inferior new  
12 drug has any efficacy at all and equivalent performance  
13 may reflect simply a patient population that can't  
14 distinguish between two active treatments even if they  
15 differ considerably from each other or even between an  
16 active drug and placebo.

17           And he noted that this was a particular  
18 problem in depression.

19           So, Lou had it years before we did.

20           How do you go about determining assay  
21 sensitivity? People do this all the time. You need a  
22 combination of the historical information about the

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1 drug and assurance that the new trial is very similar  
2 to the historical trials so that whatever was true in  
3 them can be presumed to be true now.

4           So, in our guidance on non-inferiority  
5 studies this is an ICH guidance called E-10. It  
6 created the term "historical evidence of sensitivity to  
7 drug effects" or HESDE. That just means that in the  
8 past, previously, appropriately designed and conducted  
9 trials in a particular disease with a specific active  
10 drug or conceivably group of related drugs reliably  
11 showed an effect of some defined size on a particular  
12 endpoint and this was -- this is usually established by  
13 showing the previous placebo-controlled trials were  
14 pretty regularly able to distinguish drug from placebo.

15           It should also be appreciated, however, that  
16 historically controlled experience, that is, without an  
17 actual controlled trial, has been pertinent to many  
18 infectious disease non-inferiority margins and we  
19 actually cite one in a recent guidance we wrote on non-  
20 inferiority studies.

21           And, that's okay. If you know that the  
22 untreated course of a disease is that most people die

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1 and then you have experience with treatment even if  
2 it's not in a controlled trial, that does give you some  
3 information, useful information about what the non-  
4 inferiority margin might be.

5           Sensitivity to drug effects, HESDE, is an  
6 abstract conclusion about well-designed trials in the  
7 past. Assay sensitivity means that you have reason to  
8 believe that this effect size would still be true in  
9 the current trial which can be hard to show.

10           As I said, for most symptomatic conditions  
11 there is just no good argument for saying that a trial  
12 has assay sensitivity because trials in these  
13 conditions fail quite regularly. Anxiety, depression,  
14 allergic rhinitis, asthma prophylaxis, even hear  
15 failure sounds objective and how could you lose but  
16 trials do.

17           And even for some outcome studies it would be  
18 hard to be sure that you really know what say a beta  
19 blocker will do in a post infarction trial because  
20 trials of reasonable size have failed anyway. You got  
21 to be careful in concluding that there's assay  
22 sensitivity.

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1           Just as an example, we took a look at our  
2   experience in a bunch of psychiatric indications. We  
3   only looked at trials where there were full reports.  
4   We looked at short-term treatment. Anyway, the trials  
5   had to be adequate in all these ways. And what we  
6   found over the years and we've updated this and it's  
7   still true, about half of all depression trials fail.  
8   Some trials in schizophrenia fail. We actually thought  
9   they usually worked but something like a quarter to a  
10   third of them don't seem to do so.

11           Panic disorder, obsessive compulsive, these  
12   are failures. In all of them you could not do a non-  
13   inferiority study in any of those settings. And we've  
14   looked in other places as well.

15           Okay. One of the crucial elements after  
16   you've established that there is historical evidence of  
17   sensitivity drug effects is the similarity of the  
18   current trial to the past, the constancy assumption.  
19   This depends on the endpoint, but in the infectious  
20   disease setting, if in the past the mortality in the  
21   group -- in the trials in the untreated group, was 40  
22   or 50 percent and then you improved that down to

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1 whatever it is, 10 percent, if in your new group you've  
2 included -- in your new trial you've included people  
3 who are far, far less sick where the mortality is only  
4 4 percent or 5 percent, then your assumption about what  
5 a difference between -- then your idea of what a  
6 difference between the two treatments might mean,  
7 really goes away. Your whole basis for saying, okay,  
8 as long as the -- as long as the difference between the  
9 two treatments is not more than 10 percent, I'm okay,  
10 that applied when the untreated mortality was 50  
11 percent; if the untreated mortality is 2 percent that  
12 doesn't mean anything anymore. So, you've got to worry  
13 about whether the definition of the disease or external  
14 therapies or whatever it is has been altered by other  
15 treatments.

16 And then, finally, as I said, the study  
17 quality matters tremendously if there's a wide variety  
18 of sloppiness that can get in the way of showing -- of  
19 showing a difference. So for compliance, too many  
20 crossovers that leave the study as soon as they're  
21 doing badly, a population that really didn't have as  
22 bad a disease as you thought they had, poor diagnostic

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1 criteria; these are all the same. All of those things  
2 will give you a bias toward the null; a tendency to  
3 show no difference between treatments, and in the case  
4 of non- inferiority, to conclude that the non-  
5 inferiority has been shown when, in fact, nothing has  
6 been shown.

7           Now, the ability of a trial to distinguish  
8 effective from ineffective treatments is critical. It  
9 sounds like an absolute property but it really isn't  
10 and it depends not only on the quality of the trial,  
11 the effect of the control, the size and consistency  
12 with which it has shown itself in trials in the past.  
13 So one of the things you do in deciding whether there  
14 is assay sensitivity is take a very, very, very close  
15 look at the trials in the past, who was in them, what  
16 the variability was, and so on. So I said all that.

17           We've certainly concluded over the years that  
18 equivalence trials are credible, that assay sensitivity  
19 can be defined that the effect of the control is  
20 knowable with some bacterial infections, not otitis  
21 media and sinusitis although we had in the past  
22 concluded that those were okay. We think non-



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1 inferiority trials are good for thrombolytics because  
2 the effect size is very large, deep vein thrombosis  
3 because the effect size is again very large, HIV  
4 infection because you really drop the -- drop the viral  
5 lode by a mile. So there's many settings in which we  
6 do find them credible, but there others where it's not.

7           To show a given drug placebo difference or to  
8 show the lack of such a difference sample sizes for an  
9 active control non-inferiority trial and a placebo  
10 control difference showing trial may be similar but in  
11 practice, they really aren't, because the margin for  
12 the non-inferiority trial is deduced, not measured, and  
13 must be chosen conservatively. You can't assume the  
14 biggest effect that's ever been seen or the average  
15 effect because this might be a trial that falls below  
16 that, but you tend to pick an effect size that's at the  
17 low end of the range. An effect we can more or less  
18 assume is surely there, and that makes sample sizes  
19 fairly large.

20           And I've already talked about why you don't -  
21 - you don't try to rule out loss of a whole effect of  
22 the drug but some smaller amount called M2.

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1           So there's four critical steps in using a  
2 non- inferiority design. You have to determine that  
3 the historical evidence of sensitivity drug effects  
4 exist and is reasonably applicable to the current  
5 population. You have to be able to define an  
6 acceptable non-inferiority margin. Obviously, a margin  
7 no larger than the whole effect the control will have  
8 in this new study, but one that also reflects the  
9 fraction of the effect that you consider clinically  
10 essential. You have to be able to design a trial that  
11 is very similar to the trials for which historical  
12 sensitivity drug effects has been determined. That's  
13 probably the biggest single problem here. And then the  
14 trial has to be properly done.

15           And we don't want that.

16           And I've talked about the non-inferiority  
17 margin and I think I won't show you these slides, this  
18 -- these figures because you already know this already.

19           There has been some tendency to confuse the  
20 largest possible non-inferiority margin that shows any  
21 effect and M2, that is, the margin that reflects the  
22 clinical desire to maintain a reasonable amount of

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1 effect. And it's important to keep those separate.

2           The main thing that we did in the past that  
3 was wrong and I can talk about this because I was  
4 responsible for it at the time, in cancer trials we  
5 would declare equivalence of survival, that is, an  
6 inferiority of 20 percent was excluded. We said, oh,  
7 well, that's practically the same. But what we didn't  
8 appreciate and I didn't appreciate particularly was  
9 that in most of these cases, we didn't know that the  
10 effect size of the drug was even 20 percent. So we  
11 were ruling out a clinically meaningful difference but  
12 we weren't assuring that there was any effectiveness at  
13 all.

14           And I have to say and Ed knows this, we did  
15 this to a degree in the infectious disease area, but  
16 we've stopped.

17           So, I think I've covered all this and I won't  
18 repeat it. This was just to give an example of drugs  
19 that we know work where you can't define a margin. The  
20 2V3A antagonists are anti-platelet drugs. They're used  
21 in people with acute coronary syndrome or having an  
22 intervention procedure. And there's little doubt that

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1 the drugs work. We don't doubt that. But when you do  
2 -- when you attempt to figure out what the effect size  
3 is, it's all over the map.

4           So that the average when you pull all the  
5 data from these trials is in -- this is for use after a  
6 percutaneous intervention, there was an average of 43  
7 percent reduction in death, non-fatal MI, but when you  
8 looked, some trials had a more than 50 percent effect  
9 and a whole bunch of trials had a less than 25 percent  
10 effect.

11           So how do you choose your margin? Do you  
12 work with the 43, the mean, do you take the lower band  
13 and take half of that? Anyway, it's very hard in  
14 situations, even where drugs are known to work because  
15 you need a level of precision and need to understand  
16 the relationship of trials outcome in a way that goes  
17 beyond what we usually know. You got to be -- you got  
18 to be quite careful.

19           As a general matter and you'll hear this, we  
20 tend to look at the available data and take the low end  
21 of the effect because time is past, maybe the effects  
22 aren't big enough, maybe other treatments have muted

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1 the effect of the drug we're looking in, so we tend to  
2 -- we tend to interpret these cautiously.

3 Just briefly on this, in the cardiovascular  
4 area, the absolute effect size depends a lot on what  
5 the event rate is in the control group. That is, if  
6 you pick a bunch of people that have a heart attack  
7 rate of 15 percent and you improve it down to 10  
8 percent that's a 33 percent reduction but it's a 5  
9 percent absolute difference which is -- which is quite  
10 large.

11 What we've learned over time is that what  
12 tends to be constant over time is the reduction in risk  
13 ratio, reduction in hazard, the effect on the hazard  
14 ratio more than the absolute difference. So that, for  
15 example, in looking at thrombolytics what was found is  
16 that people with a mortality rate of anywhere from oh,  
17 say, just 5 or 6 percent all the way up to 15 percent,  
18 all had an effect size when you looked at the risk  
19 reduction that was similar even though the absolute  
20 margins were different.

21 Actually, in -- in infectious disease we've  
22 tended much more to use the absolute difference in

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1 effect size and you'll hear more about that.

2           You have to take changes in practice into  
3 account if new drugs are used, new devices are used to  
4 treat pulmonary disease, maybe the mortality isn't what  
5 it was and you have to try to as best you can to think  
6 about that.

7           And then there's always a debate about how  
8 conservative to be in the choice of margins and  
9 analysis and I think I won't get further into that.

10           It's worth noting that in placebo control  
11 trials we accept an error rate of about 1 in 40 per  
12 trial or if you actually have two studies you're chance  
13 of making an error on a random basis is really  
14 something like 1 in 1,600; it's .025 squared. That's a  
15 very low risk of error of saying that a drug is  
16 effective when it really isn't.

17           If you had a known non-inferiority margin of  
18 M and a lower 97-1/2 percent bound for C-T was less  
19 than M and you showed that twice, you would have  
20 equivalent assurance that the drug actually had an  
21 effect and that's sort of where you'd like to be. The  
22 trouble is you can't really know that the control had

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1 an effect greater than M in the study because you're  
2 assuming the effect of the control how sure must one  
3 be, a constant debate.

4           And we've evolved various approaches to doing  
5 this. One has been that we take the -- a very  
6 conservative estimate of the effect size of the  
7 control, that is, the lower bound of a meta-analysis.  
8 So for thrombolytics, for example, the mean effect was  
9 about a 25 percent reduction in mortality but the lower  
10 bound was about 22 percent. So we said, okay, that's  
11 the effect we're sure these drugs have. And M1, that  
12 is the non-inferiority margin, could be .22, that is  
13 the hazard ratio of treatment -- in the treated  
14 patients would be something like .78.

15           And then we took half of that or --  
16 preserving -- making sure that you've ruled out a loss  
17 of 11 percent and then you make the 95 percent  
18 confidence interval for C-T, you say that it has to  
19 exclude a difference of about 11 percent, that turns  
20 out to give you a trial size in the neighborhood of  
21 15,000. When we took this to an advisory committee  
22 they thought 50 percent wasn't nearly good enough and

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1 wanted 75 percent but then you were over 50,000 so we  
2 compromised.

3 But those are the sorts of numbers that you  
4 are talking about here.

5 Having established what the -- what the  
6 margin is you then take -- you then look at C-T, the  
7 difference between the drug and the treatment, and you  
8 say okay, I want to rule out a loss of -- a loss of --  
9 even a little bit of that, that is, I want to rule out  
10 the 11 percent loss with 95 percent confidence  
11 interval, so you use these two extreme confidence  
12 intervals, 97-1/2 percent confidence intervals, a very  
13 conservative process, that is hard to meet. That's  
14 what we generally do.

15 I won't go into this.

16 There are other possibilities one could use.  
17 For example, you might have priors that make you think  
18 this is -- the drug is very likely to be effective,  
19 maybe you wouldn't insist on a 95 percent confidence  
20 interval or something like that. But we don't usually  
21 do that. It is something we've occasionally thought  
22 about.



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1 I won't do that either.

2 Okay, so that's the end. Be glad to answer  
3 any questions. This is probably by now fairly familiar  
4 territory in the infectious disease area and you'll  
5 hear more from Karen later.

6 BARRY EISENSTEIN: Do I have questions from  
7 the panel?

8 Any questions from the audience?

9 Thank you, Dr. Temple.

10 The next speaker is Dr. Cheryl Dixon who will  
11 be presenting clinical trial designs appropriate for  
12 antibacterial drugs.

13 I point out that Dr. Dixon is the senior  
14 statistical reviewer in the Office of Biostatistics at  
15 the FDA.

16 CHERYL DIXON: Good morning.

17 This morning I will be discussing the general  
18 considerations of clinical trial designs appropriate  
19 for antibacterial drugs.

20 I have no conflicts to disclose.

21 As an outline for my talk I will describe the  
22 characteristics of adequate and well-controlled trials.

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1 Specific to antibacterial drugs, I will discuss design  
2 issues associated with bacterial diseases with high  
3 spontaneous resolution rates as well as challenges in  
4 trial design for severe bacterial diseases. I will  
5 conclude with a brief summary.

6 Adequate and well-controlled trials as  
7 described in 21 CFR 314.126, had the following  
8 characteristics:

9 There must be a clear statement of the  
10 objectives of the trial.

11 The study design must be such that a valid  
12 quantitative comparison with a control can be made.

13 Patients should be selected to assure that  
14 they have the disease or at risk of the disease that is  
15 being studied.

16 The method of assigning patients to treatment  
17 groups should minimize bias to assure baseline  
18 comparability.

19 Adequate measures should be taken to minimize  
20 bias on the part of patients, investigators and  
21 analysts of the data.

22 Methods of assessment of outcomes or response

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1 should be well-defined and reliable.

2 Finally, the methods used in the analysis of  
3 the results should be adequate to assess the effects of  
4 the drug.

5 In the next few slides, I will address each  
6 of these points in further detail.

7 The objectives of the trial are correlated  
8 with the phase of clinical development, although any  
9 one type of trial may occur across the phases. In  
10 general, Phase II trials include the exploratory early  
11 development trials. In these trials, the primary  
12 objective is to explore therapeutic efficacy of drugs  
13 in patients by learning the exposure response of the  
14 drug and also evaluating toxicity and safety.

15 Additional objectives of Phase II trials can  
16 be an evaluation or assessment of the performance of  
17 potential study endpoints or an evaluation of target  
18 populations for further study such as mild versus  
19 severe disease.

20 The primary objective of Phase III trials is  
21 to demonstrate or confirm therapeutic benefit. These  
22 studies are designed to confirm the preliminary

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1 evidence accumulated in Phase II that a drug is safe  
2 and effective for the intended indication in recipient  
3 population.

4 Patients enrolled into the trials should have  
5 the disease and interest with his specificity. Clearly  
6 defined inclusion and exclusion criteria will ensure  
7 the appropriate target population.

8 An adequate number of subjects should be  
9 enrolled to provide reliable answers to the questions  
10 addressed by the trial.

11 Study endpoints are the response variables  
12 that are chosen to assess the drug effects and should  
13 be defined prospectively. The primary endpoints should  
14 be sensitive to provide meaningful clinical benefit and  
15 be directly related to the primary objective of the  
16 trial.

17 Session Two this afternoon will go into  
18 further discussion of endpoints for antibacterial drug  
19 clinical trials.

20 Randomization of patients to treatment  
21 protects against selection bias. It can create a  
22 balance on prognostic factors known and unknown to

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1 ensure comparability of treatment groups. Equal  
2 allocation of subjects may maximize study power.

3           Blinding is another means to reduce or  
4 minimize the risk of potential bias. Double-blinded  
5 trials where neither the investigator nor the patient  
6 know the treatment assignment are ideal. However,  
7 there are cases when it is not possible to conduct a  
8 double-blinded trial. Whether or not a trial is  
9 blinded should be taken into account in the final  
10 assessment of the trial results.

11           Various design configurations can be applied.  
12 The most common clinical trial design for confirmatory  
13 trials is the parallel group design in which patients  
14 are randomized to either test or control. In the  
15 cross-over design, each patient is randomized to a  
16 sequence of two or more treatments and hence, acts as  
17 its own control for treatment comparison.

18           In a factorial design, two or more treatments  
19 are evaluated simultaneously through the use of varying  
20 combinations of the treatments. For example, in a two-  
21 by-two factorial design, patients would be randomized  
22 to one of four possible combinations of two treatments;

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1 Drug A alone, Drug B alone, both Drug A and Drug B or  
2 neither Drug A and B -- or nor B.

3 Another design consideration is the use of  
4 multi-center trials. Multi-center trials are often  
5 used to control -- to enroll a sufficient number of  
6 patients in a more expeditious manner. They also  
7 increase the generalizability of the trial results.  
8 If multi-center trial is to be meaningful interpreted  
9 and extrapolated then one needs to ensure similar  
10 conduct of the trial at all centers.

11 Additional clinical trial conduct  
12 considerations include whether or not an adaptive  
13 design or interim analysis in general will be  
14 conducted. It is the utmost importance that  
15 maintenance of study integrity in type one error  
16 control are upheld when any looks at the data are made.  
17 Details on adaptive designs can be found in a draft  
18 guidance entitled "Adaptive Design Clinical Trials For  
19 Drugs In Biologics" that was issued in February of this  
20 year.

21 In the case of an adaptive design or interim  
22 analysis a data monitoring committee should be

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1 established. But a data monitoring committee may also  
2 be established for the purpose of ensuring adequate  
3 safety monitoring for assessing risk benefit. It is  
4 important that the details of the monitoring process be  
5 clearly defined. One can refer to the "Guidance on the  
6 Establishment and Operation of Clinical Trial Data  
7 Monitoring Committees" issued in March of 2006 for  
8 further details.

9           Some analysis considerations include the  
10 analysis population, handling of missing data and  
11 multiplicity. The analysis population should be pre-  
12 specified. The intent to treat population includes all  
13 patients who are randomized. A variation of the intent  
14 to treat population is the modified intent to treat  
15 population which includes all randomized patients who  
16 in the setting of infectious disease test positive for  
17 the disease at baseline.

18           The per protocol population is a subset of  
19 the intent to treat who are compliant with the protocol  
20 by having available measurements of the primary  
21 variable in the absence of major protocol violations  
22 including violation of entry criteria.

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1               Reasons for excluding subjects from the per  
2 population should be fully defined and documented prior  
3 to breaking the blind.

4               Consistency of results between analysis  
5 populations increases the confidence in the trial as a  
6 whole. For most trials, an ITT type population will be  
7 used for the primary analysis. However, if the trial  
8 is a non-inferiority trial the use of the ITT  
9 population may not be as conservative as it is for a  
10 superiority trial because the non-compliers included in  
11 the ITT will generally diminish the estimated treatment  
12 effect, thus making the treatments look more similar  
13 than they may actually be.

14              Missing data can represent a potential source  
15 of bias; therefore, every effort should be made to  
16 minimize the amount of missing data. Methods for  
17 dealing with missing data should be predefined.  
18 Unfortunately, there are no universally applicable  
19 methods of handling missing data that can be  
20 recommended. However, the results of the analysis  
21 should not be driven by the method for handling missing  
22 data applied.



1 Multiplicity issues may arise from multiple  
2 endpoints, multiple comparisons of treatments or  
3 interim analyses. Adjustments to control for the  
4 overall Type I error rate should be applied and the  
5 details of any adjustment procedure should be  
6 described.

7 There are various types of comparisons that  
8 can be made between a treatment and control. There are  
9 trials to demonstrate superiority, trials to  
10 demonstrate non-inferiority and trials to demonstrate a  
11 dose response relationship.

12 Trials to demonstrate a dose response  
13 relationship can be a special case at superiority  
14 trials for confirming efficacy, but they can also  
15 include the additional objectives of investigating the  
16 shape and location of a dose response, the estimation  
17 of an appropriate starting dose or the determination of  
18 a maximal dose beyond which additional benefit would be  
19 unlikely to occur.

20 Efficacy is most convincingly established by  
21 demonstrating superiority which can include superiority  
22 of the new drug over placebo, over an active control or

1 demonstrating a dose response, add-on trials, where  
2 patients are randomized to receive a new drug that is  
3 added to a current regimen or the current regimen alone  
4 is an example of a superiority trial.

5 Another example may be trials of fixed dose  
6 combination drugs where the combination may need to show  
7 superiority of each of the individual components in the  
8 combination.

9 The null hypothesis of a superiority trial  
10 assumes that there is no treatment difference between  
11 the test and control. To rule out the null hypothesis,  
12 one will want to show that the treatment difference is  
13 greater than zero.

14 It should be noted though that failing to  
15 show superiority of a new drug to have active control  
16 does not necessarily imply the two drugs are similar.

17 The objective in non-inferiority trials is to  
18 demonstrate that the test drug is not unacceptably  
19 worse than the active control based on a pre-specified  
20 non-inferiority margin which is denoted as M. The  
21 determination of the non-inferiority margin relies in  
22 part on historical data that determines the efficacy of

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1 the active control over placebo.

2 Dr. Karen Higgins will discuss non-  
3 inferiority trials in further detail in the next  
4 presentation and approaches for determining the non-  
5 inferiority margin will be discussed in the remaining  
6 presentations of the morning session.

7 Most of what I have discussed are general  
8 trial design issues but are, of course, applicable to  
9 antibacterial clinical trials. I will now move on to  
10 discuss some points specific to antibacterial trials.

11 In some bacterial diseases such as acute  
12 bacterial sinusitis, acute bacterial exacerbations of  
13 chronic bronchitis and acute bacterial otitis media it  
14 is often difficult to discern a treatment effect from  
15 the placebo due to the high spontaneous resolution  
16 rates. Therefore, the historical data based on clinical  
17 response do not provide a consistent and reliable  
18 active control treatment effect to determine a non-  
19 inferiority margin.

20 There have been previous discussions of trial  
21 designs for ABS, ABCB and ABOM at meetings of the Anti-  
22 Effective Drugs Advisory Committee. ABS trials were

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1 discussed at meetings in October of 2003 and in  
2 September and December of 2006. It was recommended  
3 that superiority trial design using a placebo or  
4 adjunctive therapy be conducted for ABS trials.

5 In 2002 and 2006, the AIDAC discussed the  
6 need for placebo-controlled trials in non-severely ill  
7 patients with ABECB and determined that there was no  
8 adequate basis for non-inferiority trials.

9 Additionally, at a 2002 meeting of AIDAC it  
10 was determined that there was no adequate basis for  
11 non- inferiority trials in ABOM. Therefore, the draft  
12 guidance for industry entitled "Antibacterial Drug  
13 Products, Use of Non-Inferiority Studies to Support

14 Approval" issued in October of 2007, states  
15 that: "For ABS, ABOM and ABECB, it is likely that  
16 available data will not support the use of non-  
17 inferiority design. We recommend that sponsors  
18 consider other study designs, for example, superiority  
19 designs to provide evidence of effectiveness in these  
20 three indications. In some cases it may be useful to  
21 compare time for clinical improvement in addition to  
22 overall cure rates."

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1           When it comes to more severe diseases such as  
2 community acquired bacterial pneumonia, nosocomial or  
3 ventilator associated pneumonia or complicated urinary  
4 tract infections, there are ethical issues in  
5 conducting a placebo-controlled superiority trial.  
6 However, active controlled superiority trials may not  
7 be feasible due to the high response rates observed.

8           There is a lack of historical placebo-  
9 controlled data for estimating the active control  
10 treatment effect which is necessary for designing non-  
11 inferiority trials. Furthermore, the endpoints used in  
12 contemporary non- inferiority trials such as clinical  
13 response are questionable since there are no data  
14 adequate available to justify non-inferiority margins  
15 for these endpoints.

16           However, determination of the non-inferiority  
17 margins for newly considered endpoints pose additional  
18 challenges and issues since more than likely this  
19 information is not available for historical trials.

20           In summary, clinical trials should be  
21 designed, conducted and analyzed according to sound  
22 scientific principles. Superiority trial designs are

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1 the most convincing trials for demonstrating efficacy  
2 and are highly recommended for less severe indications.  
3 In the absence of superiority trials, non-inferiority  
4 trials can be challenging due to limited historical  
5 data. The natural history of the diseases and our  
6 understanding of the endpoints to assess drug effect  
7 are evolving and more development work during early  
8 phase of drug development can be expected.

9 Finally, I would like to thank for his input,  
10 Thamban Valappil, Team Leader in the Division of  
11 Biometrics IV, who was originally asked to give this  
12 presentation but was unable to be here today.

13 And I would now like to turn the podium over  
14 to Dr. Higgins will discuss non-inferiority trials in  
15 further detail.

16 BARRY EISENSTEIN: Dr. Higgins is the  
17 statistics team leader at the Office of Biostatistics.

18 KAREN HIGGINS: Hi, I'm Karen Higgins. Can  
19 everyone hear me okay? Yeah. Okay.

20 So I'm going to go over introduction to non-  
21 inferiority trial design and it's nice for me that Dr.  
22 Temple went first and kind of laid out all the details

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1 and the information and I'm just kind of going to go  
2 over it again on some of the key points.

3           For those of you lucky enough to take a  
4 statistics course in the past, you probably did not  
5 learn about non-inferiority trials. So, I got my  
6 doctorate in statistics and never once heard about non-  
7 inferiority trials until I came to the FDA. So,  
8 they're really kind of a regulatory construct. There  
9 was a way for us to determine the efficacy of a new  
10 drug and we really needed to have a way to do that  
11 other than a superiority trial.

12           So, it's not a favorite topic of many it's a  
13 strange way to think about efficacy. So I think it's  
14 good that we kind of repeat these key points over and  
15 over again.

16           I have no conflicts of interest to disclose.

17           So just a brief outline, I'm going to go over  
18 just general non-inferiority trial issue, then focus  
19 sometime on how to determine a non-inferiority margin  
20 which is a difficult concept and then go over some  
21 brief conclusions.

22           So, just the main point is what's the goal of

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1 the non-inferiority trial? Well, the goal is to  
2 demonstrate the efficacy of the new drug, period. I  
3 mean, that's the goal of the trial. And we do that by  
4 showing that the new drug is not too much worse than  
5 the known effective therapy or our control. And how  
6 much is too much is the non-inferiority margin.

7           So, the margin which I'm going to call M is  
8 The degree of inferiority of the test drug to the  
9 controlled drug that the trial will exclude  
10 statistically and it cannot be larger than the whole  
11 effect of the controlled drug.

12           So, here is just my way of thinking about  
13 this in my head. I have a lot of figures and that's  
14 how my brain works. I like to picture it like this is  
15 that I have my -- my X axis here where on the left I  
16 have in favor of the control. On the right I have in  
17 favor of the test, and I'm looking at the difference in  
18 treatment.

19           And my confidence interval needs to  
20 completely exclude M, the margin, on the side favoring  
21 the test drug. And I do it like this, I don't you give  
22 you any positives or negatives in all my talks here.



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1 I'm just going to give you what side favors one drug,  
2 what side favors the other, because it kind of depends  
3 on your actual trial. It depends on if you're  
4 subtracting tests from control or control from tests.  
5 It matters if it's a positive outcome like success or  
6 cure or if it's a negative outcome like failure or  
7 mortality.

8               So, for every non-inferiority trial you need  
9 to really think about what side of that confidence  
10 interval am I interested in and where do I have to rule  
11 out M?

12              So, I don't like to give you specifics  
13 because I want you to be able to think about it for  
14 each trial you're doing, you need to think about what  
15 side you need to exclude.

16              Also in this -- in this talk and in the talk  
17 I'm going to give later in the morning, I'm always  
18 going to talk about differences in treatment. As Dr.  
19 Temple mentioned, that's typically what we do for anti-  
20 infectives, we look for treatment differences. Of  
21 course, all this applies to when you're looking at risk  
22 ratios or another measure of treatment effect.

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1           So, luckily for all of us, we have a new  
2 draft guidance for non-inferiority clinical trials.  
3 And it is full of very good information. It's long,  
4 you need to sit down probably for the weekend and read  
5 it, but I highly recommend it. And I gave the website  
6 where it's located.

7           And here are just some key points from the  
8 guidance document. The first one is -- and as Dr.  
9 Temple mentioned, they're not as good as superiority  
10 trials. This design is chosen when it would not be  
11 ethical to use the placebo. Superiority trial is  
12 entirely interpretable without further assumptions;  
13 that's very important, whereas, for the non-inferiority  
14 study it's dependent on knowing something that is not  
15 measured in the study, namely that the active control  
16 had its expected effect in the non-inferiority trial.

17           If we see two drugs active in -- and the test  
18 drug looking similar, are they equally effective or  
19 equally ineffective? We really need to have kind of  
20 outside information to make us then determine that  
21 they're equally effective.

22           Also, the non-inferiority trial relies on

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1 outside information to justify the margin. So the  
2 critical problem and the major focus of this guidance  
3 is determining M1. It must be estimated, really  
4 assumed, based on past performance of the active  
5 control and by comparison of the prior test conditions  
6 to the current test environment. So you need to know  
7 that the active control works and you need to know that  
8 it's similar enough that that information that told you  
9 the active control worked is related to your current  
10 non-inferiority trial.

11 And determining the non-inferiority margin is  
12 the single greatest challenge in the design conduct and  
13 interpretation of non-inferiority trials. And you'll  
14 note, today we're going to talk a lot about how to  
15 determine a non-inferiority margin.

16 So, just to have you visualize the difference  
17 between non-inferiority trials and superiority trials I  
18 have the same little access that I showed you on a  
19 previous graph so you'll calculate let's say a 95  
20 percent confidence interval of your treatment  
21 difference and it has to exclude M.

22 For superiority trial, you're going to

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1 calculate your 95 percent confidence interval of the  
2 difference and it has to exclude zero. So for  
3 superiority trial you're always excluding zero so  
4 there's no M to calculate. You're always excluding  
5 zero. For non-inferiority trial you have to determine  
6 what that margin should be.

7           And it's always what Dr. Temple mentioned,  
8 sloppiness of trial conduct obscures the treatment  
9 effect so it's going to make the two treatment arms  
10 look similar to each other and it's going to push it  
11 close to zero. So you can imagine in a superiority  
12 trial that confidence interval getting pushed closer to  
13 zero, you're not going to be able to conclude the drug  
14 superior. So when you conduct the superiority trial  
15 there's built-in incentives for you to conduct a very  
16 good clean trial. You're going to want to make sure  
17 that your patient population truly has the disease;  
18 that your patients take the recommended amount of  
19 medication; that you -- your outcome measure really  
20 measures the effect of the disease and that you don't  
21 have too much missing data. I mean, you're going to  
22 want that so that confidence interval can push away

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1 from zero.

2           Where for a non-inferiority trial, there's no  
3 build-in incentive. So you can imagine from the FDA  
4 perspective there's an extra concern when we see a non-  
5 inferiority trial. We're going to look at that trial  
6 extra closely to make sure the trial is conducted as  
7 good as possible. Cause we don't want that confidence  
8 interval being pushed closer to zero cause that's going  
9 to make it look like the drug might have an effect  
10 where it might not. It might just be due to poor trial  
11 conduct.

12           So here are just some general steps for a  
13 non- inferiority trial. You can imagine the first  
14 thing you'd want to know is that the active control has  
15 a demonstrated quantifiable evidence of treatment  
16 effect relative to placebo and that would be based on  
17 external data.

18           So the first thing when you do a non-  
19 inferiority trial, you'd want to know that your active  
20 control that you're comparing your new drug to actually  
21 has an affect.

22           The second is that you'd want to ensure the

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1 control effect relative to placebo is consistent under  
2 the conditions of the non-inferiority trial; that the  
3 effect you saw based on historical data, would actually  
4 be seen in the non-inferiority trial.

5 And then in the assessment of the trial,  
6 you'd want to determine whether the effect of the true  
7 treatment is not unacceptably worse compared to the  
8 active control and that's based on the pre-specified  
9 non- inferiority margin.

10 And, again, the interpretation of these  
11 results of this step 3 can be misleading if the study  
12 lacks assay sensitivity.

13 So Dr. Temple already discussed assay  
14 sensitivity. I'm just going to repeat some of these  
15 points.

16 So assay sensitivity refers to the ability of  
17 the non-inferiority trial to distinguish an effective  
18 treatment from a less effective or ineffective  
19 treatment.

20 And it has these three points:

21 So, evaluating whether a trial will have  
22 assay sensitivity is based upon the historical evidence

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1 of sensitivity to drug effect. That's the first point.  
2 That just means that your active control has activity  
3 over placebo.

4           The second, similarity of the new trial to  
5 the historical trial; that's a constancy assumption.  
6 You know, it's the same point over and over again that  
7 you have an effective reactive control and that to be  
8 confident that the new non-inferiority trial will show  
9 that same effect, so you want to make sure the non-  
10 inferiority trial has similarities to the historical  
11 data; similar endpoints, similar timing of the  
12 endpoints, similar patient population.

13           These first two points are really points  
14 regarding the choice of the non-inferiority margin,  
15 your justification and would take place preferably at  
16 the protocol stage and be included in the protocol.

17           The third point is the quality and the  
18 conduct of the new trial. Certainly you should have  
19 things in your protocol that would explain how you're  
20 going to do a well-conducted trial, follow-up patients,  
21 et cetera, but would also be in the -- after the study  
22 is conducted and the assessment of how the trial was

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1 conducted.

2           So the first two points is -- again,  
3 regarding this non-inferiority margin. So the non-  
4 inferiority margin is based on two parts, M1 and M2.  
5 "M1 is based on the historical evidence of the  
6 quantitative effect of the controlled drug." The quote  
7 is from the ICH Guidance Document, "E10 Choice of  
8 Control Group and Related Issues in Clinical Trials"  
9 which it should reflect on certainties and the evidence  
10 on which the choice is based and should be suitably  
11 conservative.

12           "M2 is based on clinical judgment and it's  
13 really how much efficacy would we be willing to lose?"

14           And then M is going to be this -- my notation  
15 for the margin used in the trial, "It could be the  
16 entire effect of the controlled drug, M1 or it could be  
17 smaller, M2, if there were need to assure preservation  
18 of more than just any of the control effect."

19           And my next slides -- so I'm just going to go  
20 over these same points but more visually.

21           So, here's my -- on my X axis I have my  
22 difference between the control and placebo. So now I'm



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1 looking at the historical evidence of the active  
2 control. So now I'm going to look at control versus  
3 placebo.

4 On the left it favors the control drug; on  
5 the right it favors the placebo.

6 So, let's say I have some historical  
7 information that tells me I have a benefit of my active  
8 control over placebo based on previous placebo  
9 controlled trials. Let's say I pool that information, I  
10 get a pooled estimate of that effect of about 25  
11 percent. Of course, that's an estimate, there's  
12 variability about it, so I have a confidence interval  
13 ranging from 20 to 30 percent.

14 I'm going to take a conservative look and  
15 consider that 20 percent my M1. That's my effect of  
16 the active control over placebo based on this  
17 historical information.

18 Now, let's say I want to preserve 50 percent  
19 of that benefit over placebo. So my M2 is then going  
20 to be the acceptable loss of the effect relative to  
21 control. And then I choose my non-inferiority margin  
22 then based on M1, kind of the smaller of those two

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1 values.

2           So, let's say it's a more serious disease  
3 where failure is mortality and maybe I wouldn't be  
4 willing to lose 50 percent of that benefit; maybe I'd  
5 want to actually preserve more of that benefit. That  
6 would then leave me less for M2. I'd have a smaller M2  
7 and the margin would be pushed closer to zero. Or  
8 perhaps it's not a very severe disease and you can re-  
9 treat patients who fail and there's a need for more  
10 treatments out there, a strong need for that. Maybe  
11 I'd be willing to preserve a smaller amount of the  
12 benefit. I'd have a larger M2 and my non-inferiority  
13 margin would be pushed further away.

14           So either way we have M1 as fixed based on  
15 data, M2 is based on clinical judgment about the  
16 disease, et cetera.

17           So just to now bring this back to the non-  
18 inferiority trial, now I'm looking at the drug versus  
19 the -- the controlled drug versus the test drug. Let's  
20 say I set my non-inferiority margin at 5 percent. I  
21 conduct my study, calculate a confidence interval of  
22 the different between the test and the control and if

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1 it excludes that margin on the side favoring the test  
2 drug I'm going to conclude my test drug is non-inferior  
3 to the control. If it doesn't exclude that margin I'm  
4 going to conclude my test drug is not non-inferior to  
5 the control.

6 And in my perspective, where that zero is  
7 it's irrelevant. I'm excluding the M, period, whether  
8 or not it excludes the M or not.

9 So now I want to go over just some ways, how  
10 do you go about estimating M1? It's easy to say you  
11 just get an estimate, but when we actually then go  
12 through the literature, go through past trials, it's  
13 not easy to come up with that estimate.

14 So the preferred approach is using within  
15 study comparisons. So, let's say we obtain estimate of  
16 the treatment effect of the active control from  
17 multiple placebo control trials. So this would be  
18 ideal. Let's say in this graph here I had 11 placebo  
19 controlled trials of my active control. Each would  
20 have it's own confidence interval. The study sizes  
21 would be different. And I would then calculate a pooled  
22 estimate of that treatment effect which is the blue

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1 confidence interval at the bottom. I'd use that lower  
2 bound to get a very conservative estimate of that  
3 treatment effect as M1.

4 And this is just to point you back to the  
5 guidance. This is similar to the example 1-A in the  
6 non- inferiority guidance. So that would be our  
7 preferred approach. It's rare that we would have 11  
8 placebo- controlled trials, but that would be great.

9 So, the second one is -- I'm going to refer  
10 to is cross-study comparisons. It's an alternative  
11 approach. It's weaker than the previous approach, but  
12 maybe there's no placebo controlled trials available.

13 So, here we're going to get a conservative  
14 estimate of the active control from one source. So,  
15 for instance, let's say now my axis is a negative  
16 effect; let's say it's mortality or failure. So now I  
17 have my active control. I have five studies of the  
18 active control and I get a pooled confidence interval  
19 of the effect of the active control.

20 And then I'm going to get a conservative  
21 estimate of my placebo effect from another source. So,  
22 here, let's say I have 10 studies of a placebo. I

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1 mean, I'm sorry, five studies of the placebo and I'm  
2 going to get a pooled estimate of that effect for the  
3 placebo rate.

4           So I'm going to compare -- you can see a  
5 conservative estimate for the active control is the  
6 upper bound. The conservative estimate for the placebo  
7 is the lower bound and I'm just going to compare those  
8 two to get an estimate of M1.

9           And then we always leave it open to sponsors  
10 to come up with other approaches that they can come up  
11 with. And for -- I support the Division of Special  
12 Pathogens and Transplant Products, and a transplant --  
13 a sponsor of a transplant drug recently came in with a  
14 modeling approach. You know, it had a number of  
15 assumptions. It wasn't ideal but it was -- it wasn't  
16 bad and it was a new way that we had thought about. So  
17 we accepted that for this transplant drug. So, you  
18 know, we're willing to think of other ideas of how to  
19 justify a margin.

20           So, for every non-inferiority protocol that  
21 comes in we'll ask the sponsor to justify the non-  
22 inferiority margin, and we tell them it should address

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1 these three points. The first is the effect size of  
2 the control drug in the setting of the planned trial,  
3 M1.

4 And just as a quick aside, I have as the  
5 controlled drug in parentheses what the test drug is  
6 replacing. That's an important point when we come to  
7 combination drug regimens in a few talks from now.  
8 But, in general, you want to have an effect size of the  
9 controlled drug for M1.

10 Again, a discussion of the constancy effect,  
11 the constancy assumption, if that holds, how that  
12 historical data supports the design of your non-  
13 inferiority trial, and then a discussion of M2, what  
14 would be clinically acceptable for a non-inferiority  
15 margin.

16 And for the specifics of the justification of  
17 M1 the data driven estimate, we recommend that sponsors  
18 clearly state how the information was found. Was it  
19 placebo-controlled trials that the sponsor conducted  
20 themselves or most likely is it based on a literature  
21 search? What database was searched, what key words  
22 were used; we'd like that kind of detail.

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1           And, clearly state how the estimate of M1 was  
2   obtained. What model you used to estimate M1. And we  
3   always recommend that you consider the variability of  
4   the estimate. We don't want just the point estimate of  
5   the active control over placebo, we'd want an  
6   assessment of the variability and, again, probably a  
7   conservative estimate of M1 based on a lower bound.

8           Now, all of these justifications have a  
9   certain number of limitations to them. So we  
10   recommend that you just state upfront what the  
11   limitations are, what assumptions you need to make, et  
12   cetera.

13           And I always find it helpful if you come up  
14   with multiple ways to justify a margin. If you have  
15   just one or two placebo-controlled trials and you can  
16   justify a margin that way and then you can do a cross-  
17   study comparison and show that it's supportive of your  
18   previous estimate, that's certainly helpful.

19           And then the final M for the study, things to  
20   consider, are:

21           Is your M1 estimate suitably conservative?

22           Was the constancy assumption held?

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1                   How similar were those -- was that historical  
2 data?

3                   Was it from 50 years ago, was it from 5 years  
4 ago?

5                   Were they similar to the current control,  
6 current non-inferiority study endpoints, patient  
7 population, alternate treatment that a patient might  
8 receive from the historical study versus the current  
9 study?

10                  And in some cases, there's some weakness in  
11 that constancy assumption so there's then a discussion  
12 of do you need to reduce M1 even further and often  
13 that's termed "discounting." So, if the studies were  
14 from 50 years ago and maybe you're not comfortable that  
15 even though you took the lower bound of the confidence  
16 interval, that the constancy assumption completely  
17 holds maybe it's best to reduce that a little more to  
18 be a little more conservative.

19                  And then how to choose M2, things to consider  
20 is do you need to preserve a certain amount of that M1?

21                  It's also sometimes M1 is very conservative.  
22 Maybe you've determined your M1 based on the activity



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1 of your active control over another active therapy.  
2 Well, that would be a very conservative estimate for  
3 M1, so maybe your M2 doesn't need to be discounted  
4 further from your estimate of M1, so just some things  
5 to consider.

6           So, in conclusion, superiority trials should  
7 be conducted instead of non-inferiority trials whenever  
8 possible. And for non-inferiority trials you need to  
9 consider the historical effect of the control in the  
10 setting in which the effect was seen, M1. And it needs  
11 to be of extremely high quality to be interpretable.

12           And in the antibacterial setting, non-  
13 inferiority trials can be very challenging due to  
14 limited historical data. Obviously, if you see  
15 penicillin work to treat a disease way back when you're  
16 not going to conduct 11 placebo-controlled trials to  
17 make sure you're sure of that effect so the historical  
18 data is limited antibacterial setting.

19           Okay. Thank you.

20           BARRY EISENSTEIN: Given the fact that we're  
21 running a bit ahead of schedule which to me is a very  
22 pleasant anomaly, we should have some time for

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1 questions from either the panel first or from the  
2 audience.

3 Any questions?

4 JOHN FARLEY: I do.

5 BARRY EISENSTEIN: Please.

6 JOHN FARLEY: Yes, I have one. And, first,  
7 Karen, I wanted to thank you for a very clear  
8 presentation.

9 When I first came to the Agency, Karen was  
10 actually the only one that could actually explain this  
11 stuff successfully to me. So I appreciate that as  
12 always.

13 We're about to sort of present some examples  
14 of approaching -- approaches to determining an NI  
15 margin and I'm realizing that our use of the word  
16 "placebo" is about to be used very loosely. So I'm  
17 kind of wondering, and I'm going to give you a couple  
18 of examples, and wondering what the statistical  
19 implications are.

20 For example, say there would be and I  
21 actually don't think there are, but say there would be  
22 in trials of diabetic -- historic trials of diabetic

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1 foot infection where good nursing care and debridement  
2 was compared with antibiotics, and how would that  
3 figure into this? And I think also in VAP trials, for  
4 example, you might have a clearly ineffective  
5 treatment, group of patients, being compared with an  
6 effective -- with patients who received an effective  
7 treatment.

8 KAREN HIGGINS: Uh-huh.

9 JOHN FARLEY: So could you comment on that a  
10 little bit?

11 KAREN HIGGINS: So, for the first one, so  
12 let's say good nursing care versus antibiotic  
13 treatment, I would be comfortable with that as long as  
14 the antibiotic arm also got good nursing care.

15 So, you know, and if it were a randomized  
16 trial, all the better, you know, if you'd randomize two  
17 good nursing care, plus antibiotic versus good nursing  
18 care and you show a difference I'd be happy with it  
19 even if the good nursing care alone patients didn't  
20 actually receive a placebo pill. If we have, again,  
21 the cross- study comparisons which is more likely the  
22 case, you know, again, certainly I'm more comfortable

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1 with randomized control trials and I think this would  
2 just fall into a situation where you're not comparing  
3 actually randomized treatment arms and there's just  
4 going to be some -- a lack of comfort with the estimate  
5 that you come out with.

6 But I would certainly be comfortable with the  
7 -- with the nursing care example.

8 With the active treatment of the active  
9 control versus a less effective drug, as long as I  
10 could feel comfortable that that less effective drug  
11 wasn't harming patients, again, I would feel completely  
12 comfortable with.

13 And if it was less effective but still a  
14 little bit effective, then I'd be very happy with that  
15 cause then I'd actually have a more conservative  
16 estimate of M1. A less effective drug would be better  
17 than a no effective drug. So that would just give me a  
18 more conservative estimate and make me feel a little  
19 bit more comfortable about the non-inferiority margin  
20 estimate.

21 BARRY EISENSTEIN: Can I follow-up on that  
22 last question and answer. A very interesting point and

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1 we're going to get to this during the panel discussion  
2 when we talk about therapy for antibiotic resistant  
3 organisms.

4           So let's take a hypothetical case where  
5 you're dealing with ventilator associated pneumonia and  
6 a case of acinetobacter slips in on both arms. It  
7 turns out later that the active control is totally  
8 ineffective in vitro against the acinetobacter but you  
9 know that all antibiotics have potential adverse  
10 events. How do you balance that then in providing the  
11 relative drug effect of the -- what is now the testing  
12 or the test drug?

13           Let's say, you know, to make matters even  
14 more stark, 5 percent of the active control produces  
15 nephrotoxicity to the point that you could  
16 extraordinarily adversely affect the outcome?

17           KAREN HIGGINS: So, I'll start answering this  
18 and maybe some of my clinical colleagues can follow-up.

19           You know, certainly if, let's say there's a -  
20 - I'll start with the -- there's a high amount of  
21 adverse effects of the control or even the test drug.  
22 My initial concern, and I would have to kind of think

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1 about the whole protocol and how it was designed and  
2 how -- or the dropouts were treated. There's kind of a  
3 lot to think about.

4 But, certainly if there was kind of an  
5 adverse event and a large number that required patients  
6 to stop taking medication, go on to alternative rescue  
7 therapy, et cetera, I would have a concern regarding  
8 that -- regarding the kind of sloppiness of the trial.  
9 Not that that's something you could necessarily keep  
10 from happening but it would make me concerned in that  
11 maybe the treatment effects seen in the past wouldn't  
12 be relevant to the treatment effects seen in the  
13 current trial.

14 Of course, if that was seen in your  
15 historical database, let's say 5 percent of patients in  
16 the historical database couldn't tolerate drug and had  
17 to stop taking therapy and it was still considered  
18 better than placebo, then I'd feel confident that at  
19 least the current study would still have a kind of the  
20 constancy assumption and would still be able to assess  
21 the difference between the active control and placebo  
22 if placebo were in the trial.

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1 I don't know how --

2 BOB TEMPLE: It's the -- if the active  
3 control has an important toxicity, the usual effect  
4 that has is to make you accept a margin closer to M1  
5 and not insist on sort of being better or ruling out  
6 any loss. That's the main effect it usually has. We -  
7 - we go more conservative -- a less conservation  
8 margin.

9 I guess it calls into question the whole  
10 issue of what have you got here? That makes it very  
11 hard to deal with.

12 You also specifically asked about resistant  
13 organisms. The historical experience is mostly  
14 intended to reflect the effect in settings where  
15 there's a sensitive organism. The new drug, if it  
16 works in the resistant organism is obviously going to  
17 be superior to the control drug which has no effect in  
18 that.

19 But that's a little bit outside the terms of  
20 the study.

21 BARRY EISENSTEIN: I think this is a great  
22 setup for the panel discussion later because clearly

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1 the issue of antibiotic resistance is what we're  
2 confronting with as both physicians and people trying  
3 to develop new agents.

4 Thank you very much.

5 Let's move on then to the last speaker before  
6 the break, Dr. Joseph Toerner, is the Associate  
7 Director for Medical Affairs Office of Antimicrobial  
8 products at the FDA.

9 JOSEPH TOERNER: Hi, good morning. Thank you  
10 for that introduction. And, as Dr. Farley had  
11 mentioned, we're now going to move into a discussion of  
12 the more nuts and bolts of what the -- my statistical  
13 colleagues and clinical colleagues have struggled with  
14 in determining a non-inferiority margin. And I'm going  
15 to kick off the next series of three lectures with a  
16 discussion of approaching the non-inferiority margin  
17 for skin and skin structure infections.

18 And I have no conflicts of interest to  
19 disclose.

20 So, this is just an outline of what I'll be  
21 talking about. I'll be going through the published  
22 papers on skin infections and trying to describe the



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1 treatment effects of antibacterial drugs. I hope that  
2 you can appreciate the limitations and uncertainties of  
3 this approach to a non-inferiority margin justification  
4 and then stress the importance of the endpoints and the  
5 timing of the endpoints that describe the treatment  
6 effect.

7               So for acute bacterial skin and skin  
8 structure infections that are more severe, the active-  
9 control trial is an appropriate clinical trial design  
10 and we can consider then the non-inferiority trial  
11 design approach. And we need to define, as you've heard  
12 in previous lectures, we need to clearly define the  
13 treatment effect of the active-control drug over  
14 placebo and we can get this through historical evidence  
15 of sensitivity to drug effects.

16               We also need to define the endpoints and the  
17 timing of the endpoints that are used to define that  
18 treatment effect. And as our regulations say, we can  
19 just -- for example, we can reference previous placebo  
20 controlled studies if it were only that simple and this  
21 is one case where we don't have the luxury of having  
22 placebo controlled trials to justify a non-inferiority

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1 margin.

2           Now, there are some placebo-controlled trials  
3 in the literature but these are for the milder skin  
4 infections of skin abscesses and impetigo. And for  
5 several placebo-controlled trials for what I would  
6 consider minor skin abscesses there -- the treatment  
7 effect of antibacterial drugs was not observed.

8           Now, all of these patients underwent surgical  
9 incision and drainage and so that appears to be the  
10 principal treatment effect here for minor skin  
11 abscesses.

12           For studies of impetigo, the treatment effect  
13 was observed and in these studies that I've listed  
14 here, the results are quite variable and -- but the  
15 treatment effect is small and I can refer you to the  
16 retapamulin product where the label -- the treatment  
17 effects are described in the placebo group and you can  
18 see there's a very high rate of response in the placebo  
19 group, but, of course, the retapamulin was a higher  
20 response rate.

21           But for these milder skin infections that are  
22 often self-limited with non-antibacterial treatments,

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1 for example, surgical incision and drainage for a minor  
2 abscess, superiority trials are recommended.

3           So, when we move to more severe acute  
4 bacterial skin and skin structure infections, what are  
5 -- how are we defining this clinical entity? And we  
6 think there should be a sufficient amount of soft  
7 tissue inflammation so approximately 75 square  
8 centimeters of surface area of cellulites. And we also  
9 are considering abscesses, wounds and burn infections  
10 that have that sufficient amount of soft tissue  
11 inflammation that's surrounding that skin infection.

12           And so when we consider this definition,  
13 there are no placebo-controlled studies; however, we  
14 did find two controlled studies in the literature that  
15 used a non- antibacterial control. And these are  
16 patients with erysipelas. And we identified 470  
17 patients in two studies that received either  
18 ultraviolet light therapy or an antibacterial drug.  
19 And -- a sulfanilamide drug was used in these studies.

20           Mortality rates were low and were equally  
21 distributed among the treatment groups in these two  
22 studies. They were conducted at the Ruchill Hospital

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1 in Glasgow, Scotland. And patients were admitted to an  
2 erysipelas ward. And, you know, when we're paying this  
3 close attention to studies published in literature, we  
4 will often try to contact the authors and -- but in  
5 this case, the hospital closed in 1990 and we're just  
6 simply unable to audit the data.

7 But the publications themselves offer some  
8 strength. The authors randomized patients' treatment  
9 assignment. The authors pre-specified the endpoints  
10 that they were going to look at which quite frankly is  
11 something unusual for such an early historical paper.  
12 They looked at objective signs of the skin infection,  
13 body temperature and daily measurement of the size of  
14 the lesion. And all patients were admitted to that  
15 erysipelas ward so they all had similar background  
16 therapies.

17 But there are some obvious limitations when  
18 we're using these -- these studies to describe the  
19 historical evidence of sensitivity to drug effect.  
20 Only two studies and these were patients that had  
21 erysipelas and erysipelas is a clinical entity that --  
22 that -- unlike cellulitis doesn't involve deeper

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1 subcutaneous tissues, and so the demarcation of the  
2 area of inflammation is a little more clear for  
3 erysipelas patients. It's usually caused by  
4 streptococcal infections, although rarely  
5 staphylococcal infections can cause an erysipelas-like  
6 syndrome. But that is a limitation. It is only  
7 erysipelas patients that were evaluated in these two  
8 papers.

9           Treatments were open label and each of the --  
10 there were three clinical endpoints that they looked  
11 at. Each were evaluated separately and the third  
12 clinical endpoint that they looked at was toxemia. And  
13 even the authors themselves point out this was a very  
14 subjective determination of how the patient looked in  
15 the bed on that ward on a daily basis.

16           So the authors presented their data on a --  
17 really from day one to day five. And the paper they  
18 presented the proportion who had achieved cessation of  
19 spread of the erysipelas lesion and the proportion that  
20 had resolution of fever at these time points.

21           And here on this table I chose three time  
22 points, 48, 72-hour and 96-hours. And just to mention

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1 two of the -- Prontosil was the antibiotic that was  
2 used but it later was known that it metabolized to  
3 sulfanilamide.

4           The treatment difference -- the greatest  
5 treatment difference was noted at the 48-hour time  
6 point. And as you go further out to 72-hours and 96-  
7 hours, the treatment effect diminishes. And so, the  
8 results of Study 2 were also very similar. The  
9 greatest treatment difference was the 48-hour  
10 assessment of the lesion size and resolution of fever.

11           Similarly, as you go further out, the  
12 treatment effect, although in this particular study,  
13 only on the cessation of the lesion spread, the  
14 treatment effect had diminished over time.

15           So we used the results of these two clinical  
16 endpoints in a meta-analysis at the 48-hour time point  
17 of the cessation of spread of the lesion and resolution  
18 of fever. And you can see from the lower limit of  
19 these two clinical endpoints, the lower limit treatment  
20 effect is approximately 18 percent.

21           Now, as I had mentioned, the authors had  
22 evaluated each of these clinical endpoints separately

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1 and even the authors themselves point out that an  
2 individual patient may have had cessation of spread but  
3 has continued fever or vice-versa, has had -- has  
4 resolved their fever but their lesion had continued to  
5 spread and so they didn't analyze the results on an  
6 individual patient basis in that way.

7 But the way they presented their data, we can  
8 make some assumptions, and calculate the greatest  
9 proportion of patients who would achieve both  
10 resolution of fever and cessation of spread. The  
11 greatest proportion in the UV light treatment group and  
12 then the least proportion that would have achieved that  
13 endpoint in the antibiotic treatment group.

14 And really, the treatment difference didn't  
15 change all that much in this meta-analysis. The lower  
16 bound of the treatment difference is approximately 17  
17 percent.

18 And so from these studies we can provide a  
19 numerical estimate for a treatment effect based on  
20 historical evidence of approximately 17 percent. Now,  
21 that's using a responder endpoint of an evaluation of  
22 lesion size and resolution of fever.

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1           And just to highlight again for you the  
2 Limitations and uncertainties of these data, only two  
3 studies, they were patients that had the clinical  
4 syndrome of erysipelas, this responder endpoint was not  
5 evaluated by the authors in those papers, the  
6 treatments were open label and there was a lack of  
7 clarity for how the clinicians actually measured the  
8 lesion size on a daily basis.

9           So we feel with these limitations and  
10 uncertainties, that we should discount the magnitude of  
11 the margin size for the treatment effect by  
12 approximately 30 percent. So we're able to estimate an  
13 M1 that -- of about 12 percent. And, so, this is --  
14 this M1 of 12 percent is using a responder endpoint of  
15 -- an assessment of lesion size and fever resolution at  
16 an early time point, at 48-hours.

17           And we recognize that further developmental  
18 work needs to be done because this particular type of  
19 endpoint had not been evaluated in recent -- recently  
20 conducted clinical trials of skin infections. The  
21 developmental work on this endpoint needs to be done --  
22 really the focus -- the base endpoint is an evaluation



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1 of lesion size and this can be done, for example, in  
2 Phase II studies.

3           So some questions to answer with this  
4 developmental work is what's the expected proportion  
5 that would achieve the responder endpoint at an early  
6 time point in the active control group? And it's been  
7 expressed that there are some concerns with the use of  
8 fever resolution as a principal endpoint. Patients may  
9 not present with high fever with their skin infection.  
10 There are some concerns with the evaluation of a body  
11 temperature on -- during a trial.

12           And, also, how else to capture symptom  
13 improvement that's important to patients; for example,  
14 improvement in pain? And so those are some of the  
15 things to think about when developing an endpoint for  
16 efficacy in skin and soft tissue infection.

17           So the selection of the final M2 or the non-  
18 inferiority margin, really depends upon this additional  
19 work. And the example I give here if you're just  
20 choosing the cessation of spread of the lesion as a  
21 principal endpoint, you might expect that greater than  
22 95 percent would achieve that endpoint by 48 to 72

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1 hours. And, therefore, your non-inferiority margin  
2 justification might be 5 percent because you want to  
3 preserve a great proportion of that treatment  
4 difference. And those assumptions in a sample size  
5 calculation will also -- this would also be a trial  
6 size that's very feasible to conduct.

7           So, are there other sources of data we can  
8 look at to get a sense of what -- how this early time  
9 point measure performs? And in a 1928 study of 480 --  
10 it was a description of 480 patients with erysipelas at  
11 a time when there was no antibacterial treatment, at an  
12 early time point, a very small proportion of the  
13 patients were cured. Now, they didn't define what a  
14 cure was but if it meant complete resolution of signs  
15 or symptoms of the skin infection, if you look at the  
16 Day 14 time point where two-thirds were cured, and  
17 think about some of the more recently conducted  
18 registrational trials that evaluate a test of cure  
19 visit after a period of observation after completion of  
20 antibacterial drug treatment, you can see that two-  
21 thirds of the patients would have -- would have or  
22 might have been resolved without antibacterial drug

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1 therapy. So this just provides some emphasis that the  
2 treatment effect that we're trying to measure in a non-  
3 inferiority study should be that early time point.

4           There is also a more recently conducted study  
5 in 200 patients with cellulitis and this was a study  
6 designed to evaluate intravenously administered  
7 antibiotics in the home or in the hospital. But they  
8 chose an endpoint of cessation of lesion spread in this  
9 study. And as I had mentioned cellulitis involves more  
10 deeper subcutaneous tissues, perhaps the measurement of  
11 lesion size may be a factor to consider. But this  
12 provides some support for a constitute assumption  
13 because a great proportion, 90 percent or greater,  
14 achieved cessation of lesion spread at the Day 3 time  
15 point in this study.

16           So we can draw some comfort that the patients  
17 with erysipelas in 1937 on a cessation of spread  
18 endpoint, that patients today with cellulitis would  
19 behave very similarly on that endpoint.

20           So, in summary, we can assign a numerical  
21 value for M1 of approximately 12 percent for acute  
22 bacterial skin and skin structure infections and that's

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1 at an early time point, 48 to 72-hours. And, of  
2 course, the trial design should be planned to evaluate  
3 the sustained response during the remainder of  
4 treatment and for a period of observation after  
5 treatment.

6 The M1 is derived from within study  
7 comparisons of treatment groups that did not include a  
8 placebo. It was antibacterial drug versus UV light.  
9 There were some data from earlier studies that I don't  
10 have time to go through that UV light actually had some  
11 advantages and -- at that period of time.

12 The treatment effect was derived from  
13 patients with erysipelas but we feel it's appropriate  
14 to extrapolate the treatment effect of patients with  
15 cellulitis and how we've defined acute bacterial skin  
16 and skin structure infections with that surrounding  
17 cellulitis of a wound infection or a major abscess.

18 And that early time point is a consideration  
19 for clinical trial. And as you think about the  
20 discussion on endpoints later on today and the  
21 discussions about clinical trial site monitoring  
22 tomorrow, really the emphasis is on that early time

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1 point and that an assessment of time points after 72-  
2 hours are really problematic when assigning a primary  
3 endpoint in these trials.

4 And I wanted to thank you for your time and  
5 I'd be happy to take any questions.

6 BARRY EISENSTEIN: Panel, any questions,  
7 comments? Please, introduce yourself, please.

8 HOWARD HAIT: My name is Howard Hait from  
9 Paratek Pharmaceuticals.

10 Just a quick question on the idea of the non-  
11 inferiority margin and I'm referring really to Slide  
12 17, sorry Slide 15 where you were talking about the 17  
13 percent lower bound.

14 Two questions; one would be: Given the age  
15 of the study that was used for this, if you're looking  
16 at infection types these days that would be considered  
17 a lot more complicated than what might have been  
18 studied back in 1937, wouldn't the expected treatment  
19 effect size probably be a bit larger today than the 17  
20 percent that's being used for the basis of comparison?

21 And then the second question would be:  
22 Following that, how do you -- where do you come up with

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1 the idea of the 30 percent discount in margin size?

2 JOSEPH TOERNER: Well, to answer your first  
3 question, I think it is appropriate, and as you've  
4 heard some of the earlier speakers, we think it is  
5 appropriate to be very conservative when choosing an M1  
6 on the basis of historical studies. And, as you say,  
7 they were conducted a number of years ago and we don't  
8 have contemporary studies where we can look to the  
9 treatment effect today. And so we feel it appropriate  
10 that we be very conservative on this justification.  
11 And, you know, the antibacterial drugs, the sulfa drugs  
12 actually may not be -- we have better antibacterial  
13 drugs today for that particular indication for skin  
14 infection.

15 And so, you know, and UV light therapy may  
16 have had an effect so that we're not -- that treatment  
17 difference isn't actually against placebo, it may  
18 actually be a slight -- against a slightly effective  
19 therapy.

20 So, taking all those things into  
21 consideration, we feel very confident that there is a  
22 treatment effect there. But for those reasons, that's

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1 why we chose a conservative approach.

2           For the -- for the discounting we just feel  
3 that -- again, there were a number of limitations and  
4 uncertainties and -- and, you know, you may choose --  
5 you know, you may choose to present -- a sponsor may  
6 choose to present a different approach to how to  
7 discount that - - that limitation uncertainty. We just  
8 chose 30 percent to arrive at a margin of or to arrive  
9 at an M1 of approximately 12 percent.

10           BARRY EISENSTEIN: Given that we're having  
11 break very soon, Roger, one quick question or comment?

12           ROGER ECHOLS: It's a quick question.

13           BARRY EISENSTEIN: And introduce yourself,  
14 please.

15           ROGER ECHOLS: Yes. Roger Echols, I'm an  
16 independent consultant.

17           Given the fact that you've taken us through  
18 M1 and put a number of 12 percent out there, and the  
19 fact that skin infections tend not to have a high  
20 mortality even back in the historical data relative to  
21 other infections, how much preservation of M1 would you  
22 expect in determining what the M2 is? Would it be 50

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1 percent, less than that? That's the number -- M2 is  
2 the number we really need.

3 JOSEPH TOERNER: And I think I also gave you  
4 an example of what I think we would consider also a  
5 very conservative M2 approach. But it's also a  
6 situation where you have a very high response rate and  
7 you wouldn't want your test -- and you would want your  
8 test antibacterial drug to also have that very high  
9 level of response. You wouldn't want to give up much  
10 of that high response rate when you're -- when you're  
11 designing your non-inferiority clinical trial.

12 But I think what with the further  
13 developmental work that's done that incorporates an  
14 assessment of lesion size in addition to capturing  
15 other data that's important on a patient feels or  
16 function scale, those very high levels of response rate  
17 may not be observed at that 48 to 72-hour time point.  
18 And so, a response rate that's much less than 95  
19 percent, I think, choosing an M2 that may be closer to  
20 the M1 might be appropriate in that situation.

21 BARRY EISENSTEIN: Dr. Laessig has a brief  
22 comment.



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1 KATHERINE LAESSIG: Yeah, actually, Dr.  
2 Toerner just covered it, but just to reiterate that  
3 that sort of the point of saying that more  
4 developmental work is needed because we do not know how  
5 this endpoint will perform in contemporary studies so,  
6 therefore, it's difficult to just pick an M2 out of  
7 thin air and throw it out there.

8 BARRY EISENSTEIN: Dr. Temple?

9 BOB TEMPLE: One of the points made in the  
10 non- inferiority guidance is that you can't give it all  
11 on M1 because that's your assurance that the drug has  
12 some effect. And so we're quite inflexible on that.

13 M2 is always a matter of judgment. So if you  
14 said it was really 6 percent and it came in at 6.3  
15 percent or something like that, you might make the  
16 judgment that that's good enough. It's -- it has a  
17 different implication, there's a lot of judgment in it.  
18 We accept different approaches to figuring out what it  
19 is that are somewhat less conservative than the usual  
20 way we do it.

21 So, the guidance does suggest there is some  
22 potential give in there, but still it's a matter of

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1 judgment how sure we want to be.

2 BARRY EISENSTEIN: We're now adjourned. I  
3 have 10:04, we have a 16-minute break. We'll reconvene  
4 at  
5 10:20.

6 (Recess.)

7 BARRY EISENSTEIN: Before we bring up the  
8 next speaker, Dr. Boucher, had a comment that I was  
9 inadvertently unable to get to right before the break.  
10 Helen, please make your comment.

11 HELEN BOUCHER: Thanks, Barry.

12 I just noticed that I'm the only full-time  
13 clinician on the panel and it struck me during the last  
14 several discussions, somebody mentioned that the  
15 mortality is very low in this disease and I just wanted  
16 to bring everybody back to sort of the clinical reality  
17 that the reason we are having this discussion is that  
18 antibiotics work.

19 In the pre-antibiotic era mortality was 15  
20 plus percent and it was shown very clearly with both  
21 sulfa which is inferior and penicillin which was more  
22 efficacious that that mortality has come down to the 2

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1 percent that we live with in all commerce. And in our  
2 practice at my hospital, we still lose people to skin  
3 and soft tissue infections relatively regularly. You  
4 know, more complicated than we would include in these  
5 trials but I just want to make sure that as important  
6 as all the nitty-gritty that we're discussing is, and  
7 it is very important, that we remember that we're  
8 actually really lucky to be having this discussion  
9 because the antibiotics that we have do work.

10 So, thanks.

11 BARRY EISENSTEIN: Thank you for those  
12 important comments that I think will ground the  
13 discussion particularly as we get into the panel.

14 It's my pleasure to introduce Dr. Alfred  
15 Sorbello, Medical Officer of the Office of Surveillance  
16 and Epidemiology to continue the discussion on non-  
17 inferiority trials, this time focusing on nosocomial  
18 pneumonia.

19 AFLRED SORBELLO: Good morning. I'm going to  
20 be giving you a presentation on non-inferiority margin  
21 determination using cross-study comparisons. And I'm  
22 going to focus my presentation on clinical trials for

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1 antibacterial drugs and the treatment of nosocomial  
2 pneumonia. This is an issue that I've done some work  
3 in along with two of my statistical colleagues in  
4 determining a non-inferiority margin for this disease  
5 entity, and I'll try to walk you through our approach  
6 and our analysis to coming up with a margin in doing  
7 so.

8 I have no conflicts of interest to disclose.

9 And this slide basically is going to  
10 summarize both the methodology that was used in our  
11 approach to the NI margin determination and it's really  
12 going to be kind of an outline of the presentation I  
13 have today. But the four main aspects I'll be talking  
14 about in determining an NI margin using nosocomial  
15 pneumonia as an example of a cross-study comparison  
16 focused on these four aspects.

17 First, a search of the literature -- of the  
18 scientific literature and extraction of data to try to  
19 get information to assess really what is the treatment  
20 effect of active control compared to placebo.

21 One point that I'll be mentioning multiple  
22 times during my discussion, I'm sure, is that -- and

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1 one important point to keep in mind is that in looking  
2 into the literature related to nosocomial pneumonia and  
3 ventilator associated pneumonia, no placebo-controlled  
4 studies were retrieved.

5 We did, in thinking about and looking into  
6 this issue, need to consider a primary endpoint as well  
7 as the analysis population and I'll discuss that  
8 briefly in some latter slides.

9 And then based on extracting data we then  
10 were able to proceed to weighted analyses using  
11 separate estimates where we used all-cause mortality as  
12 the primary endpoint. And looking at separate  
13 estimates of mortality for placebo and active control  
14 estimating then the treatment effect of active control  
15 over placebo by a cross-study comparison along the  
16 lines of what was discussed earlier today, and then  
17 choosing a non- inferiority margin based on clinical  
18 considerations.

19 So I'll try to walk you through these steps  
20 and help you have a better idea of our thinking and our  
21 approach about this problem. So the first issue to  
22 think about was what would be a primary endpoint for an

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1 NI trial for nosocomial pneumonia?

2           When looking over the literature we retrieved  
3 about 39 articles in the scientific literature and we  
4 came across three different endpoints that were used in  
5 those various studies, all-cause mortality,  
6 attributable mortality and clinical response. And I've  
7 tried to just in a brief tabular form put some comments  
8 with each endpoint, but the main message here is the  
9 preponderance of data that was published, really  
10 addressed all-cause mortality.

11           And we felt that that was a good endpoint, it  
12 was objective, it was clinically critical, and it was  
13 relevant to the disease under -- under study and again,  
14 was supported by the preponderance of the data.

15           In terms of an analysis population we focused  
16 on the intent to treat population basically patients  
17 who would have received at least one dose of a  
18 treatment. We felt that this was an appropriate  
19 population because of the ability to preserve  
20 randomization. And some of the trials that we did find  
21 were randomized trials, some were not. And I'll  
22 discuss them a bit later.

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1           And we wanted to avoid any potential biases  
2 inherent in using other subpopulations whether it was  
3 per protocol or valuable populations or others where  
4 bias may be a problem in trying to determine a viable  
5 margin.

6           In thinking about and looking over the 39  
7 articles that we retrieved, we were very struck by the  
8 high degree of heterogeneity. We had two main groups  
9 of studies, a number of observational studies which  
10 looked at the adequacy of -- which actually reported  
11 mortality subsequent to adequate versus inadequate or  
12 an appropriate initial antibacterial therapy for  
13 nosocomial pneumonia.

14           And then there was another large group of  
15 studies which were basically randomized comparative  
16 clinical efficacy studies. And so my examples are kind  
17 of drawn in broad brushstrokes across those two groups.  
18 And I've tried to summarize in the table some of the  
19 sources and the variables where there was considerable  
20 heterogeneity including the size of the populations  
21 that were studied, the proportion with ventilator  
22 association pneumonia, mean age, mean APACHE II score

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1 as a parameter for a severity of illness, and then the  
2 time interval for reporting a mortality data.

3           And as you can see there's a fair amount of  
4 variability in each of those parameters across the  
5 different studies and certainly I don't want this issue  
6 of time interval for reporting mortality data to get  
7 lost because there were a number of studies where it  
8 was never really clarified over what period of time the  
9 deaths were accrued. So we didn't know, and some of  
10 these studies of whether it was while they were in the  
11 ICU, while they were in the hospital, whether it was 24  
12 or -- 14 or 24 or 28 days post-therapy. It was never  
13 clarified in the publications so we obviously didn't  
14 know.

15           So considering the -- the heterogeneity that  
16 we did encounter and the fact that we would need to  
17 select studies to go forward in determining separate  
18 estimates for placebo and active control, we tried to  
19 enhance comparability of patients across these studies  
20 by looking at studies where there were some similarity  
21 based on mean age and mean APACHE II scores, with  
22 APACHE II scores being at least some indicator of



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1 comparability of disease severity.

2           Now, as I say, with the absence of placebo-  
3 controlled studies, it was difficult to try to find  
4 data that would allow us to clearly estimate the  
5 treatment effect of active-control to placebo. And so,  
6 in looking at the scientific literature that we've  
7 retrieved, we found some relative sources of  
8 information that would be comparable or possibly  
9 analogous to placebo but obviously not true placebo  
10 data. And these included two sources of information.

11           One were two retrospective studies of  
12 hospitalized patients who had pseudomonas aeruginosa  
13 pneumonia that included some patients who were left  
14 untreated. And then a larger group of non-randomized  
15 observational studies which reported mortality in  
16 relation to the adequacy of initial antibacterial  
17 therapy.

18           And in -- and of the 39 articles that we  
19 originally retrieved from literature, 20 of those  
20 articles we felt were relative to trying to estimate a  
21 placebo rate. And this flow diagram tries to go  
22 through for you the selection process that we used and

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1 excluding various studies from consideration. But the  
2 main reasons that studies were excluded in our further  
3 analysis was either that they didn't report all-cause  
4 mortality, they didn't report mean age or mean APACHE  
5 II scores; we really couldn't assess in terms of  
6 comparability. There were a couple of studies that had  
7 higher mean APACHE II scores than some of the  
8 contemporary clinical trials and we were concerned that  
9 those patients may have had -- may have been sicker or  
10 had higher risk for death than those that they might be  
11 compared to.

12           And we also excluded the two retrospective  
13 studies involving hospitalized patients with  
14 pseudomonas pneumonia including the patients who were  
15 left untreated. And the reason for that was -- there  
16 was multiple reasons, but in particular, the studies  
17 didn't give us really a lot of information about the  
18 baseline demographics of the patients. We couldn't get  
19 our arms around -- around the patients, what their  
20 illness and their past medical history and treatment  
21 was.

22           There were -- in one of the studies actually

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1 the patients who were treated did worse than those who  
2 were left untreated. And the reports themselves didn't  
3 really give an explanation of why treated patients did  
4 worse.

5           And so of the 20 articles that we felt were  
6 relevant to placebo we have selecting only two, and  
7 these are the two studies that we used in some of the -  
8 - just a summary of the characteristics of the patient  
9 groups to try to determine a -- at least an analogue to  
10 a placebo all-cause mortality rate.

11           And when a meta-analysis was conducted, a  
12 random effects meta-analysis which is displayed on the  
13 slide, it yielded a placebo all-cause mortality rate of  
14 approximately 62 percent.

15           Now, in a similar fashion, we needed to  
16 determine an active control all-cause mortality rate  
17 and again, in the absence of placebo-controlled trials,  
18 we were able to retrieve a number of randomized  
19 perspective comparator-controlled studies involving  
20 various antibacterial drugs which I've listed on the  
21 slide. And many of these drugs have been or are being  
22 used in the treatment of patients with nosocomial

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1 pneumonia.

2           In terms of trying to select patients that we  
3 would eventually use in our meta-analysis, of our 39  
4 original articles that we accrued overall, 19 of them  
5 were relevant to the active control. And then we did  
6 have to exclude some studies including those that  
7 didn't report all-cause mortality, that didn't report  
8 either mean age or mean APACHE II scores. And we had a  
9 study where patients actually had lower mean age and  
10 APACHE II scores compared to contemporary clinical  
11 trials.

12           And so of the 19 articles relevant to active  
13 control, 5 were used for the meta-analysis.

14           This slide provides you the information on  
15 the - - on the 5 clinical trials; all-cause mortality  
16 rates are in the far left column, and when this  
17 information was then used in terms of a meta-analysis,  
18 the random effects meta-analysis yielded an active  
19 control, all-cause mortality rate estimate of 20  
20 percent.

21           So, at this point, having looked at the --  
22 having searched the scientific literature, retrieved

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1 articles, 39 in total, assessing the studies, trying to  
2 exclude those that for various reasons that I outlined  
3 were excluded from further analysis, we then need to  
4 set upon determining M1 which is the treatment effect  
5 of active control over placebo. And in this case, was  
6 our analogue for placebo, it was basically data driven  
7 by non-randomized observational studies of the adequacy  
8 of initial antibacterial therapy for nosocomial  
9 pneumonia.

10           As had been discussed earlier today, in doing  
11 a -- in deriving an estimate of M1 in this manner, we  
12 looked at the cross-study difference in the 95 percent  
13 confidence intervals for the two point estimates and  
14 the slide shows you that based on looking at the  
15 difference between the lower bound of the 95 percent  
16 confidence interval for the placebo, the upper bound,  
17 the 95 percent confidence interval for the active  
18 control, there was a cross-study difference of 29  
19 percent.

20           Now, we had some concerns about this 29  
21 percent difference because, again, in reviewing the  
22 studies and reviewing the literature, there were a

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1 number of shortcomings and a lot of areas of  
2 uncertainty. And we felt that we needed to discount  
3 this 29 percent cross- study difference further. And  
4 we discounted it by 50 percent which -- to 14 percent  
5 which appears to be a fairly large amount of  
6 discounting but we felt that it was justified.

7           And I've tried to list for you the sources of  
8 uncertainty that we considered in making a decision to  
9 discount, to discount to this degree. But, in  
10 particular, a couple that needed -- needed a fair  
11 amount of thought was the differences in the  
12 distribution of measuring and measured prognostic  
13 factors for mortality.

14           This was a confounding factor. And looking  
15 at and trying to analyze the mortality data from the  
16 studies of adequate versus inadequate were  
17 inappropriate initial antibacterial therapy because  
18 they were not randomized. So we couldn't be sure that  
19 the differences in mortality amongst those two groups  
20 was due only to the difference in the antibacterial  
21 treatment alone or due to something else which may or  
22 may not have been identified in the analysis by the

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1 authors.

2           The constancy assumption: We had concerns  
3 about this. This is a concept that's been discussed  
4 earlier today but, again, you're looking at differences  
5 in study design and conduct. Keeping in mind that our  
6 analogue for placebo, these were studies that in  
7 general were cohorts of patients that were analyzed  
8 retrospectively in terms of whether their initial  
9 treatment was adequate or not and then assessments of  
10 their mortality was reported as opposed to the studies  
11 that were available for active control which were  
12 prospective, randomized and comparative studies.

13           Other differences in sources of uncertainty  
14 that we thought about was patient comparability.  
15 Again, we tried to enhance that a bit by looking in  
16 terms of mean age and mean APACHE II scores, but their  
17 obviously could be other -- other characteristics of  
18 the patient population that may be important.

19           Antibacterial treatment regimen: Again, it's  
20 important to keep in mind that the non-randomized  
21 observational studies used to look at what an analogue  
22 of placebo, what the treatment effect would be; in

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1 those studies the treatment regimen was never really  
2 clearly defined.

3 Other factors to consider: Differences in  
4 medical technology, the prevalence of bacterial  
5 pathogens, and, again, this issue of the time period  
6 for reporting of all-cause mortality. It was not  
7 standardized, it was not uniform and then in some of  
8 the trials, you really didn't know over what period of  
9 time this mortality data was being compiled.

10 Now, one other approach to determining M1  
11 that we thought about but decided not to pursue was to  
12 look at the within study difference between patients  
13 who received what was considered adequate initial  
14 antibacterial therapy compared to those who received  
15 what was thought to be inadequate initial therapy.

16 But, in looking at trying to determine M1 on  
17 that basis, we were confronted with uncertainties that  
18 were very problematic for us. First, being that  
19 adequate therapy was never really defined so you didn't  
20 know whether they were on a single or multiple drug  
21 regimens. You didn't know on a patient-by-patient basis  
22 what the pathogens were. You were really unable to



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1 confirm whether adequate therapy was even the best  
2 available treatment regimen.

3           Secondly, in some of the studies there were  
4 statistically significant within study differences  
5 between patients who received adequate and inadequate  
6 therapy. There were a couple of studies where there  
7 were different -- significant differences in the two  
8 groups based on age or severity of illness. And  
9 baseline pathogens, some studies were more informative  
10 about that and some were not, so you really couldn't  
11 always get a good handle on prevalence of pathogens.

12           And, finally, again, we're back to this issue  
13 of could other either measured or unmeasured prognostic  
14 factors for mortality be confounding the findings that  
15 are reported from those studies; this being due to the  
16 lack of randomization?

17           So with our determination of M1, as I  
18 previously described, the 14 percent, we then needed to  
19 set upon choosing a non-inferiority margin. Again,  
20 keeping in mind that the non-inferiority margin is a  
21 decrease in efficacy for the treatment -- the new  
22 treatment compared to the active control that's

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1 considered to be clinically accessible -- acceptable  
2 related to the primary endpoint.

3           And in thinking about patients who have  
4 nosocomial pneumonia and ventilator-associated  
5 pneumonia, we felt clinically that it was important to  
6 preserve a substantial fraction of M1 due to two  
7 features.

8           First, the patients who developed nosocomial  
9 pneumonia and ventilator-associated pneumonia tend to  
10 be the sickest patients in the hospital, tend to be  
11 patients in the ICU, patients who have multiple co-  
12 existing medical problems, are on multiple concomitant  
13 antimicrobials and other concomitant medications. And  
14 so they -- they're patients who overall would tend to  
15 have a high risk for death.

16           But the other key point was that when you  
17 look at the all-cause mortality rate of patients who  
18 were treated with what's considered to be acceptable  
19 therapy there's still substantial mortality, it's 20  
20 percent. And so with those two concepts in mind, we  
21 felt that it was important to preserve at least half of  
22 M1 which yielded a margin of 7 percent which we felt

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1 was an appropriate margin based on all-cause mortality  
2 involving an active control population where the  
3 mortality rate was 20 percent for the -- for nosocomial  
4 pneumonia.

5 I just wanted to comment on some limitations  
6 of our approach and a number of these issues I've  
7 mentioned previously, but it's important to keep it in  
8 mind.

9 Again, in -- due to the lack of placebo-  
10 controlled trials, we were limited to determining a  
11 placebo all-cause mortality rate using studies that  
12 would give us some analogous or comparable data but  
13 certainly was not a true placebo. And the bulk of that  
14 data related to the relationship between the adequacy  
15 of the initial antibacterial therapy and all-cause  
16 mortality.

17 The problem was because these were non-  
18 randomized studies they're potentially confounded by  
19 the unequal distribution of measured and unmeasured  
20 prognostic factors for death. And so you couldn't be  
21 sure that the all-cause mortality rate differences  
22 reported in those studies were due to only to the lack

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1 of efficacy of the initial antibacterial therapy or  
2 they were due to something else that was not evident in  
3 reviewing the paper and -- and could be tied to the  
4 fact that these were not randomized.

5 And so it did create some uncertainty as to  
6 whether the true placebo rate derived from these  
7 studies could be either over or under estimated.

8 And certainly, since our estimate of M1 was  
9 closely tied into the separate estimates of placebo and  
10 active control all-cause mortality rates, you know, we  
11 did have to do a fair amount of discounting which I  
12 tried to explain our thinking, our approach to.

13 And, also, that in deriving an estimate of M1  
14 we did need to select studies to try to get studies  
15 that we thought were -- involved patient populations  
16 that were somewhat more comparable at least in terms of  
17 mean age and mean APACHE II score for severity of  
18 illness. And so there's always the issue of selection  
19 bias and obviously publication biases from studies  
20 drawn from literature.

21 So, in summary, in terms of clinical trials  
22 for antibacterial drugs for the treatment of nosocomial

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1 pneumonia, due to the lack of placebo-controlled  
2 trials, we've relied on a cross-study comparison of  
3 separate placebo and active control all-cause mortality  
4 rates, realizing that our placebo data was drawn from  
5 studies of inadequate and inappropriate initial  
6 antibacterial therapy.

7           We estimated the treatment effect of active-  
8 control antibacterial therapy over placebo as 14  
9 percent with all-cause mortality as the primary  
10 endpoint and involving the discounting that I discussed  
11 previously.

12           And then based on clinical considerations, we  
13 felt that a fixed margin of 7 percent which would be  
14 preserving at least 50 percent of M1 was appropriate  
15 based on that endpoint and assuming that the active-  
16 control all-cause mortality rate was approximately 20  
17 percent.

18           I wanted to acknowledge Doctors Komo and  
19 Valappil who are my statistical colleagues who worked  
20 on this with me. I've listed a publication which goes  
21 through our approach to the semi-margin determination  
22 and these are the reference articles, those that we

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1 selected for the process I described for use in the  
2 meta-analysis to get our separate placebo and active-  
3 control all-cause mortality rate estimates.

4 Thank you.

5 BARRY EISENSTEIN: Because of the importance  
6 of nosocomial pneumonia, I think we should take a  
7 little bit of time to ensure that the panel has gotten  
8 questions on this presentation.

9 Do I have any comments or questions?

10 ROBERT TEMPLE: Well, this illustrates very  
11 nicely how many judgments are involved in reaching all  
12 of these. I mean, 50 percent here, 30 percent here.

13 I guess what impressed me is that while one  
14 could argue about some of those, I mean, I thought the  
15 50 percent discount on the effect size was a bit much,  
16 probably -- probably it didn't have to be that large.

17 What you end up with is something that's  
18 actually quite reasonable, 7 percent, ruling out a 7  
19 percent difference is A, doable, B, apart from  
20 maintaining 50 percent of the -- of the M1, you really  
21 don't want to be that much worse than the standard  
22 therapy anyway. So, 7 percent, even if you just pulled

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1 it out of the air, as how much assurance do I want that  
2 I'm not worse, is not unreasonable.

3           So, with all the assumptions, I guess I'm  
4 struck that you come out with an approach that is A,  
5 doable and B, seems sort of clinically sensible as well  
6 even though one could look at every one of the  
7 assumptions along the way and say, umm, that's a little  
8 extreme or it doesn't have to be that big, or maybe  
9 it's really better than that. So, I guess I'm struck  
10 with the outcome at a sort of qualitative level here.

11           BARRY EISENSTEIN: Any other comments?

12           Helen?

13           HELEN BOUCHER: So, I just have a follow-up,  
14 Dr. Temple. Could you comment on two things?

15           One is this whole discussion is predicated on  
16 a worse case scenario. And, you know, whatever  
17 sponsors end up doing has to be reviewed. And so just  
18 because one would say it's potentially acceptable to be  
19 7 percent worse or 15 percent worse or whatever we say,  
20 that's usually not the case. Right? That's usually  
21 not how things play out. And when they play out,  
22 sometimes when they're even statistically better, there

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1 are other problems that make the trial a failure.

2           So, that whole element, I think, is important  
3 to remember, especially in diseases that are as  
4 complicated as this and where some of these decisions  
5 will impact a lot of the stuff that we'll end up  
6 talking about tomorrow. How you actually do the trial  
7 and how many inclusion and exclusion criteria and how  
8 many ways you go from ITT to pro protocol and end up  
9 losing half the patients. You know, a lot of these  
10 things that impact our ultimate -- your ultimate  
11 assessment of success or failure. So I'd love to hear  
12 your comment on that.

13           Then the other one is do you see any  
14 connection or bridge to clinical endpoints from this  
15 kind of mortality argument? And we talked about it in  
16 the position paper for the VAP trials, the older  
17 guidance that talked about, you know, the treatment  
18 effect for an endpoint such as clinical failure would  
19 likely be larger than that seen with a mortality  
20 endpoint and this whole notion of getting to a  
21 hierarchical endpoint where first you survive, then you  
22 succeed to make a trial that has a clinical endpoint



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1 that's more relevant perhaps to clinicians and  
2 patients? Could you comment on that as well?

3 ROBERT TEMPLE: Just remember, I don't do  
4 I.D., so -- yeah.

5 Actually, the thing in here that most  
6 impresses me that this is reasonable is -- and this  
7 goes to your question about clinical responses and all  
8 that, is that there actually still is something like a  
9 20 percent mortality here which means to my eye, you  
10 don't have to get into these other endpoints because  
11 the previous endpoint is still good or bad depending on  
12 how you look at it. You can really use the mortality  
13 data. You don't need a substitute because this allows  
14 you to do the trial you want to do using the endpoint  
15 that you know most about.

16 The nervousness if you start switching  
17 endpoints from mortality to something else is maybe  
18 something else in the environment, I mean, devices or  
19 something may have changed the lethality of the disease  
20 and if the lethality drops below the level that you're  
21 expecting then you're non-inferiority margin doesn't  
22 mean anything anymore and you won't have ruled out

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1 anything relevant.

2           The thing that seems reassuring to me, I'd be  
3 interested in what other people think, is that there  
4 still is a material mortality here so that there's a  
5 lot of reason to think the untreated mortality would  
6 still be considerably higher, at least what it was in  
7 the past, and that somehow this -- the death rate on  
8 this hasn't gone away. So I -- you don't have to get  
9 into the somewhat thorny problem of changing your  
10 endpoint from what it was in the past. I think you can  
11 still use the mortality, and it's not that far from  
12 what you thought it used to be. So that's pretty  
13 reassuring about all of these -- all of these  
14 endpoints.

15           I don't know if that answers everything.

16           BARRY EISENSTEIN: We'll certainly get into  
17 more of this. I think we're starting to get into the  
18 meat of the discussion in terms of drug development.  
19 I'd like to have Dr. Echols make one more comment or  
20 question before we move on then.

21           ROGER ECHOLS: I just -- Dr. Temple, you are  
22 often alluding to other disciplines and other

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1 therapeutic areas and one of the things I just think we  
2 need to keep coming back to is that this is about  
3 infectious diseases. And, particularly when one thinks  
4 about what is nosocomial pneumonia? No one has  
5 nosocomial pneumonia as an underlying disease when they  
6 come into the hospital. It's something that they get on  
7 top of why they're in the hospital.

8           And so, to say that, you know, there's a --  
9 there's still 20 percent mortality probably has very  
10 little to do with the infectious disease. It has much  
11 to do with their underlying diseases. And so, this was  
12 discussed a lot at the workshop a year ago but the  
13 clinicians, the ICU, the intensivists, they're just  
14 trying to get the patient over the nosocomial pneumonia  
15 so they can deal with the other things.

16           So, the attributable mortality -- nosocomial  
17 pneumonia can certainly kill and nosocomial pneumonia  
18 is a very important thing to treat, but that doesn't  
19 mean you're going to be able to impact mortality rates  
20 overall because of the underlying diseases.

21           ROBERT TEMPLE: Isn't it a reasonable  
22 assumption though that the infection would add to

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1 whatever their underlying condition was?

2 ROGER ECHOLS: If you didn't treat it at all?

3 ROBERT TEMPLE: Yeah.

4 ROGER ECHOLS: It probably would contribute  
5 or increase the mortality, but to say that it's just as  
6 simple, you're treating an infection, it's never --  
7 particularly with nosocomial pneumonia, as opposed to  
8 skin where people come in with a skin infection and  
9 that's what they have, they may have some underlying  
10 co- morbidities but they didn't end up in the ICU  
11 because they had pneumonia. They got pneumonia after  
12 they were in the ICU.

13 ROBERT TEMPLE: Yeah.

14 ROGER ECHOLS: And that's a very fundamental  
15 difference, I think, even within the area of infectious  
16 diseases in terms of what you're trying to treat and  
17 the confounding issues of other very serious co-  
18 morbidities.

19 ROBERT TEMPLE: Well, one of the things  
20 discussed at previous meetings on this subject, was the  
21 importance of getting into your trial, people of  
22 comparably severe status. You know, there were various

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1 scores, APACHE scores and things like that. That seems  
2 particularly important here; otherwise, your past  
3 impression of what drugs do in a particular setting  
4 become irrelevant.

5 I mean, if none of these people were going to  
6 die at all, then your margins all become meaningless.  
7 So, what -- I guess what impressed me here is that even  
8 in the modern era where people, I don't know if they're  
9 picking them just as sick as they used to be, but  
10 they're still getting a material mortality so it's not  
11 crazy to believe that the contribution of the drug is  
12 not so different from what you deduced in the past  
13 which is the crucial element in a non-inferiority  
14 study. You have to believe that the control drug is  
15 still doing what you thought it did. If you can't  
16 believe that, you can't do the design. So that seemed  
17 to help a little.

18 BARRY EISENSTEIN: One more comment.

19 Roomi, introduce yourself, please.

20 ROOMI NUSRATO: Roomi Nusrato, private  
21 consultant.

22 I think Dr. Sorbello's analysis is very

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1 informative and I'd like to segway from Dr. Echols  
2 comment and make the following observations for the  
3 panel's and the audience's consideration.

4 I think when we look at nosocomial pneumonia,  
5 if you look at the underlying causes of the diseases  
6 that the patients have, you'd often find there's  
7 chronic obstructive lung disease as an important  
8 driver. They also may have acute respiratory lung  
9 distress syndrome of various source that's very  
10 difficult to confine that is concurrent with the so-  
11 called pneumonia.

12 So I think in terms of analyzing what -- what  
13 the underlying cause is and what the outcome effect  
14 with antibiotic intervention, I think, has to be parsed  
15 fairly carefully before we decide that a death is a --  
16 is the relevant endpoint.

17 Something to keep in mind.

18 EDWARD COX: Yes, I think the last two  
19 questions have gotten -- they're really to the same  
20 issue here. And I think, you know, the information that  
21 Fred's shown has shown that there is, in fact, an  
22 effect on mortality. And there's no question that these

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1 patients have, you know, a number of co-morbid  
2 conditions and that contributes to the overall patient  
3 outcomes.

4 But, you know, there is a real effect here on  
5 mortality. Fred's shown it and it seem likes really  
6 the goal of therapy here. I mean, that, you know,  
7 really is to, you know, take these very ill patients  
8 who are in the ICU who have pneumonias and be able to  
9 improve their status with regard to mortality. So, it  
10 seems like a key endpoint and an important one to be  
11 looking at.

12 BARRY EISENSTEIN: Ed, if I could just then  
13 ask you another question. It goes back to what Helen  
14 Boucher had said earlier.

15 Given increasingly small margins which we  
16 understand the scientific basis for, increases  
17 exponentially the number of individuals one must enroll  
18 in a study and given the increase seemingly in  
19 practical nature of enrolling these individuals who are  
20 already extremely complex, what about the notion of  
21 being able to provide more intrinsic power to the  
22 study, not with more patients, but actually by

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1 increasing the number of observable events that are  
2 meaningful, like getting the patient out of the ICU?  
3 Like getting the patient away from the ventilator?

4 EDWARD COX: Right. So to follow on, you  
5 know, to Bob's comment on this, you know, if, in fact,  
6 the margin that you're looking at, the non-inferiority  
7 margin is derived from a patient population with  
8 particular characteristics, for example, a patient  
9 population that has a mortality rate of 20 percent if  
10 treated, you know, it seems then that you'd want to  
11 enroll that same type of patient population in order to  
12 be able to expect that the basis for the non-  
13 inferiority margin would still be present in your  
14 future trial. In essence that, you know, the -- the  
15 drug effect that you saw before is going to be present  
16 in your future trial because you've enrolled the same  
17 type of patients.

18 So then if you start to further move away  
19 from that and look at other endpoints because your  
20 patient population won't have enough events in it, then  
21 you can start to question, you know, is the effect that  
22 you expect to have in that population still, in fact,



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1 present?

2                   So I think it can become difficult, you know,  
3 unless there's other information, not to simply move  
4 away from, you know, really what is the basis for the  
5 non- inferiority margin justification by adding other  
6 things into the endpoint because you can't make it  
7 anymore because the population may be different.

8                   HELEN BOUCHER: So, I guess if I can just  
9 follow-up. I was looking at it differently. I think  
10 all of us who take care of these patients absolutely  
11 expect that you would make it on mortality. I think  
12 the question is: Can we include some of the  
13 potentially more clinically meaningful endpoints like  
14 getting off the vent, getting out of the ICU, getting  
15 better faster, hospital days, those kinds of things, in  
16 the same trial?

17                   Because I think there are -- there's a camp  
18 who says that we're not going to give out patient any  
19 antibiotic that's not going to meet the mortality  
20 hurdle. We're not -- an IRB is not going to approve  
21 that --

22                   EDWARD COX: Right.

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1                   HELEN BOUCHER:  -- in 2010.  So how can we  
2  get to these potentially clinically meaningful  
3  endpoints?

4                   EDWARD COX:  I think I understand your  
5  question now, Helen.

6                   So you're saying your primary endpoint would  
7  be mortality and then if you want a mortality, can you  
8  start to look down at some of your other secondary  
9  endpoints that would also be important?  And that  
10 sounds like a very reasonable approach to do, you know,  
11 in a stage fashion where you outlined prospectively how  
12 you would work hierarchically through -- you know, if  
13 your trial wins on the primary, how you're work  
14 hierarchically through your secondary endpoints.

15                  HELEN BOUCHER:  Yeah, and that was discussed  
16 in two ways.  Yeah, that was discussed in a  
17 hierarchical fashion and it was discussed as part of  
18 the quo composite which I know has a lot of baggage.

19                  EDWARD COX:  Uh-huh.  Yes.

20                  HELEN BOUCHER:  But hopefully, we'll discuss  
21 both of those in the course of --

22                  EDWARD COX:  Okay.  Good, thanks.

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1           ROBERT TEMPLE: Well, it -- showing that you  
2 win on one of those secondary endpoints, that's easy to  
3 interpret. And that could be a secondary endpoint.  
4 Showing that you're non-inferior on that endpoint poses  
5 the challenge of trying to say what the effect size of  
6 the control agent is, and I'm not sure how you're going  
7 to do that.

8           Yeah, but winning -- winning is always good.

9           BARRY EISENSTEIN: And maybe as we get into  
10 the panel discussion we could talk about winning on  
11 some of those secondary endpoints in terms of the  
12 specific organisms that are pan resistant to the agents  
13 that we're dealing with.

14           Roger, one last --

15           ROGER ECHOLS: One comment, one follow-up  
16 question for Fred.

17           BARRY EISENSTEIN: -- follow-up question and  
18 then we'll move on to the next speaker.

19           ROGER ECHOLS: The discussion about  
20 complicated skin, I'm still using that old term,  
21 ABSSSI, focused on early response as being the best way  
22 for assay sensitivity to show the treatment effect, yet

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1 for nosocomial pneumonia we're looking at 30-day all-  
2 cause mortality.

3           And so, my question is why -- and this was  
4 also discussed at the workshop a year ago, why don't we  
5 look in terms of antibiotic treatment effect, look at  
6 an earlier time point to -- to determine what M1 is  
7 rather than the 30-day all-cause mortality where  
8 someone will get over their pneumonia and then die of  
9 something totally different down the road?

10           ALFRED SORBELLO: In terms of the reporting  
11 period for mortality, as I had reviewed, many studies  
12 did not describe what that was. You really didn't  
13 know. And those that did, it was all over the map from  
14 during their hospitalization, during their time in the  
15 ICU, 10-days post-treatment, 28-day mortality.

16           So the literature doesn't really give you a  
17 clear direction on what that mortality reporting time  
18 period should be. Often what you see is 28-day  
19 mortality used but the data that's out of the  
20 scientific literature for nosocomial pneumonia doesn't  
21 give you that as a clear answer. And I think trying to  
22 determine what that time period would be in many ways,

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1 also depends on the duration of treatment with  
2 antibacterial drugs for this disease.

3           Some studies were very clear in terms of  
4 having short durations of treatments, 7 to 14 days.  
5 Some of the studies went out to 21 days. So, you have,  
6 you know, the variable will future clinical studies be  
7 designed where the duration of treatment is more  
8 structured and marginalized to 7 to 14 days and then  
9 28-day mortality may be reasonable or would we be  
10 looking at clinical trials where the duration may be  
11 more open-ended and then who knows what 28-day  
12 mortality means when a patient received 21 or 24 days  
13 of antibacterial therapy, your time of observing this  
14 patient for a mortality endpoint is too short.

15           So I think that certainly these are important  
16 issues for discussion. I don't know that the  
17 literature is going to give you the clear answer that  
18 you might hope to find. And I think that maybe the way  
19 -- a discussion of how future trials would be  
20 constructed may help to put some margins on both the  
21 issue of the duration of antibacterial treatment and  
22 when that reporting time period should be for looking

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1 at an endpoint such as all- cause mortality.

2 BARRY EISENSTEIN: Thank you for the very  
3 good discussion. Just a point of reminder, we will be  
4 having this afternoon's session focused on endpoints  
5 and I think some of the discussion that we've just  
6 started can be rejoined at that point.

7 But I'd like to bring Dr. Higgins back to the  
8 podium to finish off the formal presentations of the  
9 morning describing combination regimens under the non-  
10 inferiority discussion.

11 KAREN HIGGINS: Hi.

12 So, I'm going to talk now about approaches to  
13 determining a non-inferiority margin for the situation  
14 where you have a combination regimen. And the  
15 indication I'll use as my example will be tuberculosis.  
16 And this is based on work we did a year ago to prepare  
17 for a tuberculosis workshop that actually we had about  
18 a year ago today. So this is similar to the  
19 presentation I gave then.

20 No conflicts to disclose.

21 So, just again my brief outline. I'm going  
22 to talk about combination regimens, pretty much what I

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1 mean by a combination regimen and then I'll talk about  
2 a justification of non-inferiority margins for the TB  
3 multi-drug setting and I'll give three examples  
4 depending on what -- let's say a hypothetical new drug  
5 would do and then give some conclusions.

6           And just a disclaimer, so non-inferiority and  
7 justifying margins is difficult in general but then you  
8 add these multi-drug regimens and they can be kind of a  
9 mess. So just keep that in mind.

10           So, first, what do I mean by combination drug  
11 regimen? I mean that multiple drugs are going to be  
12 used in a treatment regimen, and just, for example,  
13 that would be true for tuberculosis where typically  
14 four drugs are given and for h-pylori infection where  
15 three or four drugs would be given to treat that  
16 infection.

17           The non-inferiority margin is not dependent  
18 on the entire effect of the active-control regimen  
19 versus placebo. That would be easy if we did it that  
20 way, but it's not -- it's dependent on the activity of  
21 the specific drug or drugs that the test drug is  
22 replacing in the treatment regimen which will make our

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1 non-inferiority margin smaller, so it's too bad, but we  
2 have to look at the specific drug that that test drug's  
3 replacing.

4           So it depends on the specific study design.  
5 We can't come up with one non-inferiority margin to  
6 tuberculosis and say we're done, we have to look at  
7 each specific study, non-inferiority study that comes  
8 in and determine a new margin for each one.

9           So the first, you know, things we need to  
10 consider is the regimen in which the new drug will be  
11 tested, what the new drug replaces in the control  
12 regimen and, again, as for all non-inferiority margin  
13 justifications, we still need to consider the patient  
14 population endpoint, the timing of the endpoint.

15           For this talk, I'm really going to focus on  
16 the combination aspect that everything holds.

17           So, just an example, let's say we have the  
18 following design where we have a two-armed study where  
19 drugs A, B, C and a test drug are going to be compared  
20 versus drugs A, B, C and a placebo. That's a simple  
21 study design where we're going to have to show that arm  
22 1 is superior to arm 2. This is a placebo-controlled



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1 trial, even though your placebo arm is actually still  
2 also receiving three drugs.

3           Well, what if it's unethical to give those  
4 three drugs alone? So then let's say we might use the  
5 following design where we have arm 1 being arm A, B, C  
6 and the test drug versus arm 2 which is drugs A, B, C  
7 and D. So, it would be simple again if we wanted to  
8 show that arm 1 was superior to arm 2. Essentially  
9 that would show that the test drug is superior to drug  
10 D, but that's typically a difficult hurdle to show that  
11 your new drug is actually better than another active  
12 drug, so what would typically be the case is we'd want  
13 to show non- inferiority for -- that arm A is non-  
14 inferior to arm B.

15           And in that situation we need to know the  
16 effect of D, just D with drugs A, B and C onboard. So  
17 to do that, we would look at -- we'd need an estimate  
18 of A, B, C and D versus A, B and C.

19           So, I just want to go now into the example  
20 for tuberculosis. The standard regimen is a multiple  
21 drug regimen where four drugs are given for the first  
22 two months in an intensive phase and that would be

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1 Ethambutol, Isoniazid, Rifampin, and Pyrazinamide  
2 followed by two drugs for the next four months in a  
3 continuation phase of Isoniazid and Rifampin, and this  
4 would be the control regimen used in most current drug  
5 sensitive TB trials.

6 And you can imagine a new drug could come  
7 along and could replace any of these drugs for any  
8 amount of the duration.

9 Some considerations that I'm going to make  
10 for the rest of this talk is again, that this -- this  
11 standard regimen that I just talked about will be the  
12 active control regimen and I'm going to change my  
13 notation slightly to shorten it where I'll have 2EHRZ  
14 as in two months of those first four drugs, followed by  
15 four months Isoniazid and Rifampin.

16 The primary endpoint through the rest of  
17 these examples would be the proportion of events with  
18 event defined as either death, treatment failure,  
19 meaning it didn't clear the tuberculosis, plus one-year  
20 post therapy relapse.

21 I'm only going to consider the non-HIV  
22 patient population, only consider drug-sensitive

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1 tuberculosis and in most of this talk -- well, in all  
2 this talk, I'm going to assume an interchangeability of  
3 kind that fourth drug, Ethambutol with Streptomycin  
4 labeled as typically over the years, Ethambutol has  
5 taken the place of Streptomycin as the fourth drug in  
6 this regimen and most of the historical information is  
7 based on using Streptomycin.

8               We did look to see if this was a reasonable  
9 assumption; it appeared to be a reasonable assumption,  
10 but it is one I had to make throughout this.

11              So, let's talk about the first example.  
12 Let's say we have a new test drug, T, and maybe it has  
13 shown very good activity and the sponsor wants to  
14 replace -- replace it in the regimen in place of R,  
15 Rifampin which is probably the strongest drug in the  
16 regimen. So you can imagine a two-drug -- two-armed  
17 trial where the test regimen is the standard regimen  
18 where T is replacing Rifampin versus the regular  
19 standard regimen with Rifampin.

20              So to justify the non-inferiority margin or  
21 M1 and I'm going to really focus on M1 here, we need an  
22 estimate of the effect size of the contribution that

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1 six months of Rifampin gives to this standard regimen.

2 So, to do this, we need an estimate of the  
3 standard regimen versus the standard regimen without  
4 Rifampin.

5 So, the first thing we're interested in the  
6 preferred approach is the information from within  
7 randomized trials. So we conducted a literature  
8 search. And for tuberculosis, luckily, the amount of  
9 studies conducted in tuberculosis is unbelievable. I  
10 mean, there are so many randomized studies. So, we're  
11 in a very good situation here to actually try to find  
12 some information.

13 The problem is there are no randomized  
14 studies that actually compared the standard regimen  
15 with the standard regimen without Rifampin. We did  
16 find three studies that showed the efficacy of Rifampin  
17 in the standard regimen but it wasn't versus the  
18 standard regimen without Rifampin, it was actually  
19 reversed to something a little better than that.

20 So, the first one, number one, it showed that  
21 Rifampin was better than Ciprofloxacin in its place, so  
22 that actually would give a conservative treatment

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1 effect, and that two and three removed Rifampin only  
2 from the continuation phase. So it didn't give the  
3 whole effect of Rifampin but it would help us get an  
4 effect of at least part of Rifampin, at least its  
5 activity in the continuation phase.

6           So, here, just to describe my graph, on the  
7 left I have favors the regimen with Rifampin; on the  
8 right it favors the regimens without Rifampin. And  
9 here are the three studies. You can see they're of  
10 varying size so the largest confidence interval for  
11 study one comes from a fairly small study whereas  
12 studies 2 and 3 were larger.

13           And in all of them we see that the regimen  
14 with Rifampin is favored over the regimen without  
15 Rifampin which is good and we calculated a pooled  
16 estimate of the effective Rifampin and it ranged from  
17 3.3 percent to 12.3 percent. So that would support an  
18 M1 of 3.3 percent.

19           The problem with 3.3 percent is it would lead  
20 to studies of about 1,000 patients per arm, probably  
21 unfeasible and on top of that, we know this is a very  
22 conservative estimate. It's really not getting us at

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1 the whole effect of Rifampin. So we wanted to go  
2 further and see if we could find more information.

3 So, again, because of the limited information  
4 available, in order to estimate the effect of Rifampin  
5 in the standard regimen within studies, we're going to  
6 now look at cross-study comparisons.

7 Now, the one good thing, it was nice to see  
8 that we actually found an effect, the 3.3 percent. So  
9 we're going to do the alternative approach where we get  
10 the conservative estimate of the standard regimen,  
11 compare that to a conservative estimate of the standard  
12 regimen without Rifampin and compare.

13 So, here, this graph is along the X axis. We  
14 have 22 different studies that we found. The Y axis  
15 gives the event rate with 95 percent confidence  
16 intervals. Again, it's a negative event so there --  
17 the lower the values the better.

18 On the panel to the far left I have the  
19 standard regimens with Rifampin, so I have 13 regimens  
20 that I found of the -- that looked at the standard  
21 regimen.

22 In the middle panel, I have four studies that

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1 looked at the standard regimen without Rifampin for the  
2 whole six months.

3 And in the final five, I have five studies  
4 that looked at a standard regimen without Rifampin in  
5 the continuation phase only. So it had Rifampin in the  
6 intensive phase but not in the continuation phase.

7 And one thing to first look at which I  
8 thought was a good sign, is the standard regimen with  
9 Rifampin had the lowest event rates which is what we  
10 would hope for. The next you'd see is the -- when we  
11 have standard -- when we have Rifampin only in the  
12 intensive phase, and that would be the panel in the far  
13 right, and then the highest event seen when we have no  
14 Rifampin at all. So in a way we kind of see a nice  
15 little dose response. It makes us feel that this data  
16 is showing us something.

17 But really the first two panels are what  
18 we're going to look at here, and I got a pooled  
19 confidence interval for the regimens with Rifampin of  
20 2.5 percent to 5.6 percent and a pooled confidence  
21 interval of the regimens without Rifampin, 11.5 percent  
22 to 20.8 percent.

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1           And then I'm just going to plot them on a --  
2 on one graph together so the confidence interval on the  
3 left is the regimens without Rifampin compared to the  
4 one on the right, the regimens -- the regimens with  
5 Rifampin compared to the regimens without Rifampin and  
6 the difference between those is 5.9 percent. And that  
7 would give us an M1.

8           So the conclusions for this first example are  
9 the -- we did see an effect within studies of 3.3  
10 percent which was encouraging but we know it's very  
11 conservative. The effect we saw using data from  
12 separate sources using a cross-study comparison gave us  
13 a 5.9 percent margin. We need to consider is  
14 discounting needed? And a big problem with this data  
15 and with all of our -- the TB studies we looked at, is  
16 in the historical studies there's a large proportion of  
17 missing data which is completely expected with a one-  
18 year post-therapy follow- up. You're going to have  
19 some missing data and the missing data ranged from 7  
20 percent to 43 percent. So it's a large amount of  
21 missing data.

22           And in these historical data -- the



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1 historical studies in literature did not give much  
2 information at all about this missing data; they just  
3 excluded them and, you know, all we know is the initial  
4 M and then the M they used in their final analysis.

5           So it is a problem with our -- with our  
6 information and we should consider this missing data  
7 and how it would effect a future non-inferiority study.  
8 And then there should be some consideration as needed  
9 as to an appropriate M2.

10           So, the second example is, let's say, we have  
11 a new test drug and maybe it has some activity against  
12 tuberculosis, but maybe it's thought it might be a  
13 weaker drug or that it might be an easier study to  
14 actually compare it against Ethambutol, the weaker drug  
15 in the regimen.

16           So, here I have a test regimen which is the  
17 standard regimen but now the test drug's replacing  
18 Ethambutol compared to the standard regimen.

19           So, now if we want to do non-inferiority for  
20 this study, we need to have an estimate of the effect  
21 size of the contribution of Ethambutol and the standard  
22 regimen. And, again, we need to compare the standard

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1 regimen with the standard regimen without Ethambutol.

2           And I actually found two studies that  
3 compared the standard regimen with the standard regimen  
4 without Ethambutol. Actually, these two studies I said  
5 I was assuming an interchangeability between  
6 Streptomycin and Ethambutol; the two control regimens  
7 in these studies both had Streptomycin instead of  
8 Ethambutol. So, in fact, this is getting us closer to  
9 the effect of Streptomycin in the standard regimen.

10           The problem is my pooled estimate of the  
11 confidence interval didn't exclude zero so I have no  
12 estimate of M1 from this information. So I -- it does  
13 not support an M1.

14           So we then took the next step and thought  
15 we'd look at data from separate sources, do a cross-  
16 study comparison. This is similar to the slide I  
17 showed you before. We had the same 13 studies of the  
18 standard regimen and then I have three studies of the  
19 standard regimen without Ethambutol. We have the same  
20 confidence interval for the standard regimen and now my  
21 confidence interval for the regimen without Ethambutol  
22 ranges from zero 13.7 percent. You put them on a graph

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1 and there's no separation between those confidence  
2 intervals. Again, no information for an M1 estimate.

3           So based on the information reviewed, there's  
4 not a large enough treatment effect of Ethambutol in  
5 the standard regimen in order to justify a non-  
6 inferiority margin for an outcome that includes one  
7 year relapse, plus treatment failure, plus death.  
8 Granted the data's limited. I'm not saying Ethambutol  
9 doesn't have an effect; we weren't able to measure it  
10 and maybe it would have an effect on a different  
11 endpoint.

12           Okay. The last example is a little more  
13 complicated situation. Now, we have our test drug, T,  
14 is going to be added to our regimen to allow for a  
15 shorter duration of therapy. So it's going to be  
16 studied in a randomized double blind two arm non-  
17 inferiority study where our test regimen is going to be  
18 T added onto Ethambutol, Isoniazid, Rifampin and  
19 Streptomycin. No, I'm sorry, Pyrazinamide given for  
20 months one and two, then in months three and four, it's  
21 going to be given with Isoniazid and Rifampin. And  
22 then nothing's going to be given in months five and

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1 six. So it's going to be given in a four-month  
2 treatment regimen.

3 And I'm going to compare that to the control  
4 regimen, the same standard control regimen. I just  
5 broke out the last two months of the continuation  
6 phase.

7 So how do we determine a non-inferiority  
8 margin? In a way, it looks like it's an add-on trial,  
9 but just for part of it, you know. So think about how  
10 to do -- determine a non-inferiority margin.

11 So, it is a non-inferiority study, and what  
12 you need to think about is what -- what is T replacing  
13 in the standard regimen? And T is actually replacing  
14 Isoniazid and Rifampin in months 5 and 6. So the part  
15 of the control-regimen being replaced by T is H & R  
16 during months five and six. So to justify a non-  
17 inferiority margin, we need to understand the standard  
18 regimen compared to the standard regimen without H & R  
19 in month five and six which I've just had this other  
20 little box here which, in general, is you're comparing  
21 the standard six-month regimen versus the standard four  
22 months regimen.

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1           So what's nice is they're actually two  
2 studies that were conducted that did this. The  
3 Singapore study actually had a randomized study where  
4 the six months was compared to the four months  
5 directly. This other one I have labeled EA 4 and 5;  
6 it's the East African four-study versus the fifth East  
7 African study where they checked -- they tested the  
8 four arm -- the four drug, four-month regimen in a  
9 randomized study, stopped that study and then  
10 immediately started a six-month regimen study  
11 immediately after and the same study cites a lot of  
12 similarity. So it's actually not a randomized study,  
13 it's probably as close as you're going to get to that.  
14 So we considered this one of our two within study  
15 estimates.

16           We calculated a pool, the estimate of the  
17 effect of H & R in months five and six. And we got a  
18 confidence interval of 4.8 percent to 12.1 percent.  
19 And that would lead to a conservative margin of 4.8  
20 percent for M1.

21           So for our conclusions for the treatment  
22 shortening, we believe a 4.8 percent M1 is justified

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1 using the information from within studies, the data is  
2 limited to only two studies, we have the same missing  
3 data concern that we had before and again, do we need  
4 the consideration as to perhaps small -- making that  
5 smaller or are we willing to have our M2 be M1 as well?

6           And just some brief conclusions, the multi-  
7 drug setting really sets the stage for many possible  
8 non- inferiority designs, all which require their own  
9 non- inferiority margin justification. And to  
10 illustrate this with the TB example, replacing of  
11 Rifampin led us to a 5.9 percent M1. The replacement  
12 of Ethambutol we couldn't determine a margin. And for  
13 the treatment shortening we got a 4.8 percent margin.

14           And because of the many backgrounds drugs,  
15 the treatment effect and subsequent non-inferiority  
16 margin is typically smaller compared to considering one  
17 drug by itself. So the problem with then discounting  
18 and two being smaller were already at such a small  
19 value as it is it's going to be difficult to do that.

20           That's all. Any questions?

21           BARRY EISENSTEIN: Any questions from the  
22 panel?

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1                   Please?

2                   FELIX GYI:   Probably more of a comment and  
3 more of a placeholder for tomorrow's discussion, but it  
4 seems to me that at least for this particular example,  
5 tuberculosis, it doesn't seem as if an IRB would feel  
6 comfortable approving those types of regimen especially  
7 in light of what you presented.   And so I wonder if  
8 there would be a study or these types of studies would  
9 be conducted off-shore as opposed to being conducted  
10 here in the United States?

11                  EDWARD COX:   You know, that's an interesting  
12 comment.   We did talk about justifications for NI  
13 margins for drugs for TB, I guess it was about a year  
14 ago now, and it was interesting, you know, after Karen  
15 gave the presentation then, one of the first comments  
16 we received is I don't want to give up anything for TB  
17 therapy, I want something that's at least as good as  
18 what I get with Rifampin.

19                  So, we understand your comment and, you know,  
20 I think that really gets to what the heart of M2 is  
21 which if how much are you willing to give up.   So the  
22 presentation provides information about, you know, an

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1 approach to justifying an NI margin works through some  
2 of the complicated issues with combinations. But, yet,  
3 it still really is an important clinical, you know,  
4 discussion and decision point as to how much you'd be  
5 willing to give up. And maybe the answer is is not  
6 much. And maybe the answer is sometimes that you  
7 wouldn't want to give really much of anything up.

8               So, good point. Thank you.

9               BARRY EISENSTEIN: Any other questions from  
10 the panel or from the audience on this last  
11 presentation before we move into the panel discussion.

12              Not seeing any, I'd actually like to ask Dr.  
13 Sorbello a question. I got text messaged during the  
14 last presentation by George Talbot who many of you know  
15 who sent a very interesting question. And that is,  
16 given the very recent history with failed, if you will,  
17 failed VAP trials for Tygacil and for Ceftobirpole, can  
18 we extract meaningful data that goes beyond just  
19 mortality that would help us?

20              ALFRED SORBELLO: That's a -- it's a  
21 conundrum that we actually talked about at the workshop  
22 in 2009, which was can we extract an NI margin for a



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1 clinical response endpoint using mortality data? And  
2 in our thinking, meaning myself and my statistical  
3 colleagues, we didn't think that that was very well-  
4 founded to do that.

5 In looking at the data, there's really no  
6 prospectively compiled placebo or placebo analogue data  
7 in terms of what happens for clinical response as the  
8 endpoint.

9 The -- the data that we used as our analogue  
10 for placebo was very problematic as I tried to explain  
11 with a lot of uncertainties. You know, we couldn't --  
12 you know, you couldn't even be certain that -- that  
13 someone who responded say to an inadequate or  
14 inappropriate empiric initial treatment regimen that  
15 you could use that as a surrogate for survival and so  
16 make some type of an extension between mortality or  
17 survival and clinical response.

18 So, we had a lot of problems in trying to  
19 extrapolate from a mortality endpoint to clinical  
20 response. Unless there's, you know, other data that  
21 would be uncovered, but we did not find any there.

22 BARRY EISENSTEIN: Dr. Boucher, you want to

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1 make

2 --

3 ALFRED SORBELLO: We didn't have any  
4 confidence in trying to do that.

5 BARRY EISENSTEIN: Dr. Boucher?

6 HELEN BOUCHER: Yes, I totally hear you on  
7 the difficulty there with that specific question, but I  
8 was taught that looking at the failures in non-  
9 inferiority trials is actually one of the most  
10 important exercises because of the nature of these  
11 trials and because of the tendency of biasing towards  
12 the known.

13 So, understanding the failures is very  
14 important. And I'm a little bit perplexed that we  
15 can't learn anything from the failures in these huge,  
16 you know, trials that were conducted in good faith with  
17 lots and lots of patients around the world and just  
18 wonder if -- if there isn't some way perhaps that more  
19 could be gleaned from all that data to help us as we  
20 design future trials.

21 BARRY EISENSTEIN: Perhaps in a similar  
22 fashion to the great insight we received with the

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1 failed Daptomycin/Ceftriaxone community-acquired  
2 pneumonia trial. There was a tremendous amount of  
3 information from that.

4 EDWARD COX: But I do think we learn some  
5 from those situations, you know, where there's  
6 unfortunate failure in a clinical trial. You know, to  
7 actually get to the non-inferiority margin sometimes  
8 the failures are not quite so large or quite so bad  
9 that they may, you know, get to actually approximating  
10 what an untreated patient might experience.

11 So, but I do think we learn something from  
12 the - - you know, the failures.

13 And, you know, to Barry's point too with  
14 Daptomycin, I mean, I think, you know, what we learned  
15 from that experience was really quite remarkable and  
16 it's a credit to the folks that did, you know, really  
17 interrogate that data more to see what we could learn.

18 And in addition too, you know, instances  
19 where, you know, there is a failure, I mean, you know,  
20 it really underscores, I think the importance of, you  
21 know, what it is that we're trying to learn from the  
22 trial and about the effect of the drug. And if it's a

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1 situation where, you know, mortality is, you know, the  
2 endpoint, and that's where the drug is not performing  
3 as well, it really, you know, I think underscores the  
4 importance of really understanding what the effect is  
5 of the drug on mortality.

6 BARRY EISENSTEIN: And just to underscore the  
7 Daptomycin experience again, although mortality was not  
8 statistically significantly different, the overall  
9 success failure was quite different and that's, in  
10 fact, where the true inferiority was seen with  
11 Daptomycin.

12 EDWARD COX: Right. And I'm sorry, I didn't  
13 mean to imply that that was Daptomycin, but just more  
14 in general. So thanks for clarifying that, Barry.

15 BARRY EISENSTEIN: Before going to the panel,  
16 unless there's a specific question on the last  
17 presentation, did you --

18 WILEY CHAMBERS: This is Wiley Chambers. I  
19 actually want to come back to the previous discussion.  
20 Isn't the real problem that there hasn't been a trial  
21 in a while that's had a mortality of 20 percent? I  
22 mean, I don't -- if somebody can tell me when the last

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1 trial was that had a mortality of 20 percent, but I  
2 think it's been over ten years.

3 EDWARD COX: Yes, so, I mean, we did look at  
4 some of that. And, I don't know, Joe, do you want to  
5 comment on some of what you found? I mean, there's  
6 been a range of morality over time in studies.

7 JOSEPH TOERNER: Yeah, that's right. Looking  
8 at recently conducted -- more recently conducted  
9 studies that were submitted to us as registrational  
10 trials the mortality was -- was quite variable and was  
11 anywhere from 8 percent to 28 percent. But trying to  
12 understand why there was variability in those studies,  
13 we came to a general conclusion that the studies  
14 enrolled a sicker patient population with -- with  
15 ventilator associated -- or studies that enrolled a  
16 greater proportion with patients on a ventilator, had a  
17 higher mortality rate that approached and was around 20  
18 percent.

19 BARRY EISENSTEIN: So in starting off the --

20 BOB TEMPLE: It just makes that point that  
21 you are to a degree the slave of your past. I mean, if  
22 the data on what the effect of drugs is comes from

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1 people -- from trials in relatively sick people and  
2 that's all you have, that's really your only basis for  
3 doing a non- inferiority study. So it's very important  
4 to get those people into the trials. Unless somehow  
5 you can translate that survival into some other  
6 endpoint and I think everybody's been thinking about  
7 that and having a lot of difficulty doing it.

8           BARRY EISENSTEIN: In setting up the panel,  
9 I'd like to make some perhaps obvious -- almost obvious  
10 points to get the discussion going. In a world of  
11 increasing antibiotic resistance with drugs that  
12 uniquely depreciate with use, antimicrobials being  
13 unique in all of therapeutics, how do we develop new  
14 lifesaving antibiotics on a regular basis, because we  
15 need a regularity in terms of the -- replacing the  
16 depreciation in an era as well where business  
17 considerations recognize that return on investment for  
18 antimicrobials are typically viewed as significantly  
19 lower than for many other therapeutic areas.

20           So, the two big questions then that are  
21 posed, the number one challenge is justification of the  
22 non- inferiority margin for antimicrobials, we could

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1 think of this as the fact that antibiotics first used  
2 over 70 years ago before the year of modern trial  
3 design, severity of many infectious disease conditions  
4 precludes using placebo which prevents us from using  
5 the preferred superiority approach, leaving the non-  
6 inferiority margin then based of studies done 60 plus  
7 years ago, running into major issues in the constancy  
8 consideration.

9           So how can these challenges be overcome?

10 That's question number one.

11           And question number two: In increasing  
12 situations involving MDR, XDR, or PAN resistant  
13 bacterial infections, how might we perform a  
14 superiority trial ethically? What about to remind us  
15 of a presentation given by Dr. Brad Spellberg last week  
16 at the other workshop? What about organism specific  
17 approval under conditions of low incidence of pathogen  
18 infection at any one particular site where we could get  
19 aggregated data from multiple sites under conditions  
20 where PK, PD, local penetration, action of  
21 antimicrobial in vivo models, et cetera are well  
22 understood.

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1           The issue raised earlier by Dr. Boucher about  
2 mortality and skin. We only need to think about the  
3 pre- antibiotic era with bacteremia due to staph  
4 aureus, mortality of 82 percent. And dealing even in  
5 the modern era with a mortality of 25 to 35 percent in  
6 many of these PAN resistant organisms get us well into  
7 that category.

8           So, I will open it up with those two  
9 questions.

10          Scott, you've been quiet so far.

11          SCOTT HOPKINS: I'm struck by not only at  
12 this conference but over the years really how there has  
13 seemed to be a different orientation to problems that  
14 we all acknowledge are here in terms of developing  
15 compounds between people in the audience, clinicians or  
16 people in industry and people at FDA.

17          And I think that results or that's because  
18 the FDA in terms of this particular therapeutic area is  
19 not sufficiently Bayesian and I'm struck by Bob's  
20 comment which he kind of tossed off during his very  
21 good talk that we really don't think about priors too  
22 much in terms of the anti-infective area.



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1           But, I think, that is an area that we need to  
2 think a lot more about and it causes, I think, some of  
3 this difference in approach from one side of the  
4 microphone to the other. I.D., in my view, is an  
5 inherently Bayesian sort of practice. And I.D. Docs  
6 whether overtly or closet, are Bayesians.

7           And by that I mean, if you think about  
8 infectious diseases and training, you start off in a  
9 laboratory with bugs that have been isolated from a  
10 patient and your pathogen is right there in test tube  
11 or on a plate and you can characterize the resistance  
12 mechanisms and apply antibiotics to it and so forth and  
13 learn an awful lot that you can't learn in virtually  
14 any other therapeutic area. So we've got not only from  
15 in vitro data but in vivo data. We've got animal  
16 models that in some cases are very predictive so that  
17 we've even built this edifice of PK PD which in some  
18 situations like quinolones and community acquired  
19 pneumonia are really amazingly predictive. And anyone  
20 who knows me knows that I'm not a fan of PK PD, but it  
21 does show that prior information that we have available  
22 is actually quite powerful but we don't seem to take

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1 advantage of all of that information.

2 And I think the result is that it leads to  
3 what many of us view as an overly conservative  
4 approach, particularly to coming up with discounts to  
5 treatment effect.

6 So I am -- and I'm not sure what the answer  
7 is to making use of this information but it's powerful  
8 information that we don't have really in any other  
9 therapeutic area and we should try and make use of it  
10 in some form or fashion.

11 Now, I do have -- I do hold out some hope for  
12 the FDA because there is a spark of Bayesian there and  
13 that goes back to the anthrax and the Cipro business.  
14 So when the chips are down the Bayesian comes out.

15 BARRY EISENSTEIN: I'm sure the other people  
16 sitting on this side of the table might like to  
17 respond.

18 BOB TEMPLE: Well, just a little bit. You  
19 know, not burdened by any experience in infection  
20 disease I've always thought that in vitro sensitivity  
21 in animal data should count a lot. In fact, in some  
22 cases I wouldn't be totally horrified if we used those

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1 sort of surrogates as actual endpoints. They're  
2 unusually plausible.

3 But what I'm told by all the people that do  
4 know about infectious disease is that sometimes your  
5 expectations don't really work out, that it doesn't get  
6 to the right place in the body blah-blah-blah. So, I  
7 think, everybody in this area is a little bit inclined  
8 to think sensitivity tells you something but how far to  
9 go is not clear.

10 Now, I went through my last couple of slides  
11 fairly quickly, but there is clearly room in the non-  
12 inferiority guidance to make use of your prior beliefs  
13 about such things in terms of not insisting on a 97-1/2  
14 percent lower bound but making it a little narrower, 95  
15 percent or 80 percent confidence interval, something  
16 weird like that. We don't do that very often and it  
17 would make us very nervous to actually do it, but those  
18 are plainly things to think about. And it's okay.

19 Even the less conservative approach to M2  
20 that is clearly discussed in the guidance reflects some  
21 view that once you know that it works at all you're  
22 well along the way and you can -- you can use your head

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1 on some of the other matters.

2           One of the points you raised was resistant  
3 organisms. My assumption is that if you could actually  
4 treat resistant organisms and show a nice effect in a  
5 bunch of people who would be expected to have a 20 to  
6 30 percent mortality, even a single arm study might be  
7 persuasive. I think that needs to be discussed. But  
8 there may be no intelligent comparison if it's the  
9 first drug that works in it.

10           And so I don't think there's anything  
11 impossible about even using historical controls in that  
12 setting as we do in a lot of places. You treat a  
13 really bad cancer and cure it, you don't need a control  
14 group usually. And I'm -- my guess is some of those  
15 situations would obtain here. But somebody who knows  
16 more about it needs to address that.

17           BARRY EISENSTEIN: I think I'm perhaps  
18 hearing a breakthrough comment in terms of the single  
19 armed study. Dr. Cox, do you want to respond?

20           EDWARD COX: Let me just say a couple of  
21 things. I think, you know, Scott, I had to chuckle a  
22 little bit because one of the reasons we had the

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1 workshop was to get out there to sort of bring in some  
2 of our thinking to you to sort of, you know, help  
3 provide some clarity as to how we're approaching some  
4 of these issues, thinking that that would be helpful  
5 collectively for everybody.

6           So, I know you're trying to bring us around  
7 and I think we're trying to provide you some more  
8 information that we think will be helpful to the  
9 community-at-large to address some of the challenging  
10 that have been facing the world of antibacterial  
11 trials. So just sort of starting there.

12           And I do think the prior information that we  
13 have about an antibacterial drug, you know, is very  
14 helpful and should really help us to design, you know,  
15 trials that will be informative.

16           And, you know, it's interesting that if you  
17 look at antibacterial drugs, usually things pan out but  
18 then occasionally there are things that don't work out.  
19 We've got a couple of recent examples where, in fact,  
20 the clinical trials were informative and the drug  
21 didn't work out and perhaps after the fact people go  
22 back and look and then understand why maybe, in fact,

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1 the biology didn't work out as they thought it was  
2 going to be, but without that clinical trial pointing  
3 us in the direction of oh, maybe something didn't work  
4 here, I'm not sure that that would have been found out.

5           So, it -- you know, the clinical trials  
6 really do add something, I think, to understanding  
7 what's going on but, you know, the prior information is  
8 helpful too. And the prior information is particularly  
9 helpful, I think, in how you might design a study, you  
10 know, to show the effect of the drug clinically that  
11 you've seen in other areas.

12           BARRY EISENSTEIN: Ed, what are your thoughts  
13 about -- Paul Ambrose has frequently talked to me about  
14 the use of exposure response in particularly difficult  
15 situations. What's your thought about using that in  
16 dealing with some of these very difficult PAN resistant  
17 infections?

18           EDWARD COX: So, you know, exposure response,  
19 I think, you know, we've talked about this some and  
20 it's come up at previous workshops. I mean,  
21 essentially if folks are randomized to different  
22 exposures or different durations then essence, you've

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1 got a randomized trial and you can try and sort of sort  
2 through it.

3 I think the difficulty becomes that, you  
4 know, there's always the lingering question of, you  
5 know, is there something that's related, you know, to  
6 why the patient may have a lower exposure that may, you  
7 know, impact upon their outcome. So there's always  
8 sort of this residual concern about degree of  
9 confounding there that makes it difficult to rely on  
10 that type of information alone.

11 I mean, I can tell you, you know, we are  
12 looking at that all the time and folks are doing it all  
13 the time and it can be, you know, helpful information  
14 both with regards to safety and efficacy if you see  
15 exposure response. But there is always that lingering  
16 degree of concern about, you know, could there be  
17 factors other than the actual exposure here that may be  
18 contributing to the observed outcome and that's what  
19 makes it tough.

20 Bob, you may want to comment on that.

21 BARRY EISENSTEIN: And then -- and then given  
22 that I and many of the other practicing physicians in

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1 the room probably just received a Dear Doctor letter  
2 last week from Pfizer about the fact that there's a  
3 mortality imbalance in Tygacil as shown by aggregated  
4 data from Phase III, isn't there also the possibility  
5 of early approval, provisional approval, if you will,  
6 for very difficult to deal with infections? We're  
7 talking about the PAN resistant bacteria where you may  
8 not have as much as information as you would typically  
9 want, but obviously, you've got then opportunities for  
10 pharmical vigilance and further follow-up later.

11 EDWARD COX: Right. So in the, you know,  
12 highly resistant organisms, it may be an area where at  
13 least some folks I've heard talk about this, talk about  
14 the possibility of doing, you know, either an add-on  
15 study where you take the new age and you add it on to  
16 standard of care versus standard of care.  
17 Alternatively, you might do the new agent compared to  
18 standard of care, again with the goal of trying to show  
19 superiority.

20 And then a second approach or I'm sorry, a  
21 third approach may actually be to either try and change  
22 the dose or duration of the experimental agent. So,



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1 and then, you know, Bob's mentioned the idea of  
2 possibly a historically-controlled approach.

3 So, you're depending upon how well you  
4 understand and how predictable the effect of, you know,  
5 standard control therapy might be, a historical control  
6 might be a possible way to go here.

7 So, there are study designs and if you have  
8 an agent that adds something to what's currently out  
9 there, it should be a situation where you would hope  
10 you would be able to show that benefit in a feasible  
11 and ethical trial design.

12 As far as accelerated approval, you know, it  
13 would sort of depend. You know what I mean? You know,  
14 what's the endpoint that you're going to be looking at?  
15 You know, one of the things that we can do in  
16 antibacterial drug trials because, you know, the trials  
17 are a relatively short duration is is that we usually  
18 can get to the endpoint fairly quickly. So it does  
19 allow us pretty good insights into, you know, what's  
20 happening with, you know, the ultimate outcome that  
21 we're looking for for an antibacterial -- you know,  
22 sort of a traditional antibacterial drug where the

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1 trial, you know, may be looking at endpoints within a  
2 period of say, seven, ten, fourteen or maybe thirty  
3 days or thereabouts.

4           So, you know, if there's an idea about an  
5 accelerated approach, I think that's something that  
6 we'd probably need to talk with people about a little  
7 bit more and see what the -- what the possibilities  
8 might be or what the approaches might be.

9           SCOTT HOPKINS: Yeah, I'd like to enlarge on  
10 that thought a little bit. And by picking on the use  
11 of the word "provisional" that Barry used.

12           Really, when an antibiotic or any drug is  
13 approved, it's provisional in the sense that we by far  
14 don't know everything about those compounds. And we  
15 find out later on in other clinical trial situations  
16 and whatnot. We find out more about them, whether it's  
17 Tygacil or Daptomycin or whatever.

18           But I would -- I would maintain that we know  
19 a lot more about an antibiotic and its potential  
20 efficacy effects at least than we do the standard  
21 antidepressant. And I think if Ed spent six months  
22 there looking at anti-depressive agents he would

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1 probably be aghast and come back real fast to where he  
2 is now.

3               So, my point is that we can, I believe,  
4 because of all the information that we know, we can be  
5 much more provisional when we approve a drug than we  
6 have been in the past and that we should take advantage  
7 of that particularly where we have very difficult  
8 situations and where we know that over time we're going  
9 to learn more as clinicians use these drugs and other  
10 studies come out and so forth.

11              But it's a shame to have to wait ten years  
12 for that to happen after approval.

13              BOB TEMPLE: Can you say more what you mean  
14 by provisional? Like, with no evidence that it works  
15 or what do you have in mind?

16              SCOTT HOPKINS: Well, again, I think that  
17 Daptomycin is an example. We talk about how it failed  
18 in community-acquired pneumonia. Well, it didn't fail.  
19 And we know that it has an activity and works in a  
20 variety of situations and I suspect very strongly that  
21 even in community-acquired pneumonia that it would show  
22 efficacy compared to placebo and, in fact, the

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1 mortality difference was zero and only in the now  
2 discredited global clinical endpoint was there a  
3 difference.

4           So, I again come back to the fact that with  
5 all the prior knowledge that we have from in vitro to  
6 animal models to clinical trials, we're in a much  
7 better situation generally than we are with most other  
8 if not -- it's hard for me to think of another  
9 therapeutic area where we have as much information.  
10 And that relates to the fact that the pathogen, the  
11 cause of the problem is something that we can isolate,  
12 we can take out of a patient and we can study in  
13 isolation the impact of our interventions.

14           We certainly need clinical trials but it's --  
15 the practicality and, you know, where you -- how much  
16 you discount and so forth, that is what makes them  
17 either very easy, moderately difficult or impossible to  
18 do.

19           BARRY EISENSTEIN: Just another question  
20 related to this. Will it take literally an act of  
21 Congress to be able to get orphan drug status type  
22 approval path for antimicrobials particularly for the

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1 escape type pathogens?

2 BOB TEMPLE: What do you mean by an "orphan  
3 drug approval path?" You think it's different from  
4 other approvals?

5 BARRY EISENSTEIN: I know that there are  
6 opportunities for these provisional approvals, what is  
7 it, sub-part H, but in addition, there's extension on  
8 patent life and the like with market exclusivity that  
9 provides significant financial incentive to get my  
10 colleagues from industry to get their business partners  
11 more willing to invest in this extraordinarily  
12 important area.

13 BOB TEMPLE: I'm not sure some of these  
14 aren't eligible for orphan status already. If you're  
15 treating a tiny fraction of all the people that have  
16 infection you probably are eligible.

17 Just -- just let just remind everybody what  
18 accelerated approval is. If you had resistant  
19 organisms that didn't have any good treatment there  
20 isn't any question not to say that would be what the  
21 judgment is, but their -- that is a situation in which  
22 accelerated approval sub-part -- so-called sub-part H

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1 approval could be entertained, that's where you rely on  
2 a surrogate that is quote "reasonably likely to predict  
3 clinical benefit" as a basis for approval while you  
4 presumably do the real studies later. And that  
5 certainly could be based on microorganism sensitivity  
6 if everybody was comfortable with that and if you could  
7 find such a population, it would be certainly legal.  
8 I'm not sure whether we've ever done that, but that is  
9 -- that is after all a surrogate endpoint; an in vitro  
10 test is a surrogate endpoint. And it could be used.

11 And indeed those tests have been used for  
12 Cipro in the past.

13 BARRY EISENSTEIN: Helen, and then we'll let  
14 Dr. Cox respond.

15 HELEN BOUCHER: Yeah, I mean, I think that  
16 we're clearly there in terms of having patients before  
17 us with these infections and I know John Bartlett  
18 presented their data on acinetobacter from Hopkins last  
19 week. And I treated a young girl, young Tufts  
20 University student who had urosepsis due to ESBL e-coli  
21 in the hospital. You know, things we have not seen in  
22 our life as I.D. docs are happening routinely.

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1           And I don't think it's beyond the pale to  
2 think that we could design a study that would allow the  
3 collection and perhaps a one arm fashion of a number of  
4 well-characterized cases of patients with documented  
5 infections due to pathogen X acinetobacter. Perhaps a  
6 variety of sites of infection but all due to the same  
7 pathogen that could be well -- the population could be  
8 well-characterized, the PK could be elucidated. You  
9 know, all those things.

10           And that -- having available such a drug  
11 would be such an advantage over what we have now which  
12 is Colistin that we're trying to figure out how to dose  
13 and the pharmacist tells us one thing one day and one  
14 thing the next. So I think that we're really there and  
15 anything we can do to help expedite that being seen as  
16 an option would be incredibly -- incredibly useful.

17           EDWARD COX: Yes, so maybe just a comment on  
18 the historically-controlled studies.

19           I mean, they do present real challenges. And  
20 I was just flipping through Fred's slides here. What  
21 I'm wondering is is if you look across, you know, the  
22 trials that he is if you couldn't find one of those

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1 controlled trials that if compared to another  
2 controlled trial wouldn't in essence show superiority  
3 of one arm of one of the studies compared to another.  
4 My guess is is that you probably can. So that's sort  
5 of one issue I think to keep in mind.

6           The other thing and I'm guessing this won't  
7 be surprising to folks is that, you know, the patients  
8 that get enrolled in the clinical trial are, you know,  
9 somewhat different than what we see overall in the  
10 overall population. And it's always been instructed to  
11 me when I look back at clinical trials that are  
12 performed and I look at say the mortality rate, you  
13 know, based on, you know, a group of patients who would  
14 have been categorized by port score, for instance, to  
15 be in a particular mortality risk category. And, you  
16 know, we've seen this on several -- not several but it  
17 seems like most of the times we look at the data, the  
18 mortality rate really isn't quite as high as you would  
19 expect and sometimes it's a -- you know, significant  
20 fraction of what you might expect.

21           So, there really are some real challenges out  
22 there and if the effects size is really large enough



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1 and reliable enough that you can, you know, design a  
2 historical control trial where, you know, the results  
3 are going to be reliable, then, you know, it can be  
4 very informative.

5 But, you know, I think it's just important to  
6 keep that in mind so that you don't end up in a  
7 situation where you've done a bunch of work and then at  
8 the end of the day the results are really -- you know,  
9 they don't quite get you where you want to be as far as  
10 understanding what the effect of the drug is.

11 SCOTT HOPKINS: We will find that out though  
12 and it will be a variable length of time. But we will  
13 find out just as we found out with these other  
14 compounds their activity or lack of activity in certain  
15 circumstances and their mortality profiles and so  
16 forth.

17 To me, the difference between the anthrax and  
18 Cipro business and the problems that we have in front  
19 of use now with ESBLs and, you know, things that don't  
20 even respond to Colistin is that this has been a little  
21 bit more slow moving. So we haven't had all of these  
22 all of a sudden dumped on top of us so that it doesn't

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1 kind of scare everyone and so forth.

2 But I think our thought process should not be  
3 that different. And we can accept, because of  
4 everything that we know about antibiotics and  
5 infectious diseases from the last 70 years, some  
6 greater uncertainty than we think is reasonable  
7 particularly when we compare this area to other  
8 therapeutic areas.

9 And we will find out within a few years  
10 whether restrictions need to be made or even something  
11 needs to come off the market.

12 BOB TEMPLE: That's not as reassuring as you  
13 think it is. We really don't want to discover that a  
14 drug that was approved for treating dreadful infections  
15 doesn't work. It's not really a good outcome even  
16 though maybe it's -- I don't even know if it's true.

17 We've actually written at some length about  
18 how to evaluate historical controls; it's in the ICHE-  
19 10 document which is most known for non-inferiority but  
20 has a very good section also, I think, on historical  
21 controls.

22 And as Ed says, you know, you can't just take

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1 some tiny little difference and trump with that and  
2 say, oh, I know everything. But where the differences  
3 are very large, very consistent and there are oncologic  
4 cases where this is true, we have made use of them and  
5 I think it would be very valuable exercise for someone  
6 to look to the historical data and try to make that  
7 case. And I think everybody's ready to listen but  
8 knowing that it will come out in the wash later is not  
9 a comfortable position. Maybe it's our fault cause  
10 we're all regulators and stuff.

11 SCOTT HOPKINS: No, that's a --

12 BOB TEMPLE: But that's really not so great.

13 SCOTT HOPKINS: No, when -- but when Colistin  
14 doesn't even work, the question's what is your  
15 alternative? And when Ciprofloxacin doesn't work -- so  
16 we have to consider that -- the situation that we're  
17 in.

18 BOB TEMPLE: Right. But if it's really like  
19 that and those things work very poorly and the outcomes  
20 are terrible it shouldn't be that hard to show that the  
21 outcome where the drug does work is better. That  
22 should be doable.

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1           HELEN BOUCHER: But, I think the real -- the  
2 pragmatic challenge is you can't randomize that patient  
3 to a standard of care when you know it doesn't work.  
4 You have to try a higher dose of Colistin, you have to  
5 try Amikacin, you have to try whatever and that's  
6 really, I think, the crux of this dilemma.

7           And so the young girl came in and got a  
8 carbapenem IV. You know, that's what you do.

9           BOB TEMPLE: But all of those things are  
10 possible, but in addition, you can -- you have to be  
11 convincing, make the case that we already know that  
12 conventional levels of these other drugs are not going  
13 to do much and here drug wonderful just made it all go  
14 away and did it in two days. You know, clean urine and  
15 all that. Those can be convincing. There's no --  
16 there's no rule against that.

17           Can I actually add one other thing about  
18 looking at blood levels and concentration response  
19 relationships? There's another, yet another -- sorry,  
20 ICH guidance called E-4 in which there's a lot of talk  
21 about looking at concentration response relationships.  
22 That's in there at least partly because the document

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1 was heavily written by Carl Peck who's a clinical  
2 pharmacologist who's got a major interest in that.

3 But he was convincing enough. But even in  
4 there there's some reservations about the possibility  
5 that these relationships can be confounded. But the  
6 apparent better response with a high dose may just mean  
7 that there's some other feature that went -- high  
8 concentration. There's some other feature that went  
9 along with that that you weren't smart enough to  
10 recognize.

11 So there's always that sort of nervousness.  
12 That having been said, our Pharmacia Matrix group does  
13 this all the time and they all totally believe it.  
14 Some are more skeptical, but there's -- there's a lot  
15 of those kinds of analyses going on and they can be  
16 quite convincing. And if you're lucky enough to have a  
17 drug that gives you highly variable blood levels, there  
18 may be a lot of room to discover things. If everybody  
19 gets the same blood level you're not going to find  
20 anything.

21 So we're ready to look at those data too.

22 EDWARD COX: Yeah, just to echo Bob's point

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1 about, you know, knowing what the effect of standard of  
2 care therapy is, you know, really well and expecting a,  
3 you know, reliable and, you know, large enough effect  
4 of the experimental therapy so that an historical  
5 design would be informative. I mean, it does seem  
6 that, you know, looking at a registry or, you know,  
7 trying to look at experiences to date could be quite  
8 helpful because it -- I think it will help to inform  
9 about what the effect of standard of care therapy is  
10 and then if, in fact, the effect is large enough and  
11 reliable enough in the types of patients that you would  
12 enroll in a subsequent historical-controlled trial, I  
13 mean, that will be essential information.

14           If it turns out that it's not for whatever  
15 reason, I still think looking at the registry data,  
16 looking at the experience to date will help to inform  
17 about, you know, what does happen in this patient  
18 population with regards to therapy and how might you  
19 design a study and what endpoints would you look at.

20           So I think, you know, either way trying to  
21 understand, you know, thoroughly from a registry or  
22 from, you know, looking at patients who've gotten a

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1 particular drug with a particular resistant pathogen  
2 can be very informative information.

3 BARRY EISENSTEIN: Ed, to just pursue that  
4 and since we have folks from NIAD around the table as  
5 well, isn't this a perfectly suitable place for a  
6 request for contract or study with NIH money to try to  
7 get this sort of 21st Century information so we don't  
8 get into constancy arguments about quote, "standard of  
9 care"?

10 EDWARD COX: Right. So I won't task anyone  
11 individual government agency with doing this work, but  
12 I just think in general, it is, you know -- certainly,  
13 I don't have the authority to do such a thing, but it  
14 is something that could be valuable and, you know,  
15 there may be any of a variety of different groups who  
16 could actually do such work, but I think it could help  
17 inform the field.

18 BARRY EISENSTEIN: Before we break for lunch,  
19 I have some distinguished colleagues from industry who  
20 are highly experienced in drug discovery and more  
21 importantly, development for today's discussion. We'd  
22 just like to ask any of them if they have any comments

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1 or questions of the panel? Or anybody else from the  
2 audience for that matter?

3 EDWARD COX: If I might just make one more  
4 comment too. One of the things that we didn't talk  
5 about today that has come up in other settings that I  
6 think is really important and came up at the workshop  
7 just last week, and that is is what can we do to  
8 improve the rate at which we detect microbiologic  
9 ideology in these patients? And I think that can have  
10 a huge impact on these studies.

11 And there was the paper that was talked about  
12 at the workshop last week from Joe Hanson and to the  
13 extent that we can, you know, double the rate at which  
14 we detect microbial ideologies for patients, I mean,  
15 that can have obviously, you know, a huge impact on  
16 sample size. So I think that's something else to think  
17 about in addition to a lot of the things that we talked  
18 about here today.

19 I just wanted to throw that in, Barry.  
20 Thanks.

21 BARRY EISENSTEIN: Excellent comment.

22 I see somebody from the audience. Please.



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1 JERRY SCHENTAG: Hi, Jerry Schentag,  
2 University of Buffalo.

3 It's relatively easy to find patients that  
4 are failing antibiotics, it happens all the time. Our  
5 problem is to try and figure out how to get those data  
6 that you'd collect if you gave a new drug into a  
7 reasonable format so that it would be useful to you in  
8 evaluating whether that drug worked or not.

9 And we all need to know that because we don't  
10 really want non-inferior drugs. I hate to announce  
11 that, but, you know, we -- if the drug isn't any better  
12 than what we got it isn't of any use to us anyway and  
13 the hospitals generally don't want to pay for it. So  
14 we really have to resolve this ground floor dilemma  
15 here that we've got that I've heard a lot about today  
16 too, about how to test drugs in the patients that have  
17 the resistant organisms. Cause when you set up a non-  
18 inferiority design usually you test them in the  
19 patients that aren't very sick, don't have resistant  
20 organisms and at the end you don't detect any evidence  
21 that it's any different than what we've got because it  
22 isn't.

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1           So, you know, I'm -- I'm very constructively  
2   arguing that we do more work with superiority at the  
3   individual patient level by collecting very informative  
4   data on individuals who have either failed an  
5   antibiotic already or at least have an organism that  
6   we'd expect them to fail that we can treat with the new  
7   one. We just need to make a commitment to that and  
8   Phase II is the place to do that. I mean, we really do  
9   need to start making the commitment to take the risk of  
10   a new drug earlier on before we know everything about  
11   it in treating a sick patient.

12           BARRY EISENSTEIN: Comments?

13           EDWARD COX: Maybe just one brief comment.  
14   It's somewhat related to what Jerry said, but a little  
15   bit off a tangent. But another important point too I  
16   think is the, you know, issue of if you conduct your  
17   trial and the patients who enrolled in your study,  
18   there's a high rate of resistance to your control drug,  
19   you didn't know that at the time that you started your  
20   trial out, the plan was to do a non-inferiority design  
21   with a margin of X, now you find out that a number of  
22   the patients in the control arm are, in fact, resistant

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1 and unless you -- and for some reason, you know,  
2 they're still in your analysis population, well, I  
3 mean, you can see the scenario I'm sort of setting up  
4 here which is is that you -- in that setting, you would  
5 not expect the control drug to have the effect, you  
6 know, to bare out its non-inferiority -- you know, the  
7 non-inferiority margin that you chose so you'll have to  
8 look carefully at that.

9           And those patients ideally would not be in  
10 the analysis population. So, you know, a high rate of  
11 resistance that was unanticipated can have affects on a  
12 clinical trial because the control drug has to have an  
13 effect against the pathogens that you're treating.

14           Unless, in fact, the goal is to show  
15 superiority. So --

16           BARRY EISENSTEIN: Could you show non-  
17 inferiority against the susceptible pathogens and  
18 superiority against the subset of those that happen to  
19 have been randomized into the drug resistant arm and  
20 then declare victory?

21           EDWARD COX: Yeah, it seems scientifically  
22 valid to do such a thing. And to the extent that

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1 you're -- you know, that you aren't surprised by the  
2 rate of resistance that occurs in your arm and if  
3 you've been able to sort of plan ahead for that, that  
4 sounds like a very prudent way to approach the problem.

5 BOB TEMPLE: Would that make you believe that  
6 more general effectiveness had been documented? Let's  
7 say you work on the people who have responsive organism  
8 to the other drug and you don't see much difference and  
9 I don't know whether you rule out your margin or not.  
10 But I the people who have a resistant organism you wipe  
11 it out.

12 EDWARD COX: Yeah, I think that's very --  
13 very helpful information.

14 BOB TEMPLE: It gives you -- not just for the  
15 resistant organisms but for everybody?

16 EDWARD COX: Well, I didn't follow. What I  
17 thought you were saying is that your non-inferior for  
18 susceptible organisms.

19 BOB TEMPLE: Well, let's say you don't quite  
20 know.

21 EDWARD COX: And then you're superior --

22 BOB TEMPLE: Maybe it's not a big -- maybe

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1 it's not big enough to get a definitive answer on the  
2 non- inferiority part. But you definitely wipe out the  
3 drug and the people with resistant organisms. So you  
4 prove that your effective in this condition, but you've  
5 proved it entirely by sort of a placebo-controlled  
6 trial.

7 I just wondered, do you think that gets you  
8 the broad claim, that is, I work in this infection or  
9 do you just get I work in this infection if you happen  
10 to have an organism that doesn't respond to everything  
11 else?

12 EDWARD COX: Yeah. So --

13 BOB TEMPLE: You may not want to answer yet.  
14 You know, I --

15 EDWARD COX: I was going to say -- I haven't  
16 fully digested the question but I do think if you end  
17 up superior in a particular subset and that's a  
18 baseline characteristic, I think that's a very -- you  
19 know, a very important finding and really contributes a  
20 lot to your understanding of how the drug works.

21 Now, you know, is there reason to believe it  
22 wouldn't work in the other population? Are there

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1 reasons to believe it would? I mean, I'd -- you know,  
2 I mean --

3 BOB TEMPLE: You should look at the data for  
4 that.

5 EDWARD COX: Yeah, we'd try and figure that  
6 all out. But I think the finding that it works in the  
7 resistant population is very helpful.

8 BOB TEMPLE: Yeah.

9 SCOTT HOPKINS: Just a pragmatic point is  
10 once the susceptibility sheet comes back and there's a  
11 big R on it, those patients get put on something else  
12 and so particularly if they're very sick.

13 Just the sort of patients that you'd really  
14 like to have this information in. So it's also a kind  
15 of practical clinical trial design issue.

16 BARRY EISENSTEIN: Yeah, and to follow up on  
17 that we had explicit experience with that with  
18 Daptomycin and our VRE study where too many of the  
19 patients were -- we were finding were resistant to  
20 Linezolid as well which was the comparator arm and then  
21 they fell out and we ended up with two few patients and  
22 the attributable mortality was difficult to determine

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1 given the background confounders anyway.

2           So here we have a drug that -- with Bayesian  
3 argument would seem to work extraordinarily well, but  
4 could never be able to prove it to the -- you know, to  
5 the level that was required.

6           With no other comments or questions we break  
7 for lunch and -- oh, sorry, Jerry, okay, one more.

8           JERRY SCHENTAG: A protest. I was not  
9 arguing to do this within a non-inferiority trial. We  
10 have to do this separately from it.

11           EDWARD COX: Yeah, that's fine. I sort of  
12 took your point and sort of spun off of it a little bit  
13 of a side direction.

14           JERRY SCHENTAG: I know. I thought I was  
15 making progress.

16           EDWARD COX: No, no, no. But I was trying to  
17 excuse myself before I did that just so that people  
18 would have that sort of point just for illustration if  
19 you will, Jerry.

20           BOB TEMPLE: But don't lose the possibility  
21 that you frequently don't know what the organism is  
22 when you start the study and that you might within this

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1 trial of all cumpers learn something that gets you both  
2 answers.

3 JERRY SCHENTAG: Yes.

4 BOB TEMPLE: Don't rule that out.

5 JERRY SCHENTAG: Well, I've always done it  
6 that way. But I've always been forced into non-  
7 inferiority trials to answer this question, except for  
8 the situation where we did Linezolid with compassionate  
9 use where everybody came to us was failures. That  
10 really worked great, you know. You really do need to  
11 kind of create a salvage therapy option within the  
12 trial process of the drug.

13 I'm not arguing we shouldn't do non-  
14 inferiority trials, I'm just arguing that that's not  
15 where you're going to get your superiority information,  
16 particularly because they're designed not to do that.

17 BARRY EISENSTEIN: Yeah, Dr. Laessig has a  
18 comment.

19 KATHERINE LAESSIG: Just listening to all  
20 this very good discussion, I'm sort of thinking about  
21 how HIV products were developed and that some of that  
22 may be applicable. So, you know, there you had



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1 patients that were multiply drug resistant and, you  
2 know, you did standard of care plus placebo versus  
3 standard of care plus the test drug and I'm kind of not  
4 following the logic why that wouldn't be possible in a  
5 situation.

6 BARRY EISENSTEIN: I think there's a lot to  
7 digest. The panel discussion this afternoon I'm sure  
8 can pick up on some of that and integrate it with the  
9 discussion we're going to be having on endpoints which  
10 is quite relevant.

11 We'll see you back here at 1:30 after lunch  
12 break.

13 (Session ended.)

14 (1:20:48)

15 DR. SHORER: Okay. I'm going to start.  
16 Welcome to session two in support for antimicrobial  
17 drugs and controlled trials, and the first speaker is  
18 going to be Elektra Papadopoulos, from the FDA, and she  
19 will talk about the endpoint selection and  
20 qualification.

21 DR. PAPADOPOULOS: All right. Good  
22 afternoon. I'm going to start this afternoon with a

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1 discussion of endpoint selection and qualification. I  
2 have no conflicts to disclose. I'll first start with  
3 some key considerations for endpoint measures, and then  
4 I'll describe a process for drug development tool  
5 qualification. So, this is just a framework of the  
6 discussion.

7           At the end of the day I think everyone wants  
8 to have, you know, a treatment benefit established that  
9 can support claims and labeling, so I'll start with  
10 these. But, underlying all of that is really how do we  
11 get there, and I'll also go through that process. So,  
12 treatment benefit is broadly defined as the impact of  
13 treatment on how a patient functions, survives, feels  
14 or functions, and it can be related to either  
15 effectiveness or safety. For example, a treatment  
16 benefit could be an improvement or delay in the  
17 development of disease- related symptoms, or in terms  
18 of safety, it could be a reduction or delay in  
19 treatment-related toxicity.

20           A claim is defined as any statement of  
21 treatment benefit, and can be found anywhere in FDA-  
22 approved labeling or in advertising. And, claims must

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1 be supported by substantial evidence. They also must  
2 not be false or misleading. So, claims may appear, for  
3 example, in the indication section, clinical studies,  
4 or in adverse reactions section of labeling. And, we  
5 have heard this morning a very nice discussion of  
6 substantial evidence briefly summarized here. These  
7 are supported by reports of adequate and well-  
8 controlled investigations, and for our review we need  
9 sufficient details of the study design, conduct and  
10 analysis. And, this slide summarizes characteristics  
11 of an adequate and well- controlled studies, which  
12 again were discussed this morning. I just want to draw  
13 your attention to item six here, which specifies that  
14 appropriate methods of assessment of outcomes must be  
15 used.

16               So, what do our regulations tell us?  
17 Basically the methods of assessment of such response  
18 should be well-defined and reliable; the protocol for  
19 this study and reports results should explain the  
20 variables measured, the methods of observation, and the  
21 criteria used to assess response.

22               So, now that I have gone through some of the

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1 regulatory framework, I would like to now focus on the  
2 bottom part of this triangle, and really what we need  
3 to know first before we can get started with  
4 measurement is what is the measurement concept; what is  
5 the thing that we were trying to measure; and the  
6 context of use. So, for example, what type of trial is  
7 this measure going to be used in? What is the  
8 objective of the trial? So, these are very important  
9 considerations, and only from there can we then select  
10 an instrument that will measure that and put it into  
11 our clinical trial endpoint. So, as I alluded to the  
12 goal of measurement is the concept, and this is the  
13 specific thing or event that will be measured into the  
14 clinical trial, and this concept forms the basis for  
15 describing claims and labeling. So, the concept  
16 measure needs to be the same as what is being put into  
17 the label at the end of the day. Examples of concepts  
18 that could be measured would be asthma symptoms,  
19 cognitive functioning, congestive heart failure signs  
20 and symptoms. So, after deciding on the concept and  
21 the context of use, we then need to find an appropriate  
22 instrument to measure this, and an instrument is just

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1 defined as a means to capture the data, plus all the  
2 information and documentation that supports its use.  
3 Examples of instruments are diaries, questionnaires,  
4 events logs -- a ratings scale is a specific type of  
5 instrument in which basically the respondent provides a  
6 rating to a concept, and a ratings scale could be  
7 patient-reported, observer-reported, or clinician-  
8 reported. So, at its core, all a rating scale is, is a  
9 method that links the concept to its measurement. Now,  
10 underlying this questionnaire that we see, it's not  
11 only the items and response options, but we look at the  
12 recall period, the structure of the scoring system, the  
13 ratings scale, how it scored, any instructions for use,  
14 interpretation guidelines, and also very importantly,  
15 measurement property documentation. So, the standard  
16 for our review of ratings scales is described in the  
17 Patient- Reported Outcome Guidance for Industry, which  
18 was published in final form in December of last year.  
19 And, basically the adequacy of a PRO instrument, as a  
20 measure to support medical product labeling claims,  
21 depends on its measurement properties that demonstrate  
22 that it is fit for its intended use. And, I'd just

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1 like to point out in this slide that a lot of the same  
2 principles that we use for reviewing patient-reported  
3 income instruments can also be used -- can also be  
4 applied to other types of ratings scales, such as  
5 clinician rating scales.

6           So, an endpoint is basically the measurement  
7 that will be statistically compared among the treatment  
8 groups, to assess the effect of treatment, and this  
9 corresponds with the clinical trials objectives,  
10 designs and data analysis plan. And, I have outlined  
11 the types of endpoint measures here. They can include  
12 patient- reported outcomes; observer-reported outcomes;  
13 clinician- reported outcomes; objective tests, such as  
14 lab or device measurements; and combinations of the  
15 above, for example, in a composite measure. So, the  
16 PRO Guidance defines a patient-reported outcome as any  
17 report of the status of a patient's health condition  
18 that comes directly from the patient without  
19 interpretation by a clinician or anyone else. And,  
20 examples include, for example, a patient- reported  
21 outcome of pain intensity symptoms of any condition  
22 would be patient-reported outcomes. You can also have

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1 physical functioning that's patient-reported.

2           An observer-reported outcome is used when a  
3 patient is unable to report for themselves, and in this  
4 case, the observer provides observations, but not  
5 interpretations of the patient's health condition. So,  
6 importantly, an observer-reported outcome is not a  
7 patient-reported outcome, and should not be used to  
8 measure patient symptoms. Patient symptoms need to  
9 come from the patient themselves. And, typically, the  
10 observer is the person who takes care of the patient  
11 most of the time. It could be a parent or a caregiver.  
12 As an example, a parent or caregiver should not be  
13 asked, in a questionnaire, to provide a rating for an  
14 infant's pain. In acute otitis media, for example,  
15 instead of that, what we would like are observations  
16 that indicate that the child is having pain, such as  
17 crying or tugging at the ears.

18           Clinician-reported outcomes similarly is any  
19 assessment of the patient's health condition that is  
20 based upon a direct clinical observation and  
21 interpretation in this case, so examples include a  
22 vertebral fractures and signs of pulmonary

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1 consolidation.

2           The PRO Guidance describes an endpoint model  
3 as a diagram of the hierarchy of relationships among  
4 all endpoints that corresponds to the trial objectives,  
5 design and data analysis plan. And, an endpoint model  
6 defines the concepts which support the indication and  
7 the claims. And, this is an example of a hypothetical  
8 endpoint model for head and neck cancer. On the right  
9 side we see the endpoints, and on the left side we see  
10 the concepts that are measured that support the claims.  
11 And, in this example we see clinician-outcome measures,  
12 as well as patient-reported outcome measures. So, the  
13 PRO Guidance provides advice on measurement properties  
14 for rating scales and patient-reported outcome  
15 measures. And, of these, the most critical really for  
16 interpretation is content validity, and without content  
17 validity we can't really interpret what the measure is  
18 telling us, and for that reason, we can't effectively  
19 describe it in labeling. And, content validity should  
20 be established prior to evaluating other measurement  
21 properties, and these include construct validity,  
22 reliability and the ability to detect change.



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1           So, I'm just going to take a minute to  
2 describe content validity a little bit more, and this  
3 is evidence that the instrument measures the concept of  
4 interest, including evidence that the items and domains  
5 of the instrument are meaningful, comprehensive,  
6 appropriate and interpretable relative to the  
7 measurement concept population and use. And, as we can  
8 see from this definition, content validity is very  
9 closely linked to the context of use. And, the type of  
10 evidence that supports content validity would include a  
11 literature review, expert opinion and responder input  
12 in the form of qualitative research. So, for a  
13 patient-reported outcome, we would need qualitative  
14 research using the same patient population that will be  
15 targeted for the clinical trial.

16           Now, I would just like to switch and discuss  
17 the drug development tool qualification process. So,  
18 what is this process and what does it mean to have a  
19 tool qualified. Basically the qualification means the  
20 regulatory conclusion that within the stated context of  
21 use, the results of the drug development tool can be  
22 relied upon to have a stated interpretation and

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1 utility. And, how does this translate for rating  
2 scales? This basically means that the data that's  
3 produced by a rating scale can be interpreted as  
4 clinically meaningful and that the scale can be used as  
5 a primary or a key secondary or a key secondary  
6 endpoint, and within the context of use to support  
7 labeling claims. And so, there is an upcoming draft  
8 Guidance that describes this process of how drug  
9 development tools can be qualified and that the  
10 Guidance will outline, first of all, defined  
11 qualification; it will describe the process for  
12 interaction with the agency; and it covers basically a  
13 range of drug development tools, including patient-  
14 reported outcome measures and other rating scales  
15 biomarkers and other tools. And, importantly, this  
16 process can be used to consider both new tools, as well  
17 as existing tools. The upcoming Guidance will not  
18 discuss evidentiary standards, and for PROs, for  
19 example, we will still refer to the PRO Guidance, and  
20 it's not intended to discuss drug development tools as  
21 part of regulatory, specific regulatory applications  
22 and specific drug development programs. So, this

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1 process was developed to improve the efficiency for  
2 both the industry and the FDA. If a drug development  
3 tool is qualified, then the expectation is that it will  
4 be available in the public domain. Other advantages  
5 include a more transparent advisory process, heightened  
6 awareness of good measurement principles, and  
7 ultimately better information for patients and  
8 decision-makers. And, this slide is a very high-level  
9 summary of the process, and in this Guidance the word  
10 sponsor will be used to mean DDT- submitter.

11           And so, the first stage, Stage One, is  
12 consultation and advise, and here the sponsor brings  
13 the project to Cedar; from there, an interdisciplinary  
14 working team is assembled; the information is reviewed  
15 and advice is given on how to advance and develop this  
16 project for its intended use. Then, once the project  
17 is deemed complete for a review, the sponsor will then  
18 submit the data package to the FDA and we'll conduct a  
19 full detailed review of the package and provide a  
20 decision on qualification, including a formal statement  
21 of qualification, as appropriate, and this will be  
22 issued in the form of a public notice.

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1           So, in conclusion, based on our regulatory  
2 requirements, endpoints need to be well-defined and  
3 reliable. Well-developed outcome measurement tools are  
4 tools that can link a measurement to the quantification  
5 of a specific concept. The principles of the FDA PRO  
6 Guidance document can also be applied to other outcome  
7 measurement tools. And, an upcoming draft of FDA  
8 qualification Guidance for drug development tools will  
9 provide a path for qualification of both new and  
10 existing tools.

11           Thank you for your attention.

12           DR. SHORER: We have time for a couple of  
13 questions. Anybody from the Panel?

14           (No audible response).

15           DR. PAPADOPOULOS: Yeah? Question?

16           DR. SHORER: Anybody from the room?

17           MR. RAYMOND: Dr. Papadopoulos, I'm Stephen  
18 Raymond, with PhD Corporation, and you mentioned that  
19 the DDT process would support a number of drug  
20 development tools, and then the word measurement is  
21 used. Is it restricted to measurement tools, or would  
22 analytical tools as well? Earlier in the day we had a

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1 little discussion about the value, potential value, or  
2 lack of value of Asian methods, for example; so, if we  
3 had some sort of a tool that would infer results from  
4 data, would that be something that could be submitted  
5 under that program?

6 DR. PAPADOPOULOS: Yeah. I do not know the  
7 answer to that. I think the intent of this Guidance is  
8 to be inclusive, and you know, to really promote  
9 efficient development, but I don't know the specific  
10 answer.

11 MR. RAYMOND: Okay.

12 DR. PAPADOPOULOS: A question?

13 MR. REINHART: Okay. It's Harald Reinhart,  
14 from Novartis. I am looking at your slide #29 and I  
15 see a list of hypotheses, none of which have been  
16 proven, in my eyes, sufficiently at this stage to  
17 endorse any of those claims. I don't see the claims  
18 for efficiency corroborated in the infectious diseases  
19 area with any tool. The availability obviously is not  
20 here yet of such a tool. It may make a more  
21 transparent advisory process; that's to be proven. The  
22 heightened awareness of good measurement principles is,

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1 I think, a lofty goal and may come from all of this,  
2 but again, unproven. And, better information for  
3 patients, as I hope it would come to that, because  
4 otherwise a large effort would be started without any  
5 benefit. So, my question is, do you have any evidence  
6 that this tool delivers on those points, number one;  
7 and number two, is there indeed some precedent that you  
8 can show us that would speak to the acute illness,  
9 which is usually being dealt with infectious disease,  
10 because I can't see the PRO tools terribly useful in a  
11 sepsis patient, for instance.

12 DR. PAPADOPOULOS: Well, maybe I should  
13 address the second question first. This drug  
14 development tool qualification process is not for a  
15 specific PRO tool, and I think very importantly the  
16 process says that you have to have, you know, the  
17 context of use of the tool. And, your example of a  
18 patient-reported outcome tool in the case of sepsis,  
19 you know, where a patient can't respond for themselves,  
20 you know, it wouldn't be something that would be under  
21 this type of a guidance. So, the object is to have a  
22 specific measurement tool that will be used within the

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1 context of use, and that would be how it will be  
2 qualified. And, this Guidance hasn't yet been issued.  
3 It will make public our thinking on the process for  
4 qualification of tools and so we look forward to that.  
5 However, the process is already in effect, and so, you  
6 know, we do have tools that we are considering under  
7 this process. Most of them, at this point, happen to  
8 be patient-reported outcome measures that are being  
9 considered by the study endpoint and labeling team of  
10 the FDA, as well as the appropriate review divisions.  
11 And also, we have examples of biomarkers, at least, you  
12 know, that I am aware of. We do have some examples of  
13 biomarkers at various stages of development. So, I  
14 hope that answers the question.

15 Okay, any other questions?

16 MR. TEMPLE: Well, let me just make a comment  
17 on that, and I am interested in what you and Ed think  
18 about this. One of the things that's been considered  
19 for things like otitis and conditions like that is to  
20 look for speed of improvement in the two drugs; that  
21 is, if you do a placebo-controlled trial and you  
22 wouldn't leave them off therapy for very long, but

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1 you'd look in the first few days about whether there  
2 was improvement. Well, one way to measure improvement  
3 in otitis, you could have a physician questioned, but  
4 you could also ask the patient about a well-developed  
5 set of symptoms that could be measured by a PRO. That  
6 always seemed of potential benefit in those areas, if  
7 there were proper scale. Is that what you had in mind?

8 MR. COX: That's fair, Bob, but you know, in  
9 a setting of otitis media, a caregiver-administered  
10 instrument of some sort, to be able to assess, you  
11 know, how the patient is responding might allow for  
12 assessments to be made earlier on that could, you know,  
13 provide, you know, data on the impact of therapy. And,  
14 you know, in other disease conditions, either mild to  
15 moderate severity, AB, ECB, you know, people have  
16 talked about the possibility of using a PRO tool there  
17 to assess outcome. So, you know, using a PRO tool could  
18 actually, you know, help to better define, you know,  
19 patient response in that setting.

20 MR. SCHENTAG: Yeah, Schentag, Buffalo. Just  
21 to carry on the analogy you are talking about here, a  
22 lot of times when you are trying to validate a tool, or



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1 at least trying to establish the use of a tool for  
2 measuring something in, let's say, a hospitalized  
3 patient population, you run into the situation where  
4 there is not very much data if you wanted to go back  
5 and try to figure that out from previously collected  
6 data. The clinical trials didn't measure a lot of the  
7 things that you'd want to do very often, particularly  
8 for time-related events. So, the logical thing for us  
9 academics would be just to go back to real patients or  
10 start studying real patients prospectively since we've  
11 got hospitals full of those, lots of evidence of  
12 patients that aren't responding, so you can start to  
13 work your score out that way. What I'm curious about  
14 is what's your thinking on how to integrate the  
15 clinical trial process where you sometimes have a  
16 little bit of data and the real world process where you  
17 could collect a lot of data and still try to get this  
18 working in our lifetime. You know, we've got a real  
19 time clock here. We are trying to make Phase Two  
20 trials work with this, but it takes a while to do this.  
21 So, I'm sort of interested in how us academics,  
22 particularly to have access to patients, get in on this

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1 game. And, PK/PD is just one example of that. There  
2 are a lot of biomarkers this applies to, and not to  
3 mention all the symptom scoring that you can do in  
4 hospitals.

5 DR. COX: So, the point about how do you sort  
6 of get this going; I mean, --

7 MR. SCHENTAG: Yeah. Can I use this process?  
8 Is it okay? Is it simple enough I can use, or is this  
9 only a company that can do this --

10 DR. COX: Yeah. I mean, --

11 MR. SCHENTAG: -- as a sponsor?

12 DR. COX: Yeah. No, I would expect others  
13 could use it, is that fair, Laurie?

14 MS. BURKE: Absolutely. That's absolutely  
15 true.

16 MR. SCHENTAG: Right. Right.

17 MS. BURKE: And, for someone who wants to  
18 consider going down this path, we have some very  
19 specific -- you know, there is some specific discussion  
20 that can take place very early and the earlier the  
21 better, to make sure tat the FDA and all relevant  
22 parties, divisions and groups at the FDA, who would

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1 care about this, come together and make sure that our  
2 goals are aligned for whatever the measurement is. And,  
3 we have some examples of how this has happened in the  
4 recent past in anti- infective drugs, but also in other  
5 disease areas. So, we need to summarize and make sure  
6 we are all thinking about the same thing, but yet  
7 that's the most efficient path forward.

8 MR. SCHENTAG: So, I can work with you on this  
9 and follow the Guidance then?

10 MS. BURKE: Yeah.

11 MR. SCHENTAG: Great. That's encouraging.

12 DR. COX: And then, as far as, you know,  
13 getting things going, depending on the type of  
14 information that may have been collected previously, it  
15 may be possible to, you know, try and learn things from  
16 what's been done in the past; whether it be previously  
17 conducted clinical trials or other ways of trying to,  
18 you know, understand, you know, the time course of  
19 events and the setting of antimicrobial treatment; how  
20 that may relate to the treatment effect of the drugs.  
21 So, it's possible that already available information  
22 may help to inform this. It's also, depending upon

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1 what's being looked at, what type of information is  
2 available, it may also be that additional work, you  
3 know, prospectively designed data collection could also  
4 contribute to the process. So, there may be some data  
5 that's already out there and available that could be  
6 used, and then prospective work could also help to  
7 inform too.

8 MR. SCHENTAG: Thank you.

9 DR. SHORER: Thank you. Our next presenter  
10 is Dr. Sumati Nambiar. She's a Deputy Director of  
11 Safety at the Division of Anti-Infective Ophthalmology  
12 Products at the FDA, and she will talk about primary  
13 efficacy endpoint in antibacterial drug trials from the  
14 FDA perspective.

15 DR. NAMBIAR: Thank you, Dr. Shorer, and good  
16 afternoon everybody. So, in the next half hour or so,  
17 I will provide an FDA perspective on primary endpoints  
18 and antibacterial drugs trials. I have no conflicts to  
19 disclose.

20 The following is an outline of my  
21 presentation. I'll briefly go over the evolution of  
22 indications for antibacterial drugs over the last

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1 several decades. I'll go over some definitions and  
2 attributes of endpoints, provide examples of clinical  
3 endpoints that we'll use as primary efficacy endpoints  
4 and previously conducted trials of antibacterial drugs,  
5 and briefly discuss new endpoints providing two  
6 examples and discuss some of the challenges with  
7 evaluating new endpoints.

8           So, very early, antibacterial provers, 1962  
9 and prior, usually focused more on the bacteria for  
10 which the antibacterial drug had activated rather than  
11 the specific body site. So, this is an example from  
12 the Vancocin product label. So, the emphasis here is  
13 that it's useful in therapy of staphylococcal  
14 infections and then goes on to describe the different  
15 clinical conditions where it may potentially be used.

16           Since 1962, approvals have described the  
17 particular strains of susceptible bacteria and have  
18 also included general categories of infections. So,  
19 for example, a drug may be approved for the treatment  
20 of lower respiratory tract infections, which could  
21 include pneumonia, both nosocomial pneumonia and  
22 community- acquired pneumonia, and then it would list

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1 the pathogens against which the drug has activity, or  
2 it would be a product, like skin and skin structure  
3 infections without necessarily separating them into  
4 complicated and uncomplicated. And, the indications  
5 were generally derived from subset analyses because  
6 these studies involved patients with different types of  
7 infections that were caused by a variety of different  
8 micro-organisms. And often, no formal statistical  
9 hypothesis testing was performed in these studies.

10           And, moving on to the 1990s, recommendations  
11 on clinical trial designs for many indications were  
12 outlined during this time. The FDA Points to Consider  
13 document was published in 1991. And, the supplement to  
14 the Clinical Infectious Disease was published in 1992,  
15 where IDA say FDA guidelines for clinical trials and a  
16 variety of clinical conditions were outlined. Based on  
17 the recognition of differing clinical course, differing  
18 microbial etiology, the need for differing dosing  
19 regimens and factors at different sites of infection  
20 that can impact outcomes, there was a move towards more  
21 controlled trials and trials were also designed to  
22 enroll patients with particular clinical conditions,

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1 such as community-acquired pneumonia, rather than a  
2 mixture of clinical conditions.

3           So, from this point on, indications were more  
4 specific, so a drug would be approved for, say,  
5 nosocomial pneumonia, and again you would list the  
6 organisms against which activity was demonstrated. Or,  
7 similarly, community-acquired pneumonia, and again, the  
8 organisms against which activity was listed.

9           Now, we have seen this definition several  
10 times already today, so in addition to what is outlined  
11 in the

12           21 CFR 314.126, there was a Federal Register  
13 notice published in 1992 where a surrogate endpoint was  
14 defined, and inherent in that definition is the  
15 definition for a clinically meaningful endpoint, and an  
16 important concept that a clinically meaningful endpoint  
17 is a measure of how a patient feels, functions or  
18 survives. The biomarkers definitions working group in  
19 2001 provided the following definition for a clinical  
20 endpoint: a cataclysmic or variable that reflects how  
21 a patient feels, functions or survives, and goes on to  
22 say that the distant measurements or analyses observed

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1 in a clinical trial that reflect the effect of a  
2 therapeutic intervention.

3 So, what are some of attributes of endpoints?

4 I think we have made this point very clear; that they  
5 should be clinically meaningful and should reflect how  
6 a patient feels, functions or survives. It's also  
7 important that these endpoints be reliably measured;  
8 they have to have some relationship to the baseline  
9 signs and symptoms that got the subject into the trial  
10 in the first place. And, for non-inferiority trials,  
11 again, this concept has been discussed already. There  
12 has to be a relationship with the historical data from  
13 which treatment effect was derived, both with respect  
14 to the nature of the endpoint and the timing of the  
15 endpoint.

16 So, I'll just go over some examples of  
17 endpoints, again in broad terms, and then I will go  
18 into specifics later. So, by and large, most of the  
19 endpoints that we have evaluated in antibacterial  
20 trials have been clinical endpoints. So, examples of  
21 clinical endpoints could be clinical response or all-  
22 cause mortality. Clinical response can be assessed at a



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1 fixed time point, which, by far is a more common method  
2 of assessment, in some cases a time to vent analysis  
3 has also been done. Clinical response is generally  
4 based on clinician- reported outcomes, but, in some  
5 instances, can be based on patient-reported outcomes as  
6 well. There are few examples where microbiologic  
7 response has been used as the primary endpoint, such as  
8 gonorrhea, streptococcal pharyngitis and urinary tract  
9 infections. In some instances, a combination of  
10 clinical and microbiologic response, where one has  
11 required microbiologic eradication and resolution of  
12 clinical signs and symptoms. And, in very rare  
13 instances, at least I am aware of one example, where a  
14 surrogate endpoint was used.

15           So, I'll go over some examples of primary  
16 efficacy endpoints that have been used in previously  
17 conducted trials. This is not meant to be an  
18 exhaustive list, but just to give you some examples.

19           All-cause mortality was the primary endpoint  
20 in a trial of Drotrecogin Alpha or Xigris. This was a  
21 multi-center randomized double blind placebo-controlled  
22 trial in adult patients with sepsis. Twenty-eight-day

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1 all-cause mortality was the primary endpoint, and  
2 Xigris- treated patients did better than the placebo-  
3 treated group, which is again represented here in a  
4 diagrammatic fashion.

5           A second example would be clinical response  
6 where the assessment was made at a fixed time point.  
7 The assessment here is made by the clinician, and this  
8 trial was done as a superiority trial. Retapamulin, or  
9 Altabax, was studied in randomized, double blind,  
10 multicenter placebo-controlled trial, where it was  
11 compared to placebo in patients with infantago. And,  
12 clinical success was defined as the absence of treated  
13 lesions, or if the lesions had improved to such an  
14 extent that no further antimicrobial therapy was  
15 needed. And, the results of the trial were as follows,  
16 so either at the end of therapy or assessment or at a  
17 follow-up assessment of Retapamulin-treated patients  
18 did better than placebo-treated patients and,  
19 statistically, superiority was demonstrated.

20           The third example -- again, I'm not going to  
21 pick a specific drug here because we have several  
22 examples where this type of endpoint has been used --

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1 which is, a clinical response endpoint in patients with  
2 complicated skin and skin structure infections (cSSSI).  
3 Again, the assessment here is made by a clinician. It  
4 happens at a fixed time point, which is usually the  
5 test of cure visit, and it is done in the context of a  
6 non- inferiority trial. To be called a cure, all signs  
7 and symptoms of CSSSI should have a result or improved  
8 to such an extent that no further antimicrobial therapy  
9 is needed. You could fail for one of many reasons;  
10 either your complicated skin and skin structure  
11 infection was persisting; or, it had not result; or, in  
12 fact, it was worsening such that there was need for  
13 alternative antimicrobial therapy; or, there was a need  
14 for unplanned surgical intervention; or, there was a  
15 treatment-limiting adverse event that led to study drug  
16 discontinuation; or, you died from the skin infection.  
17 Similarly, in community-acquired pneumonia, the  
18 clinical response endpoint was assessed by clinician at  
19 a fixed time point, which is the test of cure visit,  
20 and these trials were all non-inferiority trials.  
21 Again, to be called a cure, your signs and symptoms of  
22 pneumonia should either have resolved or improved to

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1 such an extent that you did not need further therapy.  
2 You could fail it for more than one reason; either the  
3 pneumonia was persisting or getting worse, such that  
4 you needed alternative antimicrobials; or, there was an  
5 adverse event that led to discontinuation of study  
6 drug; or, you died from the pneumonia.

7           This is the last example of endpoints that we  
8 have used in the past; clinical response endpoints in  
9 traveler's diarrhea. Here, the primary endpoint was  
10 timed to last on formed stool based on reports by the  
11 patient captured on a diary card. So, this was a time-  
12 to-event analysis. Rifaximin was evaluated in placebo-  
13 controlled trials in patients with traveler's diarrhea,  
14 and the results are as follows; where Rifaximin was  
15 superior to placebo for the time to last unformed stool  
16 endpoint. So, recently we have had a lot of discussion  
17 about endpoints as they relate to antibacterial trials,  
18 and our goal here is really to measure endpoints in an  
19 objective, accurate and reliable manner. There have  
20 been scientific advances in our understanding of both  
21 non- inferiority trial and clinical trial endpoints,  
22 and as I have alluded to earlier, for non-inferiority

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1 trials, assessment of treatment effect of the  
2 controlled drug should take into consideration the type  
3 of endpoint, the timing of the assessment and the  
4 population enrolled. We have also had a lot of recent  
5 discussion on instruments for measuring patient-  
6 reported outcome, and as Elektra just mentioned in her  
7 presentation, instruments for measuring clinician-  
8 reported outcomes as well around the development.

9           Now, what are some of the issues that have  
10 come up in recent discussions with endpoints that have  
11 been used in previously conducted trials? I think one  
12 of the main criticisms is that endpoint assessment  
13 currently is very subjective. There is inconsistency  
14 both within and between trials, because the assessment  
15 is often based on investigator assessment without  
16 objective criteria. Now, having reviewed the natural  
17 history of some of these infectious diseases, it's  
18 apparent when assessment occurs very late in the course  
19 of illness, it is often difficult to differentiate the  
20 treatment benefit from the drug from spontaneous cure  
21 that occurs over a period of time. And, lastly,  
22 because these outcomes are generally clinician-

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1 assessed they are important; however, they may not be  
2 optimal for assessing patient's symptoms in a clinical  
3 trial.

4           So, I'll briefly review some of the recent  
5 discussions we have had, specifically for community-  
6 acquired bacterial pneumonia and acute bacterial skin  
7 and skin structure infections. So, the endpoints that  
8 we have discussed for CABP include mortality, clinical  
9 response based on clinician's assessment, or clinical  
10 response based on patient-reported outcomes. For  
11 mortality as an endpoint, we have the best evidence for  
12 treatment effect from historical studies; however, as  
13 mortality rate is really not high in CABP except in  
14 very small subgroups or very specific subgroups, it may  
15 not be feasible to use as an endpoint for all CABP  
16 trials.

17           A clinician-assessed clinical response is  
18 certainly clinically meaningful, and it is feasible for  
19 the conduct of future trials; however, it is less well-  
20 characterized historically than we would like, and  
21 hence there is a need to better define it for future  
22 trials.

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1           Another major shift in our recent discussions  
2 compared to how we did trials before is that the  
3 primary analysis population is now patients with  
4 microbiologically-documented infections rather than the  
5 outcome of population. So, when we review the  
6 historical data for clinical response in CABP, it was  
7 evident that treatment effect occurred early on. The  
8 bars in red are data from a Bullowa study of 600-odd  
9 patients, with pneumococcal pneumonia, who received no  
10 treatment. So, when compared data from that case  
11 series to patients who were treated with sulfonamides  
12 -- that's the yellow bar and the blue bar -- it is very  
13 evident that around day three or day four there is a  
14 huge treatment effect. So, based on this, the proposal  
15 is that clinical response or clinical improvement in  
16 CABP is probably best assessed at an early time point,  
17 somewhere around day three to day five. However, there  
18 are issues with this endpoint as well. Because, by day  
19 three to day five, signs and symptoms of pneumonia only  
20 improve, they rarely do not resolve, and hence there is  
21 a need to standardize the definitions for improvement  
22 based on both signs and symptoms. And, improvement in

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1 these characteristics should be with respect to  
2 baseline; so, it's important that the signs and  
3 symptoms that you are using to assist improvement were  
4 in fact present in baseline and need to be part of the  
5 inclusion criteria. It's also important that we  
6 continue to evaluate outcomes at later time points for  
7 two reasons: both, to document resolution of the  
8 infection; and also to look for relapses.

9           Similarly, in ABSSI, Dr. Toerner has already  
10 discussed this in his presentation, where the best  
11 historical evidence is for the endpoint of cessation of  
12 spread of lesion; however, there are issues with this  
13 endpoint as well. Here, the data are limited to  
14 patients with erysipelas. It does not capture several  
15 other aspects of skin infections, such as erysipeloid,  
16 pain or tenderness, extension to deeper tissue planes  
17 or fever. There is also room for measurement errors,  
18 because we don't have standard methods for wound  
19 measurements, and there can be significant of inter-  
20 observer variability. And, the correlation of this  
21 early endpoint of cessation of spread of lesion at 48 to  
22 72 hours with sustained cure remains uncertain.



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1           So, what are some of the challenges, as we  
2 try to define endpoints for future trials? For  
3 clinical response endpoints, especially in the context  
4 of non- inferiority trial, again it's very important  
5 when we measure the treatment effect for the controlled  
6 drug we look at all these characteristics, such as the  
7 endpoint, the timing and the population. However, the  
8 historical data that we have reviewed thus far for many  
9 of these indications are often limited with respect to  
10 the very variables that we are most interested in, and  
11 it makes it difficult to fully characterize a clinical  
12 response endpoint.

13           The second topic that we have had a lot of  
14 discussion on is clinical improvement at early time  
15 point as a primary endpoint. It is clinically  
16 meaningful, but there is a need to define it, both  
17 objectively and reliably, and as I have already  
18 mentioned, it is important to continue to look for  
19 clinical response at a later time point, and need to  
20 factor that in, in the overall assessment. Challenges  
21 continue.

22           We have had some discussions this morning

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1 about mortality as an endpoint, and though it's a very  
2 objective endpoint, it's certainly not feasible for  
3 many of the clinical conditions for which antibacterial  
4 drugs might be studied.

5           There have been several discussions in the  
6 past about stable vital signs, such as resolution of  
7 fever; should it be part of a clinical response  
8 definition, because they could be considered as  
9 biomarkers, and they may or may not really capture how  
10 a patient feels, functions or survives.

11           And, we need to learn more about impact of  
12 prior therapies, especially on early endpoints. So,  
13 effective both prior antibacterial therapies and non-  
14 antibacterials, Dr. Schleiser (ph) brought this article  
15 to our attention where Anceds (ph) can, in fact, have  
16 an affect on the early endpoint of cessational spread  
17 in  
18 ABSSSI.

19           Another topic where we have had a fair amount  
20 of discussion is whether or not you would like to  
21 enroll prior failures in these trials where early  
22 endpoints are being evaluated. Traditionally, we have

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1 been enrolling these patients if there is documented  
2 evidence that they have failed prior therapies;  
3 however, we don't know if the disease course in that  
4 group of patients would be the same as those who are  
5 treatment-na?ve, and especially when you are assessing  
6 early endpoints. Superiority trials are probably a  
7 good option, however, again, feasibility would be a  
8 problem, and I think this has been discussed this  
9 morning. It is difficult to demonstrate superiority  
10 against active controls, as most of the active controls  
11 we use aren't highly effective, and placebo-controlled  
12 trials are feasible for very few indications. Maybe we  
13 have to think of alternate ways to re-demonstrate  
14 superiority in a time-to-even analysis, or do we  
15 demonstrate superiority based on length of therapy,  
16 i.e., is a shorter regimen superior to a longer  
17 regimen? Is there a need to revisit a role of  
18 microbiologic endpoints?

19           So, given all these uncertainties and how a  
20 new endpoint might perform, our recommendation would be  
21 to consider piloting new endpoints before proceeding  
22 with Phase Three trials, and I have listed some options

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1 here. Ideally, evaluating the performance  
2 characteristics of the new endpoint in Phase Two trial  
3 would be optimal. Maybe you could evaluate how the  
4 endpoint performs using existing data that have not yet  
5 been mined, or maybe we'll have to go with a  
6 collaborative approach, and an example would be some of  
7 the recent work that has been done with the foundations  
8 for NIH, which would be covered in Judy Siuciak's  
9 presentation later.

10               So, in summary, I have provided some examples  
11 of primary efficacy endpoints that have been used in  
12 previously conducted antibacterial trials. I have  
13 discussed the reasons to characterize endpoints  
14 appropriately. I have discussed the importance of  
15 responding to the advancing science in the area of  
16 endpoint assessment, meaning that we need to do it in  
17 real time, and sort of not do it after the fact when we  
18 have lost a few years. I have discussed challenges  
19 associated with defining endpoints, and I have also  
20 discussed some options of a path forward.

21               Thank you. That ends my presentation.

22               DR. SHORER: Thank you. Questions from the

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1 Panel?

2 DR. EISENSTEIN: Yes. Hi. A question about  
3 function and their definition. It seems that we want  
4 to have things that are objective, measurable, subject  
5 to statistical analysis, hopefully connected to the  
6 reality of the treatment effect. So, a question that I  
7 have is, in dealing with pneumonia, would something  
8 like oxygenation on a measured amount of nasal oxygen  
9 be considered a function that could be put into your  
10 endpoint analysis?

11 DR. NAMBIAR: I can give you my opinion. I  
12 think the answer is yes.

13 DR. EISENSTEIN: Good. Okay. Thank you.

14 DR. NAMBIAR: I don't know if that is  
15 everybody's opinion, but that's mine.

16 DR. EISENSTEIN: I was told something  
17 contrary at a recent meeting of the FMIH and I just  
18 wanted to get a physician's opinion rather than a  
19 statistician's opinion. Thank you.

20 DR. NAMBIAR: I think, Dr. Eisenstein, that  
21 also brings up the point about fever, because I -- you  
22 know, there has been a lot of discussion about does

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1 fever capture how you feel, function or survive; or is  
2 that really a biomarker and distinction between  
3 temperature and fever? So, I think there is more than  
4 one opinion in that particular area.

5 DR. TEMPLE: Wouldn't oxygenation  
6 unequivocally be a surrogate? The question is, whether  
7 it's a surrogate you like, which I think most people  
8 probably would, but it is -- it's not a measure of how  
9 you feel, and it's not what function usually means.  
10 Function usually means doing your chores.

11 DR. EISENSTEIN: That's what I was getting at  
12 with the concept of function, but here you have the  
13 function of the end organ that's actually damaged by  
14 the disease process, and one would think that if you  
15 can get that end organ to function better and measure  
16 it by a very objective, measurable reproducible  
17 statistical --

18 DR. TEMPLE: Or, just call it a surrogate you  
19 really think is worthwhile, because being de-oxygenated  
20 really seems scary. I think most people would like  
21 that fine.

22 DR. SHORER: You have a question from the

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1 Panel; from the floor?

2 (No audible response).

3 DR. SHORER: Thank you. Our next presenter  
4 is Dr. Scott Hopkins. He is the Chief Medical Officer  
5 from Rib-X Pharmaceuticals, and he will give us the  
6 industry perspective on the same issue.

7 DR. HOPKINS: Okay. Well, we have had a, I  
8 think, encyclopedic view almost of endpoints, so I'm  
9 not sure I'll have a whole lot to add other than a few  
10 twists from the standpoint of a sponsor. First of all,  
11 I am the one who is totally conflicted, and you can see  
12 I have been in industry for a long time.

13 So, I think in terms of kind of major take  
14 home points that I would like to make. One, is that  
15 straying from usual clinical practice, as it's  
16 performed by people out in the field and in the  
17 trenches and so forth, and for endpoints, for coming up  
18 with new endpoints I think can be very problematic, and  
19 we need to be very careful how we do this. And, the  
20 second point is, which I think is abundantly clear to  
21 everyone, when we come up with new endpoints, we really  
22 are in very new territory and we have to be very

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1 careful about how we apply these things. From the  
2 sponsor's perspective, one of the important interests  
3 that a sponsor has is how we communicate the  
4 information that's been collected in clinical trials to  
5 the end user, which is a physician, and secondarily, or  
6 sometimes primarily, to patients, and then also to  
7 other parties, such as payers and so forth that are now  
8 an important part of the whole mix.

9           So, I'll talk about four different points in  
10 varying depth: \* What's the purpose of a primary  
11 endpoint that's collected in a clinical trial for  
12 regulatory review; \* What makes for useful endpoints  
13 with really kind of the sponsors view of that; \*  
14 What's the relationship to the usual practice of  
15 medicine; and \* What is the impact of this, or how  
16 does this fit into package insert and promotional  
17 activities?

18           So, we have heard a lot already from the  
19 previous speakers really about how the FDA views  
20 endpoints, and of course, the ultimate goal is  
21 assessing safety and efficacy of the test agent, and to  
22 allow the regulatory procedure to move forward. From a



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1 sponsor's point of view, however, that's really -- it's  
2 not the beginning, but it's almost the beginning of the  
3 process, because the point is to get the compound out  
4 to the market and to practicing physicians, and to  
5 communicate that information to them. And, again, a  
6 recurring theme of my slides is that the further that  
7 we stray from what practicing physicians are doing in  
8 their day-to-day practice in terms of how they evaluate  
9 patients and how they practice medicine in terms of the  
10 new endpoints that we come up with, I think the more  
11 peril we are taking on, the more risk we are taking on  
12 for divorcing the clinical development process from the  
13 practice of medicine. In this day and age that also  
14 applies to communications with patients. There is, you  
15 know, obviously direct advertising to patients, for  
16 better or for worse, and pairs are obviously in the mix  
17 of this also. And, how these new endpoints and new  
18 approaches to arriving at efficacy will be communicated  
19 to pairs and under what circumstances I think is a very  
20 difficult question, but it's obviously something that  
21 we have to think about and be comfortable with. And,  
22 again, all of this ultimately comes down to the package

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1 insert and the promotional activities of the sponsor,  
2 however you would define those. So, these endpoints  
3 are not something that exists in a vacuum, but they  
4 have very real, every day sorts of applications to the  
5 practicing physician, to the patient, to whoever is  
6 paying for the care of that patient and so forth. So,  
7 we have heard lots of things about what a useful  
8 endpoint is, and just kind of stepping back a little  
9 bit from the details; what are we interested in, in the  
10 infectious diseases sense; what are the clinical and  
11 bacteriological effects that we are interested in?  
12 Well, ultimately it's the return of the patient to some  
13 pre-infection state of health that we would like to be  
14 able to measure in some way in a reasonably efficient  
15 and effective manner, but there are other things, such  
16 as eradication or a reduction of the organism  
17 population so that it's no longer a concern to the  
18 patient in terms of things like relapse or perhaps even  
19 spreading it to nearby people. And then, development  
20 of resistance is an issue that we are also very much  
21 interested in. But again, do the endpoints that we may  
22 decide upon, that we decide we like, do they bear a

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1 close relationship to the everyday medical practice in  
2 the condition that we are talking about? Obviously,  
3 and particularly in terms of the FDA's role, they are  
4 very interested, and physicians are very interested in  
5 discriminating between effective and less effective  
6 antibiotics, I would maintain that there is virtually  
7 zero possibility of an ineffective antibiotic for  
8 getting into clinical tryouts these days with all of  
9 the things that go on leading up to selecting a  
10 candidate and so forth, and putting the IND (ph)  
11 together and what-not. But, we have to be comfortable  
12 with what the definition of effective is, and is it a  
13 definition that, again, speaks to practicing physicians  
14 and patients? So, I think the notion of how the  
15 patient feels, functions and survives is an attempt to  
16 get at that and that sounds very good. How does  
17 something like the spread of erythema in a complicated  
18 skin or an ABSSSI study fit with that? Does the  
19 patient feel any different because erythema? Does he  
20 function? Does he survive any less than a patient with  
21 more or less erythema? It's a question. I'm going to  
22 ask a lot of questions that I don't have good answers

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1 to here, but the point is that I think we are in new  
2 territory and we have to be very careful of how we  
3 approach some of these issues.

4           Okay. So, from the industry standpoint, a  
5 very important question is, does it meet the industry  
6 needs in terms of being able to actually conduct a  
7 clinical trial, and will it be recognized within the  
8 broader medical community and so forth? So, is it a  
9 doable endpoint? And, I think our goals, in many cases,  
10 are very coincident with the FDA's, in terms of we want  
11 things to be very accurately measured. We all prefer  
12 things which are objective in the context of antibiotic  
13 trials. It's possible that things such as technology  
14 and complexity that can be used to arrive at measuring  
15 tools for things like complicated skin trials can make  
16 the trials impossible to do, such as, for instance,  
17 using MRIs to try and measure the total extent of  
18 infection. It should be very effective, but you can't  
19 schedule these things at will, and they are very  
20 expensive and so forth. The cost has to be something  
21 that, in the context of the overall trial, can be borne  
22 by the sponsors. So, an endpoint that ultimately

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1 requires a trial size of 3,000, 4,000 patients is often  
2 not going to get funding for that sort of a trial.  
3 That's simply the economics and mechanics of antibiotic  
4 trials in this day and age, and we have heard that  
5 before. Obviously patient inconvenience and safety  
6 issues and so forth, and there is issue of investigator  
7 training. Any new endpoint is going to require the  
8 cooperation of investigators and their ability to  
9 accurately and reasonably perform the measurements that  
10 we are interested in. That's something that usually  
11 can be done fairly easily, but again, it's something  
12 that we need to think about.

13           So, is this endpoint or endpoints that we  
14 come up with something that will be recognized as valid  
15 in the broader medical community, or is it something  
16 that only within the community of FDA and sponsors will  
17 really be paid attention to? How will these new  
18 endpoints be vetted? I mean, there are advisory  
19 committees. There are meetings like this, but there  
20 really does have to be buy-in from many parties,  
21 including the broader medical community, to make sure  
22 that there is not a divergence from what happens in the

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1 doctor's office and what's happening in clinical  
2 trials. Another point is that we would very much like  
3 the endpoints that are used to be broadly recognized by  
4 major regulatory agencies. There has been a lot of  
5 effort in the ICH process to harmonize what happens in  
6 Europe and Asia and so forth with what happens in the  
7 Americas. We don't want to get into the position of  
8 having endpoints in antibacterial or anti-infective  
9 trials that are accepted by the FDA, but which may not  
10 be accepted by regulators in Europe, for instance, or  
11 Asia, for that matter. So, we would be going back to  
12 the bad old days in that sense, if we are not very  
13 careful about how we go about this.

14           Now, one of the -- I've got a series of  
15 questions now that I don't have answers for, but there  
16 are all sorts of issues with the direction that we are  
17 going as opposed to where we have been in the past.  
18 Where we have been in the past is the clinician's  
19 assessment of cure or fail, however you want to --  
20 whatever words you want to use to describe that. But,  
21 it's an integrated global assessment, and that's  
22 essentially what physicians have done in terms of how

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1 they view their patients. And, by integrated, I mean  
2 they look at all of the things that we have been  
3 talking about. They look at, does the patient still  
4 got a fever; is the white count up; what does the  
5 lesion look like, if it happens to be a skin lesion;  
6 what does the chest x-ray look like; the physician  
7 talks to the patient and so forth. So, in the past, we  
8 have thought that there was great utility in that  
9 integration, which also included the knowledge and  
10 experience of physicians, and we put some premium on  
11 that integration and that knowledge and experience in  
12 terms of clinical investigators. And, if one wants to  
13 go back to the real bad old days, in the early  
14 antibiotic era, practice was essentially to find 20 or  
15 30 or 40 kind of big names in the infectious diseases  
16 world at academic sites, give them the antibiotic, and  
17 they would give it to a series of patients and publish  
18 that, and that was essentially the basis for the early  
19 approvals of antibiotics. And, it's hard to find  
20 places where they made a lot of mistakes, and that was  
21 putting a very high premium on the individual integrity  
22 and experience and so forth on the academic physician

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1 in that case, and that's something that we can't go  
2 back to because our trials have gotten too large and so  
3 forth, although we would strive for that.

4 But, the other end of the spectrum is what  
5 I'm calling granular measurements of very specific data  
6 points. We don't know right now where this is going to  
7 go, and we don't know how we are going to apply these.  
8 So, just as some examples, we might find that an  
9 antibiotic, Antibiotic A, halts the spread of  
10 induration at some time point, at 36 hours in 80  
11 percent of patients, while it takes 42 hours for  
12 Antibiotic B. But, we might also find that erythema is  
13 in the reverse relationships for those antibiotics,  
14 because erythema is a process that involves toxins and  
15 so forth, and we know that even with different  
16 organisms it behaves very differently. The erythema  
17 of erysipelas is very different from the erythema of  
18 staph aureus, and the extreme example with staph aureus  
19 is toxic shock, where you've got a little tiny lesion  
20 someplace and the patient is red all over. It's  
21 possible, using very sensitive measurements, such as  
22 thermography and measuring lesion temperatures that you



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1 could determine that Antibiotic A resulted in a reduced  
2 skin temperature several hours faster than Antibiotic  
3 B, and that might be statistically significant based  
4 upon the accuracy and granularity of that measurement.  
5 Does that mean that Antibiotic B would not get approved  
6 under those circumstances, because we are able to  
7 measure very fine distinctions between antibiotics on  
8 very specific types of endpoints? Patient temperature,  
9 again, is the same sort of issue. It's quite possible  
10 that different antibiotic classes would have  
11 differential rates of effect; that is, effect versus  
12 time on biologic processes like infection. For  
13 instance, a bacteriostatic antibiotic may behave  
14 differently in a measurable way when we are talking  
15 about very specific and granular endpoints. A  
16 bacteriostatic antibiotic may behave differently from a  
17 bacteriocidal antibiotic. So, all active antibiotics,  
18 like a beta-lactam, may behave differently from one  
19 which acts on gyrase, for instance.

20           And so, we will be in the position of having  
21 potentially a lot of very specific information that we  
22 have diligently and objectively and accurately

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1 measured, and showing distinctions potentially in  
2 antibiotics that, at the end of the day, we may not  
3 really care about; or that we only care about in very,  
4 very specific situations, but is that going to cause us  
5 to, in the future, discount the utility of some  
6 antibiotics and even not approve some antibiotics  
7 because, in these very specific sorts of situations  
8 that perhaps we didn't even anticipate, it is shown to  
9 be slightly less effective for how we define that. So  
10 again, erythema is something that I am particularly  
11 worried about. I have seen patients with little tiny  
12 staph aureus infections in one place and erythema  
13 following the tissue plains in the dependent part of  
14 the body, and it really doesn't have a whole lot of  
15 bearing on the infectious process. It's there, but  
16 it's not like the erythema of streptococcal infection,  
17 at least as I see it. Induration seems to be much more  
18 closely associated, if we are talking about bacterial  
19 skin infections, and fever one would think -- but  
20 again, we may find that a quinolone or a beta-lactam,  
21 in fact, may have a very different effect on the course  
22 of fever in a way that we can measure in a statistical

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1 way than a macrolide. The same for white blood count  
2 and other sorts of other bio markers.

3           As I said earlier, I am not a huge fan of  
4 PK/PD but, in thinking about this, it did occur to me  
5 that we have developed a tool that certainly for some  
6 classes of antibiotics has been very useful, and less  
7 useful in other situations in PK/PD types of studies.  
8 But, all of these, at the end, have been calibrated, if  
9 you will, against global clinical efficacy assessments.  
10 So, all of the PK/PD information that we have developed  
11 on community-acquired pneumonia and quinolones  
12 basically goes back to essentially clinical outcomes,  
13 global clinical outcomes, as assessed by physicians.  
14 Yet, we have found that those predictions within that  
15 construct can be amazingly effective. So, does that  
16 mean that now the global clinician's assessment is  
17 really not that useful when we have this mass of  
18 information that would suggest to me otherwise. We  
19 don't really know how the dose response relationship  
20 across a variety of potential endpoints is going to  
21 behave, so we may have a dose response for erythema  
22 that is different from the dose response for a fever

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1 for an antibiotic, and certainly for different classes  
2 of antibiotics. Skin macrolides with anti-inflammatory  
3 activity are, I think, a very good example of that.

4           So, what we will end up with is the  
5 possibility of all sorts of permeatations of outcomes,  
6 and so these are just a bunch of particular scenarios  
7 where an endpoint for Antibiotic A works better than  
8 Antibiotic B, but another endpoint for A is not as good  
9 as B. I think the best example of this we have already  
10 talked about is Cubicin, where we had a primary  
11 endpoint of death in the community-acquired -- in the  
12 pneumonia trial, where there was no difference, but a  
13 clinical outcome, a global clinical outcome, has a  
14 secondary endpoint that showed a significant difference  
15 between the two antibiotic arms. So, we are going to be  
16 in that situation, I think, again and again and again  
17 with a multitude of endpoints that can be measured with  
18 a high degree of accuracy and granularity, and which  
19 may not all perfectly track with the actual overall  
20 clinical course of the patient.

21           So, this really raises the question -- we  
22 have heard the word surrogate a few times today, and

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1 are we creating surrogates that may be somewhat  
2 removed, in fact, from the patient's self-perceived  
3 condition; for instance, erythema on the skin; or the  
4 physician's assessment of how that patient is doing?  
5 And, I just put in a few slides that I have lifted from  
6 the talk that Janet Woodcock gave a few years ago on  
7 surrogates and bio-markers, and it's a very good talk.  
8 It's in the context of HIV but, as I read through these  
9 slides, it seems to me that the cautions that the  
10 Agency is raising with respect to surrogates here also  
11 need to be thought about in the context of where we are  
12 going here in antibiotics. I am particularly  
13 interested in the statement, "There is no gold standard  
14 clinical outcome measurement in the contexting of HIV."  
15 So, HIV was, as we all know, a very difficult area  
16 where there was a high medical need, but are we now  
17 going in kind of the opposite direction in terms of how  
18 we think about surrogates with antibiotics?

19               So, going back to one of my early slides,  
20 what clinical and bacteriologic effect are we  
21 interested in? I would suggest that in most of the  
22 indications with antibiotics it's a relatively global

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1 sort of outcome that is assessed not just by the  
2 clinician, but by the interaction of an experienced  
3 clinician with the patient, and it covers a variety of  
4 things, all of the things that we have talked about.  
5 But, that's what the physicians out in practice are  
6 using as their way to handle patients, and it relates  
7 to the return basically of the patient to the pre-  
8 infection state of health, and secondarily, to  
9 eradication of bugs and resistance and relapse and so  
10 forth.

11               Yeah. I think I'm really at the end of my  
12 talk. The efficacy endpoint relationship to the usual  
13 practice of medicine I think, in many therapeutic  
14 areas, is very close; blood pressure, pulmonary  
15 function tests, circulating HIV, and so forth and so  
16 on. So, those are all things that work in the context  
17 of clinical trials and communicating that information  
18 to physicians. My concern is that we get into a  
19 situation where we are measuring things that the  
20 physician sitting in his office will say, I don't care  
21 about that; that's not how I take care of patients.  
22 And so that relates to the package insert and how

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1 companies, at the end of the day, will promote their  
2 compounds. But, I think I can finish there.

3 MR. SHORER: Okay. Thank you. As we are  
4 over time, we will save the questions for the panel  
5 discussion in the afternoon. And, the next speaker  
6 will be Helen Boucher, from Taft University, and she  
7 will give us the academia perspective.

8 DR. BOUCHER: Okay. Thanks very much for the  
9 invitation, and I am conscious of the fact that I am  
10 not only after lunch, but the last person before the  
11 break, so I'll try to keep it concise. My disclosures  
12 or potential conflicts were noted this morning, but I  
13 do provide advice and consultation to a number of  
14 antibiotic and anti-infective companies. And, I am  
15 here today on behalf of the Infectious Disease Society  
16 of America (IDSA), and I was asked to provide a  
17 perspective from academia, and I thought just to frame  
18 my comments that I would try to just bring us back to  
19 the comment I made this morning; again, about the fact  
20 that, you know, my job is taking care of patients, and  
21 the IDSA represents over 9,000 scientists, mostly  
22 doctors, who take care of patients, so I just wanted to

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1 just sort of re-emphasize the public health need; that  
2 physicians need safe and effective antibiotics for our  
3 patients, and our patients need safe and effective  
4 antibiotics. And, it's really -- it's kind of a shame  
5 that we are spending so much time talking about life-  
6 threatening infections that we face, and I am a  
7 (inaudible) care doctor, but we don't want to forget  
8 that we have the everyday infections that need oral  
9 antibiotics as well, and hopefully future discussions  
10 will focus on those.

11           So, as has been said by several of my  
12 colleagues, certainly when we look at primary efficacy  
13 endpoints, we want to scientifically justify the  
14 statistically rigorous methodologies used to determine  
15 those endpoints, and I think a lot of time has been  
16 focused on that by people much more expert than I, so I  
17 won't spend a great deal of extra time on this, but  
18 would hope that we would come back and talk a little  
19 bit more about some of the statistical issues and the  
20 science around the new discount that was added this  
21 morning, the third discount or that additional discount  
22 on the M1 that I am still somewhat struggling with to



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1 understand.

2           For our trials, as has been mentioned, we  
3 certainly want them to impact on clinical practice and  
4 measure how our patients feel, function and survive.  
5 And, something very important that I know we'll talk  
6 more about tomorrow is that the endpoints lead to  
7 design of trials that are actually feasible to conduct,  
8 and I mentioned hopefully would be useful for both oral  
9 and parentally-available agents. Ideally, our patients  
10 could be included in these trials, and I'll get to what  
11 I mean by that a little bit later. They would meet  
12 with the requirements of institutional review boards  
13 here, in the U.S., and ethics committees in other parts  
14 of the world, and would be consistent with practice  
15 guidelines, to the extent that that was feasible.

16           So, turning to skin, we published a position  
17 paper after the skin workshop back in 2008, and we  
18 looked at 90 articles looking at studies of complicated  
19 skin infections done from 1900 to 1950 in the pre-  
20 antibiotic era treating over 28,000, or looking at over  
21 28,000 patients, and found a very robust signal of  
22 efficacy of anti-infective therapies in the treatment

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1 of what we were calling then complicated skin  
2 infections. And, we focused on the type of infection  
3 and found a lower limit of antibiotic effect versus no  
4 active treatment of 28 percent for cellulitis; 42  
5 percent for wound and ulcer infections; and 14 percent  
6 for major abscesses. And, in addition to those sort of  
7 numbers, we found extensive evidence of robustness of  
8 these data looking at some time to cure studies; what's  
9 been alluded to earlier today, some data that topical  
10 and local therapy is less effective than systemic  
11 therapy; population-based studies that also added  
12 credibility to this conclusion; and then some data from  
13 the modern era where dose escalation studies show  
14 similar treatment effects. The data for impetigo has  
15 been reviewed earlier and shows concordant message.  
16 And, as I alluded to this morning, you know, we are in  
17 the fortunate position that we have actually been able  
18 to forget how deadly these infections once were because  
19 our antibiotics are so effective.

20           So, in terms of the key features for now  
21 ABSSSI trials, the non-inferior design is needed  
22 because of the issues that have been discussed. And,

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1 we advocated looking at the margin based on the  
2 specific type of infection, but as others have  
3 mentioned, you know, there are perhaps reasons to  
4 include also the organism we are talking about and the  
5 patient groups, and I don't want us to forget our  
6 little patients, the children, -- most of us are adult-  
7 focused in this audience -- but, my colleague, John  
8 Bradley, would not want us to forget the kids. And, I  
9 think we would submit that the ideal primary endpoint  
10 may not have been established. You know, the failure  
11 of a cellulitis lesion to progress at an early time  
12 point is certainly very important, but perhaps not the  
13 only outcome that we care about, and a clinical outcome  
14 at the end of therapy is the ultimate goal of me, as a  
15 doctor, and my patients, who want to get on with their  
16 lives. And, there may indeed be other considerations  
17 besides those that we have discussed.

18           Turning our attention then to community-  
19 acquired bacterial pneumonia, in a similar exercise,  
20 after the workshop there, we published another position  
21 paper noting what's been discussed beautifully by  
22 Sumati earlier; that the, you know, high mortality in

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1 the pre- antibiotic era; the immediate decline in  
2 mortality in all age groups within a year of  
3 introduction of effective antibiotics. We have seen  
4 higher rates of treatment failure among our patients  
5 infected with organisms that are resistant to  
6 flouroquinolones or macrolides, for example.  
7 Certainly, more treatment failures and increased  
8 mortality have been noted among patients who have  
9 received delayed antibiotic therapy, and that led to  
10 what we all live by now; the dreaded four-hour rule  
11 that patients with pneumonia or any chance of pneumonia  
12 must have their first dose of antibiotics within four  
13 hours of arrival at an emergency room. We can  
14 certainly discuss that the limitations of some of those  
15 data, but indeed those data are published on the  
16 internet now for every hospital and it's something that  
17 we are all held very accountable to, and I think it has  
18 applicability to the trials that we'll discuss.

19           We have seen strong correlations between  
20 antibiotic exposure and clinical success rates in  
21 various PK/PD studies. We have talked a lot about the  
22 insights into failure among the community-acquired

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1 pneumonia patients treated with Daptomycin in those  
2 trials, and we have certainly seen more rapid clinical  
3 improvement among pneumonia patients treated with  
4 antibiotics compared to those who did not receive such  
5 therapy.

6           So, in terms of looking at some clinical  
7 parameters, and there has been some discussion about  
8 signs and symptoms, I think it's pretty clear that  
9 there has been a consistent treatment effect observed  
10 with antibiotics on the time to resolution of fever,  
11 cough, chest pain, shortness of breath, and overall  
12 feeling poorly in these patients. Duration of  
13 hospitalization is another big focus right now. I get  
14 phone calls every day about getting people out, and  
15 anything to shorten the duration of hospitalization is  
16 certainly viewed as an advantage to our patients and to  
17 our bosses. The magnitude of the effect for the  
18 clinical response is 72 hours, this earlier time point  
19 that's been discussed, ranges from 35 to 95 percent and  
20 really depends on the disease severity and the  
21 etiologic agent of the pneumonia. So, non-inferiority  
22 design here, the margin is determined, we would

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1 propose, by the specific outcome measure and the  
2 severity of the pneumonia among the enrolled patients;  
3 so that for patients with severe community-acquired  
4 pneumonia, those with the higher reported scores, 15  
5 day all-cause mortality would certainly be appropriate.  
6 And, those with mild or moderate cap, we propose a  
7 hierarchical or composite endpoint where all-cause  
8 mortality would certainly be used, but morbidity-type  
9 endpoints, looking at those things that have a  
10 meaningful benefit to patients would be included, and  
11 those could perhaps be assessed with PROs and would be  
12 assessed at the end of therapy, at type time point.

13           So, turning then to ventilator-associated  
14 bacterial pneumonia, again, this has been discussed  
15 earlier; that a non-inferiority design would be needed;  
16 the use of all-cause mortality at 30 days was proposed  
17 again. And, this paper just came out recently based on  
18 the proceedings of the workshop for this entity. A  
19 superiority design was put forward looking at an  
20 experimental agent with the standard of care versus  
21 placebo with a standard of care, and I think that has  
22 some interesting pros and challenges we could discuss.

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1 And then, the possibility of a historical controlled  
2 study, as we talked about this morning, looking at  
3 those much more resistant pathogens that cause us, you  
4 know, great difficulty in treatment and obviously have  
5 very immediate need might be considered.

6           So, what about the primary endpoint for a  
7 ventilator-associated pneumonia? All-cause mortality  
8 of 30 days in the microbiologic MITT population was  
9 certainly agreed upon as a reasonable endpoint,  
10 although it was based on still rather limited data.  
11 The group certainly expressed a great desire for  
12 including clinical primary endpoints, and I think as  
13 has been alluded to, limiting to mortality only  
14 endpoints really doesn't reflect everything we do in  
15 clinical practice and that our patients experience.  
16 And, we look at a variety of bio-markers, like  
17 resolution of fever; ability to wean from the  
18 ventilator; improved oxygenation status, and all these  
19 things are very important as we look at the impact of  
20 any therapy and this disease.

21           So, another idea that was raised was the  
22 potential adjudication of salvage therapy, and we

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1 haven't really gotten into this today and I'm not sure  
2 that we will, but I think this is a uniquely different  
3 group of patients when you approach salvage therapy.  
4 But, the idea was raised of looking at mortality  
5 without considering salvage therapy; so just counting  
6 the bodies at the end of a month or whatever the time  
7 period was, or using mortality with some assessment of  
8 the potential impact of salvage therapy. This becomes  
9 very difficult and really you would like to have  
10 blinding to minimize the bias about why someone got the  
11 salvage therapy, because right there you think they are  
12 doing worse. That's a problem. And, at the very least,  
13 you want to have some specific criteria to instruct  
14 your investigators to use when they are going to turn  
15 to a salvage therapy. And, believe me, I think that  
16 everyone who has tried to do this would recognize it's  
17 very hard to think of every possible reason Dr. Jones  
18 would need to turn to salvage therapy for Patient  
19 Smith. And, although I think it's something that  
20 should be discussed and thought about, it's a tough  
21 thing to operationalize.  
22 And then finally, including mortality as part



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1 of the endpoint and superiority components in a  
2 hierarchical fashion is very desirable, so first you  
3 must survive and then meet certain clinical endpoints  
4 would be something that might serve multiple goals.

5           So, coming back to our patients, let's look  
6 at skin. You know, this was addressed earlier. The  
7 early measure of decrease in size of a lesion or lack  
8 of spread of a lesion is very relevant in terms of  
9 knowing that our patient is doing well, but it doesn't  
10 tell us how he or she will ultimately do, and really  
11 that's what our patients want to know; do they have to  
12 stay in the hospital on the I.V.; can they go home; can  
13 they go back to work? So, somehow we would like to  
14 incorporate those types of things into our endpoints,  
15 if possible.

16           In terms of pneumonia, I think that there are  
17 a number of issues that impact on the actual study  
18 design here that I want to just bring up. One of them  
19 has to do with comparator choice. So, in the United  
20 States we follow the ATS-IDSA Guidelines for community-  
21 acquired pneumonia that suggests that atypical coverage  
22 should be included. That means a second agent in many

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1 cases, and that causes trouble with some of the designs  
2 that we are talking about. And, I think that some of  
3 these studies may not be feasible in the United States,  
4 and I just want to come back to that. So, the second  
5 issue is this prohibition of prior antibiotics, and we  
6 learned from some recently conducted studies that prior  
7 effective antibiotics can indeed impact our outcome in  
8 the community-acquired pneumonia study. And, that  
9 said, the feasibility of seeing, enrolling, randomizing  
10 and treating a patient in the emergency room within  
11 four hours is a very lofty goal. So, I think that, to  
12 think that in a U.S. hospital that's going to happen  
13 and you are not going to violate the four-hour rule is  
14 a real problem, and I have done a little research with  
15 some IRBs and I have been told pretty clearly that  
16 that's not likely to fly. Even though one could make  
17 the scientific argument the four-hour rule may not be  
18 100 percent scientifically justified, it is the letter  
19 of the law for how we operate. So, I think that's  
20 going to lead to potentially these trials leaving the  
21 U.S.

22 So, why else do patients go outside the U.S.?

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1 And, I don't know if anybody here saw; there was a very  
2 interesting, I thought, article in the New York Times a  
3 couple of weeks ago that I quoted at the bottom here,  
4 if you are interested. These authors talked about the  
5 fact that a number of trials, an impressive number of  
6 trials are being conducted outside the United States in  
7 2010, and certainly there are a number for this; some I  
8 understand, some I don't, but in other countries, it's  
9 perhaps easier for patients to stay in the hospital for  
10 the duration of a trial; it's perhaps less expensive.  
11 There are certainly different standards of care. Not  
12 every country has the four-hour rule and CMS, you know,  
13 putting stuff on the web. There are different issues  
14 with choice, with control agents, and it brings up  
15 whether one can use the same control globally. And  
16 then, there are some study conduct issues. If patient  
17 trials are conducted primarily in other geographic  
18 regions, the genetic make-up of the population may be  
19 different than those here in the United States. We've  
20 talked about standard of care, but in some other  
21 countries the criteria for admission to the hospital  
22 are different; who gets I.V. therapy, different. And

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1 then, as we'll talk about tomorrow, the difference in  
2 auditing inspections may be different enough that hit  
3 impacts on these data. I think from our perspective  
4 clinically, the concern is whether the data generated  
5 in a foreign-conducted trial would be generalizable to  
6 our population, and that's something, as treating  
7 doctors, we really want to know more about.

8           And finally, I just wanted to comment a  
9 little bit about some ethical issues that this raises,  
10 you know, and I don't how much people in the room  
11 really think about it, but as somebody who sits on a  
12 hospital ethics committee and has been on an IRB, you  
13 know, I think we have to ask ourselves the question, if  
14 it's okay for patients in other countries to have  
15 potentially-delayed therapy, or is it okay for those  
16 patients to not receive an agent that's effective  
17 against legionella, because they have legionella in  
18 other countries and, at some level, I think that's  
19 something to grapple with. I don't know the answer,  
20 but I just wanted to raise it for your consideration.

21           So, finally I wanted to come back to some  
22 more, I guess we could say pragmatic issues. The way

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1 one could look at this is that there is a certain cost  
2 of selecting primary endpoints that satisfy the  
3 statistical priorities, but might not translate into  
4 data or into studies that are feasible to conduct, or  
5 generate the data that is entirely generalizable to our  
6 patients.

7           And, I think that can come in a lot of ways:  
8 the need to screen many, many patients to enroll the  
9 patients you desire; the need to exclude large numbers  
10 of patients who do get enrolled, but from whom you don'  
11 recover an organism; the need to exclude patients who  
12 don't meet other things to be in our protocol or  
13 valuable population; and then you end up with competing  
14 biases. We have heard about the bias of the ITT in a  
15 non- inferiority trial, but I think there are other  
16 biases in a PRO protocol situation where, when people  
17 fall out for reasons that were not randomized, you end  
18 up with a group that might not still be as protected by  
19 randomization as your population of interest. So,  
20 hopefully we'll be able to talk about some of those  
21 issues in the next day or so.

22           And then finally, why is this so important

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1 now, and I think, you know, our mission in IDSA, in the  
2 group that I have been working with, has been to make  
3 the message loud and clear that this decline in  
4 development of antibiotics is an emergency and it's a  
5 public health emergency, and the numbers here sort of  
6 speak for themselves about the number of new anti-  
7 infective agents that we have. So, our most recent  
8 initiative in the bad bugs/no drugs now, we are bad  
9 bugs/need drugs in the campaign for 10 new antibiotics  
10 by the year 2020. And, with that, I would like to  
11 acknowledge my colleagues on the Antimicrobial  
12 Availability Task Force listed here, and again, thank  
13 you for the invitation.

14 MR. SHORER: We have time for a couple of  
15 questions before the break from the Panel?

16 DR. TEMPLE: Somebody has to tell me if I'm  
17 getting this wrong. The desire for a wide variety of  
18 clinical endpoints similar to the ones that everybody  
19 uses runs into the problem that for active control  
20 trials, you may not have good data on the effect of the  
21 control agent. So, everybody would like practical,  
22 realistic, wonderful endpoints, but -- and they are

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1 regularly usable in placebo-controlled trials or trials  
2 that tended to show a difference, but it doesn't seem  
3 possible going back in history to figure out what the  
4 standard agents do, to find out much of anything except  
5 how they didn't survive. None of these clinical  
6 benefit endpoints seem to have been well-elucidated, so  
7 there isn't any way to set up the margin. Now, am I  
8 missing something, because I don't think we disagree  
9 about the desirability of practical, wonderful  
10 endpoints, but in the non-inferiority setting it's hard  
11 to support them.

12 DR. COX: So, I agree that the mortality  
13 benefit from the older data is in a large part of what  
14 we have. And then there is also the information from  
15 the cross- study comparisons about clinical response  
16 that we do see for the community-acquired pneumonia.  
17 But then, as you move to other endpoints, as you are  
18 describing, we really do have less information to help  
19 us understand what the treatment effect would be for  
20 other things.

21 DR. TEMPLE: So, you think you do have good  
22 data on clinical response in some of these older trials

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1 that allows you to say what the effect of treatment  
2 versus no treatment is, by some reasonably well  
3 standard measure; so then indeed you can use those in  
4 your non-inferiority margin?

5 DR. COX: Yeah.

6 MR. COVINGTON: Paul Covington, from the  
7 newly formed Furiex Pharmaceuticals. I'd like to  
8 reiterate what Dr. Boucher said about the doability and  
9 feasibility of community-acquired pneumonia studies.  
10 We have learned that the four-hour rule, which  
11 apparently has been in effect a couple, three or four  
12 years now, is making, doing a community-acquired  
13 pneumonia study virtually impossible in the United  
14 States, and that's the feedback that I have gotten. I  
15 have to tell you it's very disappointing because I  
16 think that one single entity is causing us to look  
17 elsewhere, to look at doing the clinical trial, but  
18 it's exceedingly important. We have been told that  
19 that rule alone, which hospitals are being measured  
20 from an audit position, that every physician in the  
21 emergency room and the pulmonary doctors are all being  
22 graded on how fast they get drug on board, and if are



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1 unable to do a clinical trial in the United States,  
2 then we are going to have to go somewhere else. I just  
3 want to see if the FDA Board members would comment on  
4 it.

5 DR. COX: I mean, we recognize that there  
6 are, you know, real challenges there, but I am curious  
7 if there might be other ways to try and approach  
8 enrollment in clinical trials? You know, if would seem  
9 that if the point at which patients are seeking care is  
10 through an emergency room, I mean, the possibility of  
11 enrolling patients at that point may be different than  
12 the intake point for previously conducted clinical  
13 trials. It's still, I would expect, going to be very  
14 difficult, but I am curious if, you know, those are  
15 possible options to think about. Helen, do you have a  
16 comment?

17 DR. BOUCHER: So, you are talking about the  
18 potential outpatient approach, people being enrolled  
19 from the outpatient setting?

20 MR. COX: Something about a patient who is  
21 going to be admitted to the hospital to the hospital  
22 with community-acquired pneumonia; so, a patient who

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1 has, you know, a more severe disease, whose going to  
2 get an IV therapy, and who would, I am guessing,  
3 present at the emergency room and then be enrolled into  
4 the hospital. So, you know, if the enrollment is going  
5 to depend upon the patient's arrival at the floor and  
6 then somebody recognizing the patient as being a  
7 candidate for the study, it would seem that, you know,  
8 four hours to get to -- time to enroll in the trial,  
9 just -- you know, the math doesn't work there. And  
10 then, you know, given, you know, what we have learned  
11 more recently about the effect of prior antibiotic  
12 therapy, I guess what I am wondering about is the  
13 possibility of enrolling patients who might actually,  
14 you know, be enrolled at the time they present in the  
15 emergency room. So, it would involve perhaps a  
16 different group of physicians than traditionally those  
17 that have been involved in rolling trials for  
18 community- acquired pneumonia.

19 DR. BOUCHER: Right. Well, I think I can  
20 speak to that a little bit. That has been extensively  
21 looked at, that very issue, because there has been some  
22 success, as you know, with enrolling patients with

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1 complicated or acute bacterial complicated skin  
2 infections in the emergency room. So, we have got some  
3 ER doctors who are pretty switched on to ID things.  
4 But, the problem there is, the reality is the  
5 practitioner goes to the Pyxis, takes out the  
6 antibiotics, hangs the antibiotics, then calls Medicine  
7 to admit the patient. I mean, it's because of this  
8 push that frequently a triage nurse makes that  
9 decision. So, intervening in that point and then  
10 having enough data to know that they meet your  
11 inclusion criteria; you know, having the chest x-ray,  
12 you know, the key things that you need when you really  
13 look at the feasibility. And, I know there are people  
14 much more expert than I am to comment on this, but the  
15 studies that have been looked at, at our institution,  
16 it was just taken off the table because of the -- four  
17 hours is actually a pretty short time, and they do it  
18 from when the patient checks in. So, you know, you  
19 check into triage. You sit in the chair. You know,  
20 you sort of, you go through the -- by the time you get  
21 into a bed it might be an hour, an hour-and-a-half, you  
22 know, the time is moving along. The blood is drawn.

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1 You are sent to your x-ray, you know? Then you are at  
2 three hours pretty fast. So, even if you have an ER  
3 doctor who is the PI, who is ready to go, it's pretty  
4 tough. And, if you look at some of the other studies,  
5 it's more like eight, 10, you know? It's a number of  
6 hours before those people are actually randomized and  
7 receiving the dose, from the study -- you know, drug  
8 from study pharmacy, you know, all those things that  
9 have to happen to make it feasible, you know, to make  
10 it meet the criteria. I don't know if others want to  
11 comment?

12 MR. FARLEY: I think one approach in my  
13 previous life was, if it's an academic medical center  
14 that has a centralized clinical trial center, we have  
15 had a research coordinator in-house 24 hours a day, who  
16 could be paged and is obviously dealing with a number  
17 of studies, and you have to have, of course, a research  
18 pharmacist to open, you know, and on-call 24 hours a  
19 day. It becomes prohibitively expensive. It worked  
20 very well for some flu studies during flu season and  
21 then, you know, you sort of lose the business and you  
22 don't have enough to keep that person in-house, so that

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1 kind of was the challenge.

2 MR. SHORER: Wiley? Wiley Chambers?

3 MR. CHAMBERS: Hi. It's my understanding  
4 that the rule is not a four-hour rule, six hours, and  
5 there is an exclusion for anybody that is in a clinical  
6 trial. Is that message just not getting out, or is it  
7 still undoable if everybody that's enrolled in a  
8 clinical trial is excluded from the -- I mean, it's  
9 like, it's a quality-measured count is what it is for  
10 the hospitals.

11 DR. BOUCHER: Yeah.

12 MR. CHAMBERS: And, yes, it's reported on  
13 hospital compare out to all hospitals, but you get  
14 taken off the denominator list if you are in a clinical  
15 trial, and it's been changed to six hours to deal with  
16 some of the same issues that are being talked about.

17 DR. BOUCHER: All right. Well, I think --

18 MR. CHAMBERS: My question is, it's still  
19 undoable because of the training, or -- I mean, is this  
20 an education issue, or it's never going to be fixed.

21 DR. BOUCHER: I think it may be a combination  
22 of issues, but some of the things that have come up

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1 have been, well what about the patient who you think  
2 is going to go on the trial so they don't get their  
3 antibiotic and then they opt out or the screen out, and  
4 now it's five hours, you know? This is the sort of  
5 quality people who really wield a lot of power in our  
6 hospitals now who win those discussions. I think  
7 probably others who have done the real feasibility  
8 could, you know, more than a couple of institutions  
9 could comment better than I, but I have heard comments  
10 like that.

11 DR. SHORER: Okay. Thank you. Before we go  
12 to the break, if there is anybody who is planning on  
13 making public comments, please identify yourselves now  
14 by raising your hands.

15 DR. FARLEY: You can present yourself to me  
16 or Chris Moser, Christine Moser, during the break.  
17 This will be the last chance for formal public comments  
18 folks to identify themselves.

19 DR. SHORER: Okay. This is now -- it's  
20 quarter after 3:00. We will convene back at 3:30.

21 (BREAK).

22 DR. SHORER: It's 3:30, and we are going to

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1 start on time, so if everybody could please take their  
2 seats? Our next presenter is Dr. Eileen Navarro,  
3 Deputy Director of the Division of Special Pathogens  
4 and Transplant Products at the FDA, and she will talk  
5 about the role of microbiology and antibacterial drug  
6 development. Everybody can take their seats, please.

7 DR. NAVARRO: Sorry, to do this when my sons  
8 aren't here to tell me how to do it. Good afternoon.  
9 I am going to talk about the role of microbiologic  
10 assessment in antibacterial drug development, and  
11 compared to the other speakers, I actually come from  
12 the Division of Special Pathogen and Transplant  
13 Products, where we regulate both antibacterials, the  
14 broader antimicrobial classes, as well as  
15 transplantation products. So, I am going to, in the  
16 course of my talk, try and limit this to a discussion  
17 of antibacterials; what I think the bias will show  
18 sometimes when I draw on examples. I have no conflicts  
19 to disclose. I would also like to point out that the  
20 slide set that you have in the book slightly differs  
21 from what I am going to go through here. There is  
22 something about folding warm clothes from the dryer

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1 that allows you to focus your thoughts, and yesterday I  
2 thought that that was what I would do so that -- in the  
3 hope that, you know, the message is a little bit  
4 clearer, because this talk is really conceptual. I am  
5 not going to be presenting any confidence intervals,  
6 and just hope to frame some of the discussions that  
7 will occur later in the day, but will also try and help  
8 you think about the microbiologic data that needs to be  
9 developed in defining the efficacy of an antibacterial  
10 agent. So, this is the outline of my talk.

11 I'm going to speak about the rationale for  
12 microbiologic assessments in antibacterial drug  
13 development; speak to the assessments in the varying  
14 phases of drug development starting from the non-  
15 clinical in vitro studies, moving on to the in vitro  
16 and more model studies of therapeutic and  
17 pharmacokinetic assessments of drug efficacy; and then  
18 move on to the data that necessarily comes from the  
19 Phase Two, and then moving on into Phase Three trials.  
20 Then, I speak about how this accumulated data is  
21 analyzed in assessing antibacterial drug efficacy and  
22 speak to how that information is really synthesized so



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1 that in the end we are able to come up with a  
2 reasonable estimate that the drug has the effect it is  
3 purported to have based on the trials that you submit  
4 to the Agency. And then, following a successful  
5 clinical drug development program, which I think is a  
6 shared goal between academia and the industry and the  
7 FDA. I will then talk about how the information is  
8 actually displayed in an antibacterial drug label.

9           So, why are we even talking about why we need  
10 to do microbiologic assessments for antibacterial  
11 agents? We just need to think about the recent  
12 experience, for example, in H. pylori peptic ulcer  
13 disease, or with Whipple's disease, to relearn Cox  
14 postulates and understand that the microbiologic  
15 assessment of a clinical syndrome may help establish an  
16 etiologic diagnosis, and therefore link how a patient  
17 feels, functions and survives to a particular pathogen.  
18 We have been repeatedly told that we really treat  
19 patients and not organisms in test tubes, and it is  
20 true that for most acute symptomatic infections an  
21 assessment of both clinical and microbiologic endpoints  
22 is therefore expected. So, it's important to note,

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1 however, that measurement of pathogen-directed and  
2 host-directed effects, the latter can be either  
3 modification of symptoms or unwanted adverse effects,  
4 need to actually be assessed separately and then  
5 integrated in subsequent analysis of efficacy, as well  
6 as risk and benefit.

7           It's also been mentioned several times today  
8 that the end goal of this is really guiding patient  
9 care and how that might be a challenge sometimes for us  
10 who are in the business of trying to discern  
11 antibacterial effect. Susceptibility testing helps  
12 guide selection of appropriate therapy or  
13 discontinuation should that be inappropriate, because  
14 resistance indeed is sometimes a consequence of the  
15 overenthusiasm with antibacterial use.

16           So, microbiologic assessments not only help  
17 in taking care of patients, but they also do support  
18 adequate and well-controlled studies. This is an  
19 easier task for me, because people have actually gone  
20 over what the essential attributes of an adequate and  
21 well- controlled study is, and I am just using those  
22 attributes to actually bring the discussion here.

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1 Microbiologic testing can actually clarify trial  
2 objectives, because they inform efficacy conclusions  
3 about an antibacterial agent. They provide a measure  
4 of drug effect on the pathogen, and elucidate  
5 mechanisms of activity for particular indications. For  
6 example, a microbiologic test can help us distinguish  
7 whether the indication you are seeking is to mitigate  
8 or cure a disease, or to relieve the symptoms of such a  
9 disease; because, as we have been told, antibacterial  
10 agents actually have pleiotropic effects, and in  
11 addition, are often used in combination, not just with  
12 antibacterial products, but also with other products  
13 that may modify effects. And, it's the microbiologic  
14 test that actually does link to the mechanism of  
15 action.

16           Microbiologic tests permit valid,  
17 quantitative comparisons, and when we define the  
18 outcomes of a control, the link to the historical data,  
19 that is even more enhanced. Determining the magnitude  
20 of effect attributed to an antibacterial is also  
21 particularly important, and people have actually spoken  
22 to the dose response studies and the studies where one

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1 might actually discern the effect of a new drug on top  
2 of a combination that may include drugs with similar or  
3 different mechanisms in a superiority study for us to  
4 actually maybe consider the use of a microbiologic  
5 endpoint and what it brings. People have spoken about,  
6 you know, the quantitation of pharmacokinetic and  
7 pharmacodynamic outcomes at the site of infection, and  
8 this might be better worked out in certain indications,  
9 such as urinary tract infections and less so in others,  
10 but nonetheless, these studies, because they have been  
11 validated, do permit quantitative comparison of a drug  
12 effect. Furthermore, microbiologic tests help us select  
13 patients with disease and assure baseline comparability  
14 of populations that are studied, but they can serve as  
15 inclusion criteria at randomization, and this is  
16 actually particularly maybe useful to consider now that  
17 we are on the verge of coming up with rapid diagnostics  
18 and we hope to see that happen. And, they are also  
19 useful in defining analytic populations or sub-  
20 populations of interest; for example, in resistant  
21 bacteria, and people have spoken to that already.

22 Now, standardized tests also minimize bias

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1 and can serve as appropriate methods of outcome  
2 assessment if they are reliable and well-defined. One  
3 would hope that susceptibility to interpretation bias  
4 is minimized by the use in objective standardized in  
5 vitro method, and when outcomes are also pre-defined.  
6 Exemplified here is that standardized procedures, quality  
7 control limits, testing of cross-relevant strains and  
8 correlation with clinical outcomes is actually the  
9 basis for coming up with reliable, interpretative  
10 criteria, and one cannot be more standardized than  
11 that.

12               So, using that as a framework, I'd like to  
13 walk you through now the information that actually  
14 comes from various phases of drug development, and in  
15 the subsequent part of my talk, I'm going to actually  
16 refer to a guidance that our good folks in microbiology  
17 have put together. Much of the thinking that's here is  
18 actually also framed by the information that's  
19 contained in that document. So, the non-clinical  
20 microbiology tests usually serve as the initial  
21 evidence of activity of a candidate drug, and this  
22 ranges from either a mechanism of action studies to

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1 studies that actually showed modification of that  
2 activity. And, they range from in vitro axis of  
3 susceptibility and to more sophisticated newer tools  
4 that allow us to discern the molecular methods by which  
5 a drug may work. And, as well, people have spoken  
6 about the possibility utility of animal models here.

7           The other modifiers of activity are also  
8 important to discern early, and this can range from  
9 assessing protein binding of a drug to its activity in  
10 relevant body fluids, and I think people have given you  
11 the examples of conditions where that was actually very  
12 crucial to understand. Furthermore, activity of a drug  
13 in combination and potentially the impact of resistance  
14 and cross-resistance are also important early in non-  
15 clinical microbiologic tests. So, to just walk you  
16 through some of these details, and again, some of this  
17 is actually in the Guidance, early in vitro  
18 microbiologic tests actually are designed to study the  
19 effect of a drug against a range of human pathogens.  
20 This is known as the spectrum of activity assessment,  
21 and the utility of this is actually to try and focus  
22 development towards indications where activity is

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1 expected. What's important to point out here is that  
2 these strains that are tested actually need to have  
3 come from recent clinical trials, and should adequately  
4 represent the variance of pathogens that are relevant  
5 to human disease. People have spoken about the  
6 difficulty of enrolling locally, and if trials are  
7 actually performed outside of the U.S., you will need  
8 to actually tell us how relevant that information to  
9 our populations. Additionally, because diseases change  
10 and human needs change, there might be a need to  
11 actually reassess this information over time, even for  
12 older products.

13           In addition, if the clinical trials do not  
14 come up with significant numbers of strains that are  
15 highly resistant or have increased virulence, and we  
16 need to understand the utility of a product,  
17 particularly for that indication, we may need to  
18 actually require testing and, in fact, it is useful to  
19 do testing against compendial strains or strains from  
20 specimen banks.

21           Moving along to activity in animal models as  
22 proof of concept, these are generally helpful, in that

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1 they help determine whether there is reasonable  
2 activity with a new drug to proceed into early clinical  
3 trials. Therapeutic studies in relevant animal models  
4 give us a reasonable estimate of how a drug might be  
5 expected to perform for a particular indication, but in  
6 addition, the utility of these studies is that they can  
7 actually help. If we do the pharmacokinetic studies in  
8 an insightful way, they may help those select and  
9 inform those in intervals. It would be also useful in  
10 identifying activity in sheltered sites or  
11 pharmacokinetic compartments, and are particularly  
12 helpful in assessing drug interaction, and when one  
13 needs to do factorial design studies, we must also  
14 think of them as potential early sources of information  
15 about bio-markers or new assays that can then be  
16 explored.

17           So, moving on along into the first inpatient  
18 studies, which are your phase two clinical trials. All  
19 of the prior information helps inform what those might  
20 be explored in phase two, and the essential utility for  
21 phase two is actually to help us decide what dose to  
22 then carry forward into our larger phase three studies.



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1 We cannot overemphasize the utility or the importance  
2 of adequate dose exploration, and I think many people  
3 have actually spoken to this already at this meeting,  
4 because with a robust dose exploration, concentration  
5 effects that may be gleaned from earlier trials can  
6 actually be clarified and antibacterial dosing may be  
7 optimized. But, in addition, if we find a dose to  
8 actually be superior to another dose based on relevant  
9 endpoints, this finding may actually help to support  
10 antibacterial efficacy and actually support labeling.

11           People have spoken about when is it relevant  
12 to do microbiologic tests? When you are particularly  
13 interested in the new clinical syndrome, it may be more  
14 helpful to actually discern when the optimal timing of  
15 the assessments may be, because in the smaller  
16 circumscribed study one has the utility of actually  
17 doing more intensive measurements with the hope that  
18 this can actually lead to more efficient phase three  
19 studies, because you would know exactly when it might  
20 be most useful to repeat those tests? Again, the  
21 utility of phase two in early initial testing of new  
22 assays is also one thing to consider.

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1           So, following completion of your phase two  
2 trials, it's actually a critical juncture. As you move  
3 into your phase three trials, certain information  
4 actually needs to be submitted in your protocol. In  
5 addition to the description of your adequate and well-  
6 controlled studies, certain aspects of those in  
7 relation to microbiology are actually listed in this  
8 slide. One aspect is that your outcomes should be  
9 defined in the protocol, and it will be useful if the  
10 bases of some of those definitions can be linked to the  
11 natural history of disease. Some of these are obvious  
12 in that eradication of strept, pneumo and meningitis is  
13 expected; whereas, it may be infeasible to do that in a  
14 respiratory tract infection in patients if they are  
15 highly colonized. Where I am going with this is that,  
16 if for the latter you propose a definition for an  
17 outcome, the criteria for the quantitation and the  
18 basis that led to its validation needs to part of what  
19 you submit in your protocol to us. And, while you may  
20 not need to do that in an extensive fashion for urinary  
21 tract infection, because that's relatively worked out.  
22 When you are talking about disease states, such as

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1 diabetic foot infections, for example, we believe a  
2 little bit more understanding of the basis of your  
3 proposed outcome definitions. Again, the timing of  
4 assessment can be informed by historical studies, by  
5 your earlier phase two studies, and by correlation to  
6 clinical endpoints. And, there are many examples  
7 actually, particularly for H. pylori where that has  
8 occurred.

9           The other important thing that actually is  
10 crucial at this phase is your definition of your  
11 interpretive criteria of susceptibility, because drug  
12 resistance and cross-resistance are important to assess  
13 for the identified pathogens in your phase three trial.  
14 And, for this, we generally prefer standardized  
15 methods, but we understand for a drug that truly has a  
16 novel mechanism of action or is the first in its class,  
17 this may be difficult to do, and should you choose to  
18 actually come up with a novel method that hasn't been  
19 previously described, you will need to provide detailed  
20 information regarding that and their use discussed with  
21 us early.

22           So, moving on -- and again, Dr. Marsik is

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1 here. He is actually listed in the Guidance as the go  
2 to person, so I am glad that he is here. If you have  
3 anymore detailed questions about how one can come up  
4 with provisional interpretive criteria and final  
5 interpretive criteria, I am going to refer you to him  
6 for more detail. But, this generally requires that one  
7 has an understanding of the mechanism of action and the  
8 mechanism of resistance for a new drug, and there are  
9 two approaches to this. If your candidate drug  
10 actually has been shown to have an MIC distribution  
11 that is very similar to that of an approved  
12 antibacterial, one might be able to use the criteria  
13 for the approved standard drug as your initial  
14 provisional interpretive criteria.

15           Again, with a novel drug that might not  
16 possible and you may need to provide more information  
17 to us, and that might include: a broader testing  
18 against a broader range of organisms; testing in  
19 different concentrations, with sera (ph), without sera;  
20 or testing against a range of pathogens, whose  
21 mechanism of resistance has been well worked out. And  
22 then, you'll have to provide information for both that

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1 this achievable -- these concentrations that actually  
2 have an affect on the organism are achievable at the  
3 site of infection. A final interpretive criteria  
4 actually emerge after you have completed your phase  
5 three trials, and they are generally a correlation of  
6 clinical success and microbiologic eradication is what  
7 is expected. And again, I refer you to the Guidance  
8 for the detailed discussion of what -- of how the data  
9 should be analyzed to come up with that.

10 Now, you have completed all your studies and  
11 you are getting ready to submit your NDA. There  
12 actually is guidance from the Code of Federal  
13 Regulations as to the amount of information that you  
14 need to submit, and I am going to quote it here. It  
15 says, "The description and analysis of every controlled  
16 study, including the protocol and statistical analyses,  
17 sufficient reports of everything pertinent to  
18 effectiveness from any source, and integrate the data  
19 somebody of substantial evidence of effectiveness and  
20 evidence to support dosage and administration." So, I  
21 think all relevant microbiologic information that  
22 supports the efficacy of a specific dose and regimen

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1 for a specific pathogen and other information that you  
2 want to be labeled, some of this is actually required  
3 should be submitted in the NDA. I think the rule is if  
4 you have it, it's better to send it to us.

5           So, how do we review that information and  
6 analyze it? I think people have described -- actually,  
7 Dr. Nambiar has described how we label indications  
8 currently, and they usually require a description of  
9 the clinical disease, as well as the organisms in  
10 patients that have been successfully treated, and  
11 therefore, a modern label would read as maybe  
12 community-acquired pneumonia caused by strep pneumonia.  
13 The clinical studies section of the label will also  
14 describe the clinical and microbiologic outcomes that  
15 led us to conclude that the drug has the efficacy that  
16 it is purported to have. It's also important to point  
17 out that clinical symptoms sometimes serve as de facto  
18 microbiologic endpoints, particularly for the cyst  
19 syndromes where a resolution of the symptom actually  
20 makes it infeasible to do a microbiologic assessment,  
21 such as in cellulitis, for example, or in pneumonia,  
22 when a patient is no longer coughing up any sputum.

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1 The clinical trial section, when it is important, may  
2 also describe when outcomes are discordant between  
3 clinical and microbiologic endpoints, and that is  
4 really a view that is informed by the disease and by  
5 drug activity. So, microbiologic endpoints are  
6 important, but they rarely are sufficient as the sole  
7 source of success in treating a patient. Nonetheless,  
8 they may assume greater relevance. For example, when  
9 eradication of a symptomatic infection prevents serious  
10 sequelae, such as when one treats toxoplasmosis in  
11 pregnancy; when symptom resolution may be affected by  
12 an inactive vehicle, and we have seen some of that for  
13 the topical antibacterials; when self-limiting symptoms  
14 minimize the ability to establish a cure, such as in  
15 chlamidia and gonorrhea; and when the correlation of  
16 clinical benefit is established, such as in H. pylori.

17           So, outside of the clinical studies and in  
18 the indication, where else is the microbiologic data  
19 that you acidulously worked on listed in the label?  
20 For the pathogen we have these two lists; one is known  
21 as the first list that's actually linked to the  
22 indications and usage section of the label, and lists

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1 the relevant human pathogens for which clinical  
2 evidence of activity has actually been discerned from  
3 the clinical trials. And again, that also includes  
4 what we know about the in vitro, in vivo, and  
5 pharmacokinetic data. The second list is actually  
6 based on less solid information, and therefore you will  
7 need to provide more information that will allow us to  
8 consider listing these. You will need to provide  
9 evidence regarding the pathogen's relevance to the  
10 approved indication, and they are generally listed at  
11 the frequencies shown across disease in the population.  
12 These are generally supported by MIC data for at least  
13 100 isolates, and you need to show that the inhibitory  
14 concentrations are achievable at the site of infection.

15 In conclusion, microbiology plays and  
16 important role in defining activity of an  
17 antibacterial. It is useful to determine outcomes in  
18 patients, and as well as to guide patient care.  
19 Microbiologic testing supports adequate and well-  
20 controlled studies, and helps define populations with  
21 disease. It can also be used to define analytic  
22 populations and sub-populations, for example, patients



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1 with resistant organisms. The pre-clinical information  
2 helps focus drug development and informed use in  
3 clinical studies. Phase two studies provide early  
4 assessment of potential efficacy and help select those  
5 for development, and in particular instances, may also  
6 be used to determine drug effect. The design of phase  
7 three studies is based on the data that is accumulated  
8 over your drug development period, and the utility of  
9 the microbiologic endpoints you propose to use here are  
10 best informed by historical controlled data, if that  
11 exists. Analysis of the microbiologic data from your  
12 drug development is integrated in clinical outcomes  
13 when we try and discern drug effect, and data from  
14 standardized tests into drug label informs clinical  
15 use.

16 I think I can take any questions now, but I  
17 would like to acknowledge the help of our colleagues,  
18 as well as useful discussions with colleagues in the  
19 office for their help.

20 DR. SHORER: Okay. We are a little bit over  
21 time, so if there are any questions from the Panel?

22 DR. EISENSTEIN: Thank you. I have a brief

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1 question to try to help me understand; when a pathogen  
2 that's of a certain species that then picks up another  
3 attribute that has really nothing to do with the  
4 ability of the initial antibiotic to affect it's  
5 killing, when does that become a new pathogen from the  
6 standpoint of regulatory approval? I'll give you an  
7 example: staph aureus; staph aureus that becomes  
8 penicillin-resistant; staph aureus that becomes  
9 methycillin- resistant -- and I could list a whole  
10 bunch of other antimicrobials. At what point does the  
11 staph aureus become a novel path-- a new pathogen that  
12 requires a new proof of the antibiotics ability to  
13 eradicate it, assuming that the susceptibility to the  
14 antimicrobial has not changed at all?

15 DR. NAVARRO: Okay. So, the people who  
16 understand the population genetics and bacteria tell me  
17 that the evolution of a pathogen, in that it actually  
18 mutates to the frequency that actually allows  
19 resistance to emerging pathogen while undergoing  
20 treatment, it does not happen very often, and that  
21 resistance often emerges because of the pressure of  
22 antimicrobials. But, were that to occur, I think we

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1 would need to actually collect that specimen and study  
2 it very acidulously, because it might talk about, I  
3 think, a concept that's being considered now as  
4 something that may be measured for antibacterials; that  
5 is the mutation frequency -- someone has to help me  
6 with this -- but, the ability of certain antibacterials  
7 because of their chemistry to actually prevent the  
8 development of resistance, it is felt that certain  
9 bacteria -- that certain antibacterials actually are  
10 more able to resist mutations because of the way that  
11 they are configured; the way that they actually -- it  
12 may be their pharmacokinetics, and it may also be a  
13 function of the mutation rate of the bacteria itself.  
14 So, I think the mutation frequency ratio or something  
15 is actually being proposed as a new measure for  
16 assessing antibacterial efficacy in vitro. I think  
17 that whether that actually translates into clinical  
18 importance, I am not certain is established, but I know  
19 that people have been talking about it. I'm not sure I  
20 answered you, but the other thing I was thinking about  
21 --

22 DR. EISENSTEIN: Maybe we can pick it up in

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1 the -- during the Panel questions. It's a more  
2 complicated question actually.

3 DR. NAVARRO: Okay. Thanks.

4 DR. SHORER: Thank you. Our next speaker is  
5 Dr. Judy Siuciak, from The Biomarkers Consortium, at  
6 the Foundation for the NIH.

7 Dr. SIUCIAK: All right, does anyone know how  
8 to get back to the beginning here? Perfect. I have  
9 been tasked to give you an overview on the work at the  
10 Foundation for the NIH Biomarkers Consortium, so I  
11 realize this a rather diverse audience, so I thought  
12 I'd, you know, give some background here of who we are,  
13 what it is that we do, how we do it, and then end on a  
14 project that's been referred to and is relevant to this  
15 group. Oh, I should say I have no conflicts, and also  
16 the slide set that's in the handout is slightly  
17 different. Apparently I also felt the need to do some  
18 laundry yesterday.

19 So, the Foundation for the NIH, also known as  
20 FNIH, was established by an act of Congress in 1990.  
21 It was incorporated in 1996, and that's when the actual  
22 work began. It was established as a 501(c)(3) non-

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1 profit public charity. So, the goal of FNIH is to  
2 support the NIH mission, and that is to improve health  
3 through scientific research. So, as an independent  
4 non-profit organization, our goal is to raise money for  
5 NIH. We have raised over \$460 million dollars since  
6 1996 on over 100 projects, and these projects range in  
7 size from, let's say, establishing small training  
8 grants to managing very large scientific initiatives.  
9 So, if you go to Charity Navigator -- and I don't know  
10 if everybody here is familiar with it; it's a website  
11 that ranks and rates charities -- you will find that we  
12 are one of the top ten rated medical charities. We  
13 have received their four- star evaluation for four  
14 consecutive years, and we have also shown that we have  
15 spent over 95 percent of our total funds on our  
16 programs, which means that we keep our administrative  
17 costs very low. So again, we are a non- profit  
18 organization; we are not the NIH; and we are non-  
19 governmental, and this has some benefits. We can  
20 direct solicit contributions. We have flexible donor  
21 relationships and I can explain a little bit about  
22 that. Let's say, for example, you are a pharmaceutical

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1 company and you want to participate on some of our  
2 projects. Maybe for one of our projects you can donate  
3 \$100,000 in cash. Maybe for the second project you can  
4 donate a statistician's time to analyze a retrospective  
5 data set. And, maybe for the third project you can  
6 actually analyze some samples back at your company.  
7 There is a flexibility in how you can participate in  
8 our projects. And finally, we can rapidly make grants  
9 and contracts. So, we raise our funds by direct money  
10 from private sponsors and we also create public/private  
11 partnerships.

12           And, these partnerships can include  
13 Government partners:  
14           that's NIH Institute members, as well as the  
15 FDA industry; that's Large Pharma, biotech, even  
16 diagnostic companies, academics, and also the  
17 philanthropic community, and by that I mean other non-  
18 profit organizations, as well as patient advocate  
19 groups. And, I think we can all appreciate, in this  
20 current economic environment, where funds are scarce  
21 and budgets are pressed and costs are increasing that  
22 pulling together everybody's resources, including

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1 personnel and funds is the way to resolve some of these  
2 larger scientific issues that are approaching us. And,  
3 the Foundation provides a neutral forum for all these  
4 parties to get together and come and work  
5 collaboratively together.

6           So, I mentioned that there were over 100  
7 projects going on at the FNIH, and these are some of  
8 the key initiatives. And, for example, the first one  
9 is The Grand Challenges in Global Health, which is our  
10 largest project. This is a \$200 million project. The  
11 partner is the Gates Foundation. And, I certainly  
12 don't want to spend a lot of time going over all of  
13 these. I do want to mention the third one, which is  
14 the Alzheimer's Disease Neuroimaging Initiative or  
15 ADNI, and this has been in the news lately and some of  
16 you might have heard of it. So, ADNI represents the  
17 largest brain project sponsored by the NIH. There is,  
18 I believe, \$40 million dollars provided the NIA and the  
19 NIBIB, in conjunction with the \$27 million dollars that  
20 the FNIH raised from companies and non-profit  
21 organizations. And, the goal of ADME is to see if you  
22 can combine a considerable amount of data. This

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1 includes MRI, PET scans, bio-marker assessment, as well  
2 as neurocognitive, neuropsychological testing, in  
3 tracking patients who have mild cognitive impairment  
4 and Alzheimer's disease. And, ADNI is currently  
5 tracking over 800 patients. It's actually a six-year  
6 project that started in 2004 and is thus ending in  
7 2010, and it's currently up for renewal, so they are  
8 looking at another five years. I think it's over \$80  
9 million dollars in combination with the Government  
10 funds and the private funds at this point. And ADNI  
11 has also spurred numerous ADNI-like initiatives across  
12 the world, in Japan, Australia, and other places, for  
13 example.

14           And, at the bottom of the list is the  
15 Biomarkers Consortium. And, the Biomarkers Consortium  
16 is a little unique in that it's not a single project,  
17 but is actually an umbrella for multiple projects that  
18 run underneath in it, and I'm going to spend the rest  
19 of the time talking about the BC, as it is more  
20 commonly referred to. So, the BC was officially  
21 launched in October 2006, and the founding partners  
22 were the Foundation for the NIH, the



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1           NIH, the FDA, PhRMA, CMS and BIO. We have  
2 four steering committees: Neuroscience, Cancer,  
3 Immunology and Inflammation, and Metabolic Disorders,  
4 and they became operational in spring and fall of 2007,  
5 and the first project was officially launched in 2007.  
6 So, the goals of the Biomarkers Consortium are pretty  
7 straightforward. We want to develop and validate  
8 biomarkers. We want to qualify biomarkers. We want to  
9 generate information to inform regulatory decision-  
10 making, and finally, we want to make sure that all the  
11 results from our projects are made broadly available to  
12 the scientific community. We are not about running a  
13 project and having only a few people look at the data.  
14 It's about making it available to everybody.

15           So, this is the governing body of the BC.  
16 This is the Executive Committee, and you can see that  
17 we have members of all of our founding partners here.  
18 We have members from NIH, from several institutes, from  
19 the FDA, from CMS, an industry, as well as a public  
20 member and members of the FNIH Board. And, I should  
21 say that the membership on the Executive Committee does  
22 rotate. These people aren't here for life, by any

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1 means. These are the contributing members to the  
2 Biomarkers Consortium. We are currently at 61  
3 contributing members. You can see we have a large  
4 number of four profit companies. These represent a  
5 large number of the -- Large Pharma, some biotech and  
6 some diagnostic companies, and then we have quite a few  
7 non-profit organizations. So, when companies become  
8 contributing members it allows them to participate in  
9 our steering committees, as well as participate in our  
10 project teams. So, let's say, for example, you are an  
11 Eli Lilly or a Merck and you have interests in all four  
12 of those steering committees, you can nominate someone  
13 from your company to participate in all four of those.  
14 If you are a small biotech or maybe the Alzheimer's  
15 Association, your interests are going to be smaller.  
16 If you are the Alzheimer's Association, you are only  
17 going to put someone on the neuroscience steering  
18 committee. So, there is flexibility as to what you are  
19 interested in.

20           This is the decision-making structure, so on  
21 top is the Executive Committee that I mentioned before.  
22 Then, we have our four steering committees. Each of

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1 the steering committees has two Chairs. One of the  
2 Chairs is from industry, and the second Chair is either  
3 from academia or from NIH. And, we have multiple  
4 projects within each of those steering committees.  
5 And, the majority of our projects actually fit within  
6 each of those steering committees, but periodically we  
7 get a project that doesn't quite fit perfectly into one  
8 of those four, and then we form an actual subcommittee  
9 of the Executive Committee to monitor those projects.  
10 For example, we have a kidney safety biomarker project  
11 that doesn't fit in either of those four subcommittees.  
12 In that case it sort of sits off the side of the  
13 Executive Committee. So, we are actually able to  
14 manage a diverse array of projects within the BC.  
15           So, I think my slide got a little messed up  
16 here, but this is the project development process. So,  
17 there are a couple stages to a project when it comes  
18 through the BC, and the first is the project -- it's  
19 supposed to say project concept -- so, ideas come into  
20 the Biomarkers Consortium from a variety of ways.  
21 Sometimes I get a phone call or an e-mail. Other times  
22 they come in from one of our steering committee members

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1 through the Executive Committee, and however they come  
2 in they eventually get pushed into what's called a  
3 project concept form. That's usually a three to four-  
4 page form that basically lays out the bare bones of  
5 what the project might look like. And, at this point  
6 it's a pretty early stage idea. You are asked to lay  
7 out what you think the budget might be; what you think  
8 the timeline might be; the historical perspective, et  
9 cetera. We do a bit of an IP scan and an initial  
10 funding scan to make sure that everything looks all  
11 right, and it goes before a steering committee, and the  
12 steering committee decides whether they think it's an  
13 appropriate project for the Biomarkers Consortium. So,  
14 if it passes that point it goes to the project plan  
15 stage, and this is where a project team is formed.  
16 And, our project teams are actually pretty interesting.  
17 They are usually, on average, 15 people, and they have  
18 representatives from various NIH institutes, the FDA,  
19 academia, not for profits, and a variety of industry  
20 members. And, all these people get together pretty  
21 regularly, usually via teleconference, and they hash  
22 out the details of a project plan, and our project

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1 plans can be up to 100 pages long. And, this is where  
2 you lay out everything from the exact protocol, the  
3 resources you are going to need, the IP issues  
4 associated with it, the data sharing plan, the  
5 timelines and milestones -- we always have very clear  
6 milestones on go/no decisions -- the budget, everything  
7 that you need to know about this project, and I have to  
8 say there are some pretty lively calls when you have up  
9 to 15 people participating in a project. I always make  
10 sure that when someone comes to us with an idea that  
11 they understand that what they come in the door with  
12 may not be what goes out the door, because they have to  
13 be open to participation by this diverse group of  
14 people. I know Barry mentioned earlier that he had an  
15 idea about the project that I'm going to be talking  
16 about later and he got feedback from maybe one person.  
17 The project team is where that should be discussed,  
18 because everybody needs to participate in here and sort  
19 of vote on that idea. And, it can be quite an  
20 interesting discussion and lively discussion when you  
21 have these project team meetings. So eventually, after  
22 the project plan is approved, it goes to the steering

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1 committee again and ultimately to the Executive  
2 Committee, and we actually fundraise for each of our  
3 projects at the point where the project is approved, so  
4 we don't have a pool of money sitting around and say,  
5 here is the money. Once the project plan is approved  
6 we go out to our various funders and we lay the project  
7 plan out for them, and we tell them that this is what  
8 we are looking for and they can fund it or not fund it;  
9 it's their choice. And, ultimately the contracts and  
10 project management is all put into place and the  
11 project moves forward.

12           So, what kind of projects do we have? We  
13 currently have one completed project. We have eight  
14 active projects. We have four projects that are  
15 approved and in fundraising, and we actually have a  
16 variety of other projects that are in various stages of  
17 development. And, for the last few minutes of my talk,  
18 I'm just going to spend a few minutes highlighting a  
19 few of the projects that are at the Consortium, and I  
20 have chosen these projects because they represent the  
21 diversity of projects that exist at the Consortium.  
22 They are at different stages. They have different

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1 budgets. They are on different steering committees.  
2 They utilize different resources. And, I think the  
3 last one is an obvious reason for why I am talking  
4 about it today. Our projects tend to have very lengthy  
5 titles, so we are forced to abbreviate them into one  
6 word shortened titles, like Adiponectin, instead of  
7 evaluating the utility of Adiponectin as a biomarker  
8 predictive of glycemic efficacy by pooling existing  
9 clinical trial data from previously conducted studies,  
10 or an acronym like I-SPY 2 trial; investigation of  
11 serial studies to predict your therapeutic response  
12 with imaging and molecular analysis, after you get  
13 tired to referring to them for the first hundred times  
14 by their lengthy titles, so I'll refer to them by their  
15 abbreviated title.

16           So, the first project I'm going to highlight  
17 is the Adiponectin trial. So, this was the first  
18 project was approved in 2007, and as such, was the  
19 first completed project for the Biomarkers Consortium.  
20 It's rather unique in terms of its funding, in that it  
21 was conducted entirely via in kind donations from  
22 several companies in the NIDDK. It is a data sharing

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1 project. It involved the aggregation of data from  
2 clinical trials of PPAR agonists from several  
3 companies, and then this pool data was then analyzed by  
4 statisticians at quintiles in the NIDDK. So, the  
5 results provided evidence that Adiponectin is in fact a  
6 robust biomarker predictive of glycemic efficacy in  
7 type 2 diabetes and in healthy subjects after treatment  
8 with PPAR agonists. So, these results were published  
9 in CPT in June 2009, and the team also wrote a very  
10 nice lessons learned paper that was published in May  
11 2010, also in CPT. So, beyond the scientific results,  
12 this project also demonstrated that the inclusive  
13 cross-company collaboration that was used was a very  
14 viable way to approach a project such as this.

15           So the next project I'm going to highlight is  
16 the ADNI Proteomics project, and this actually came to  
17 us as a single project, to analyze plasma and CSF from  
18 the Alzheimer's Disease and Neuroimaging Initiative  
19 that I mentioned earlier. We ended up splitting it  
20 into two separate projects for logistics reasons.  
21 Plasma launched in January 2009, and CSF launched in  
22 March 2010, so these are both active projects. The



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1 need was that there is a lack of tools for the early  
2 diagnosis and disease progression in AD. This  
3 continues to be a major hurdle in Alzheimer's drug  
4 development. And, the beauty of this project is that  
5 we are leveraging ADNI samples. So, as I mentioned  
6 earlier, ADNI is looking at biomarkers, and one of the  
7 things they are doing throughout that entire study is  
8 banking blood and CSF throughout the study of those 800  
9 patients that they are following. And, anyone, any  
10 qualified scientific researcher, can actually petition  
11 the Research Allocation Committee of ADNI to have  
12 access to their samples, and our project team  
13 petitioned them for access to plasma and CSF samples to  
14 do a proteomic study. So, our results are expected  
15 fairly soon. Our plasma samples have already gone out  
16 for analysis. We have the data back and we are in the  
17 middle of the statistical analysis right now. The CSF  
18 samples are expected to go out probably within the next  
19 month or two. And ultimately all the data will be  
20 uploaded to the ADNI data website. So, our team is  
21 doing their own statistical analysis. All the data  
22 will ultimately be loaded up to the ADNI website in

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1 conjunction with all the MRI, the PET and all the other  
2 data that's already there. These are some of the best  
3 annotated samples you can get your hands on for  
4 Alzheimer's disease. So, any other qualified  
5 scientific researcher can also download the data and  
6 analyze them as well independently.

7           So, the first project is from our Cancer  
8 Steering Committee. This is a project that is approved  
9 and in fundraising. It represents a unique  
10 collaboration. It's a very large scale clinical trial  
11 involving the NCI, the FDA and nearly 20 major cancer  
12 research centers across the country, and the goals are  
13 two-fold. They want to compare the efficacy of novel  
14 chemotherapeutic drugs in conjunction with standard  
15 therapy to standard therapy alone, and they also want  
16 to identify improved treatment regimens for patient  
17 subsets on the basis of their biomarker signatures.  
18 So, the trial employs an adaptive trial design and  
19 hopefully this will enable researchers to use early  
20 data from patients to guide decisions about which  
21 treatments might be more useful for patients later on,  
22 rather than waiting for the culmination of the five-

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1 year study that this is, and hopefully they'll be able  
2 to eliminate ineffective treatments more quickly.  
3 Again, this is a situation where you have some well-  
4 annotative tissue and blood samples that can be used  
5 for validation of qualification of biomarkers, both  
6 during the trial and afterwards. People can also access  
7 the samples afterwards and the results will be made  
8 broadly available to the research community.

9           And, the final project I'm going to highlight  
10 is the skin infection project. So, this is at the  
11 project concept stage, so this is the very early stage.  
12 The full project plan has not yet been fleshed out.  
13 The PIs are Joe Toerner and George Talbott. Certainly  
14 everybody here is familiar with them. The need I think  
15 has been reiterated throughout the day. The lack of  
16 well- characterized endpoints has created problems in  
17 terms drug development for this area. So, the goal for  
18 this project is to develop reliable and well-defined  
19 endpoints for clinical trials of antibacterial drugs  
20 for these conditions. The specific aims of this  
21 project, as they are defined in the early stage,  
22 project concept, are to conduct detailed literature

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1 searches for both conditions, and also to conduct  
2 retrospective analyses of data from several existing  
3 industry-sponsored clinical trials.

4           So, on the next slide I compiled the project  
5 team. I think you can appreciate the diversity of our  
6 project teams here that are involved, and this project  
7 team will be working in the next several months to  
8 define the specifics and work on the full-fledged  
9 project plan.

10           So, in conclusion, the Biomarkers Consortium  
11 brings together the capabilities of a very diverse  
12 group of people and they build these collaborations to  
13 solve large scientific issues. So, that's it.

14           DR. SHORER: Thank you. Questions from the  
15 Panel?

16           DR. COX: Thank you for your talk, Judy, and  
17 I just wanted to thank you and the folks at the FNIH,  
18 and all the folks that have contributed to this process  
19 and given of their time. We really do appreciate it,  
20 and as you can tell today, it is a very important area,  
21 so we are grateful for FNIH engaging on this. Thank  
22 you.

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1 MS. BURKE: I have a quick question, is that  
2 okay? Thank you. In your process diagram of how the  
3 Biomarkers Consortium works, you didn't really talk  
4 about where FDA specifically would get involved, if the  
5 goal would be qualification of that biomarker or that  
6 project that is scoped out.

7 DR. SIUCIAC: FDA is involved from the very  
8 start. They are on the project team. They can even be  
9 involved -- sometimes, in this case, it also happened,  
10 before the project concept was submitted, what we call  
11 a working group is started, and the FDA members are on  
12 the working group. So, they are involved from the very  
13 beginning.

14 MS. BURKE: Great. I just wanted to make  
15 sure that that was the case. I am more familiar with  
16 another Consortium project, and that is also the case  
17 in that situation. It is very critical to know that  
18 the project might be altered from the original concept  
19 of the project to what actually gets funded and begins  
20 through the qualification process, because we want to  
21 make sure that -- you want to make sure that everyone  
22 has the same goals, and that's really the same point I

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1 was making earlier in the discussion this afternoon.

2 Thank you.

3 DR. SIUCIAK: I think that's the important  
4 point of the Consortium is to have everybody at the  
5 same table, at the same time, not after the fact,  
6 communicating from the beginning.

7 DR. SHORER: Thank you. Questions from the  
8 floor?

9 (No audible response).

10 DR. SHORER: Thank you. And, we have one for  
11 the public comments.

12 DR. COX: Thank you. Roomi Nusrat wanted to  
13 make some comments.

14 DR. NUSRAT: Thank you for giving me the  
15 opportunity. I'd like to take the time (inaudible) I'm  
16 a community infectious disease physician. I would like  
17 to make a comment about the use of mortality in  
18 nosocomial pneumonia. Drs. Temple, Sorbello, Nambiar  
19 and Boucher have made important points about mortality,  
20 as a, or perhaps the key outcome measure for nosocomial  
21 pneumonia. I would like to mention that in thinking  
22 about mortality in nosocomial pneumonia analysis of

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1 data may require more care than expected for the  
2 following reasons. Patients with nosocomial pneumonia  
3 are not admitted to the hospital with nosocomial  
4 pneumonia. They are admitted to the hospital with  
5 other co-morbid conditions that are associated with  
6 mortality. For example, COPD, compromising both  
7 cardiac and pulmonary function, diabetes, coronary,  
8 neuro and peripheral vascular disease, mortality in  
9 nosocomial pneumonia can also be affected by airway and  
10 ventilator management strategies. And also, by the  
11 interactions with the families and the physicians in  
12 making decisions about extension of care. In summary,  
13 death in nosocomial pneumonia is affected both by  
14 baseline risk factors and patient management protocols  
15 that have nothing to do with infections. In nosocomial  
16 pneumonia, analysis of death, as a primary outcome  
17 measure, may require considerable care and may have  
18 some surprises. Thank you.

19 DR. SHORER: Thank you. Let's open the floor  
20 for the panel discussion, if there are any questions or  
21 comments from the Panel?

22 DR. COX: So, we've got two questions we

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1 thought might help to stimulate discussion, and I will  
2 just read them, and I see that somebody has stepped up  
3 to the microphone here.

4           So, what are the challenges with choosing the  
5 primary endpoint for a non-insured antibacterial drug  
6 trial, and how can these challenges be addressed?

7           And then, as a second discussion question, we  
8 also include: what are the priority therapeutic areas  
9 for development of new primary efficacy endpoints for  
10 antibacterial drug trials?

11           Now, we'll recognize the speaker over at the  
12 microphone. I'm not sure if you are going to address  
13 some of the questions, or whether you have a general  
14 comment, either are welcome.

15           DR. REINHART: No, this is a general comment.  
16 If you want to go through the questions you just  
17 raised, please go ahead.

18           DR. COX: General comments welcome. Please.

19           DR. REINHART: Yeah. Basically I really  
20 appreciate the discussions we had today regarding non-  
21 inferiority and the clarifications about the work  
22 that's been going on now for the endpoints. We are not



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1 quite there yet and I realize there is a lot of work  
2 still to be done. However, I think the process, as  
3 such, is a very complete one and a very good one. What  
4 we are needing right now though is, I think, really a  
5 consideration of feasibility, as you have heard it from  
6 various speakers today, and I really appreciate when  
7 this work came up, became some of those consequences of  
8 changes to come are really not clear. And, I'll stand  
9 here to say that it is clear on the industry side, and  
10 I venture to say it's also not necessarily totally  
11 clear on the regulatory side. So, my plea here is for  
12 flexibility, especially in light of the fact that some  
13 of the conclusions drawn and the chains of connections  
14 we make based on historically is really rather weak,  
15 and as long as we are -- I guess we are all humbled by  
16 the lack of more consistent data, but I think it should  
17 also make us more flexible in finding compromised  
18 solutions here to a conundrum, which has held us all in  
19 agony for a while. Thank you.

20 DR. COX: Yeah. So, I mean, I'll just -- a  
21 comment to your comment. Essentially, you know, we  
22 recognize, you know, the real challenges that are out

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1 there in trying to work through some of the, you know,  
2 the issues with regards to the design of clinical  
3 trials and some of the, you know, the issues around  
4 endpoints. And, I think, you know, it has been  
5 humbling, as we have looked at the data and tried to  
6 understand a little bit more or a lot more about  
7 treatment effect and what we know about, you know, the  
8 effect of these drugs, you know, in the conditions they  
9 are treating, and also recognizing too that there are  
10 limitations to the information that is available to us  
11 about treatment effect. We don't have all the  
12 information on all the different effects that we'd like  
13 to have, but certainly we are trying to do the best we  
14 can with what we've got to arrive at informative  
15 trials. And, also recognize too that, you know, it's  
16 important that there be, you know, feasible trials,  
17 because, you know, trials essentially need to be  
18 informative, feasible and ethical, in order that they  
19 be able to be conducted. So, it has been challenging,  
20 no question about that.

21 Comments on the questions at all?

22 MS. BURKE: Well, I have a few comments that

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1 I think are related to the questions. You can cut me  
2 off, if you think they are not. But, they are also  
3 comments on what I heard this afternoon that I think  
4 needs some clarification, and I think that what's  
5 really exciting about the current environment across  
6 multiple disease groups at the FDA is this increased  
7 focus on measurement and what we are measuring and  
8 whether we are measuring the right thing? And, I heard  
9 a few things today though that concern me. One of them  
10 is that they think that maybe we are not concerned  
11 about what's really the most important thing in the  
12 clinic, and I think that's exactly the opposite of what  
13 I detect in, certainly in anti-infective programs, but  
14 also in other disease areas where we are very  
15 interested in making sure that what we eventually put  
16 into the labeling is informative and useful to the  
17 clinician, even though what we do in the clinical trial  
18 certainly is in our official environment, and we admit  
19 that at the same time. But, the patient voice is what  
20 we are really trying to capture when we put together  
21 this symptom-based measure, and I think that that is  
22 very relevant to the patient and as well to the

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1 clinician, and then compare that with this former  
2 practice of using a clinician global as the primary  
3 endpoint. And, the clinician global is a wonderful  
4 idea when you don't know exactly what to measure in the  
5 patient population, because you really do trust that  
6 the clinician is going to be able to make a good  
7 judgment in that patient, in that situation with the  
8 patient. But, the problem for us and for our labeling  
9 is that we don't know exactly what they saw, what they  
10 observed, and how they formed that judgment at the end  
11 of the day. And, we really want to know the pieces of  
12 how they put that together in terms of the cure, or some  
13 kind of a global impression of patient health status.  
14 So, that's what we are trying to -- when Elektra was  
15 explaining that we are applying good measurement, as  
16 developed for the PRO Guidance to clinician rating  
17 scales, those pieces that we are talking about of that  
18 Guidance are the content validity piece. And, in this  
19 case, we need to find out from clinicians what are  
20 these important things they are observing and  
21 measuring; how do they make this judgment that the  
22 patient is improved or cured; and assemble that into

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1 some sort of a measure that can be considered reliable  
2 or accurate, or well-defined. I consider all those  
3 synonyms for the same thing.

4           And, I also heard this morning that  
5 subjectivity is a negative thing. Well, that's all we  
6 have in some of these. This clinician global is a  
7 subjective, certainly, but we can -- we have the  
8 science now to develop a measure for subjective  
9 endpoints that is well-defined and reliable, according  
10 to our regulations, and that's what we are working to  
11 accomplish, I think, with these kinds of discussions.  
12 So, we also have -- we can figure out what it is, what  
13 the thing is -- what the set of things are that we want  
14 to measure, and we also have ways to put them into  
15 instruments to measure them more rigorously in the  
16 clinical trial and to standardize that data collection  
17 process, and I think you are going to talk about more  
18 of that tomorrow, but I think this whole package is a  
19 really critical discussion, but it's predicated on  
20 being able to define our terms and not mix things up,  
21 which, you know, we are still working on, getting to  
22 that goal. For example, I also heard today that

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1 symptoms can serve as a de facto measure of micro  
2 endpoints, and I am -- you know, what is the main thing  
3 here; how the patients feel and function, and we are  
4 really trying to focus on that. The micro is  
5 important. We are not trying to minimize that, but when  
6 is it -- like, I heard Bob say earlier -- when is the  
7 micro a good indicator of what we think is going on  
8 clinically, and when is it more removed, and we have a  
9 scale of that in each clinical trial population too.  
10 So, those are just some of my observations.

11 DR. COX: We'll go to Scott and John in just  
12 a minute but, Laurie, I'm just going to ask you, do you  
13 want to comment too about other therapeutic areas  
14 outside of the antimicrobial realm and activities going  
15 on there?

16 MS. BURKE: Well, we have the same discussion  
17 going on in oncology, for example, where, you know,  
18 historically, tumor size was a very given a lot more  
19 importance than it is for some tumor types now, because  
20 we realize that it's not necessarily a perfect  
21 surrogate measure for patient's symptoms and how  
22 patients are feeling and functioning. And, GI disease

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1 is another one where we have changed our thinking in  
2 moving away from that clinician global, or even a  
3 patient global response serving as a primary endpoint,  
4 because we know that there is an array, there is a  
5 constellation of symptoms that certain patient  
6 populations experience, and treatments affect those  
7 symptoms differently perhaps, and we need to know what  
8 the essential symptoms are that the patients are going  
9 to actually have at baseline in your clinical trial,  
10 and be able to measure how they improve, or not,  
11 individually, but yet defining the endpoint as a total  
12 spore, if that makes sense. So, that's all part of the  
13 science of putting these endpoint measures together.

14 DR. COX: Okay. Thanks. So, we'll go to  
15 Scott, and then to John Quinn, and then we'll come back  
16 to Bob, unless somebody has a particular comment  
17 directly . . .

18 so, Scott?

19 DR. HOPKINS: Okay. I appreciate what Laurie  
20 has just said, but I come back to the cubicin pneumonia  
21 experience, where the primary endpoint, as I understand  
22 it, was mortality and that was satisfied. But, when

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1 the secondary endpoint of this global clinical outcome  
2 was assessed, that really trumped even the primary  
3 outcome. And so the concern is that whatever endpoints  
4 that we decide are appropriate for complicated skin or  
5 ABSSSI, or for community-acquired pneumonia, or  
6 whatever the indication, we will go through all sorts  
7 of work in trying to validate these and so forth, but  
8 that at the end of the day what's really going to  
9 matter is the global clinical assessment, and that that  
10 will trump any results that are arrived at with these  
11 new endpoints. And, not only that, that the physician  
12 community and practitioner community, in a broader  
13 sense, is going to pay attention to that endpoint,  
14 which now has been given secondary status over and  
15 above a newly constructed endpoint that we have arrived  
16 at. So, I wonder if someone could address that  
17 conundrum?

18 DR. COX: Maybe I'll start? I don't know --  
19 Barry, if you want to make some comments? But, I mean,  
20 as I think about the issue; you know, in essence, if  
21 you have a disease like community-acquired pneumonia in  
22 hospitalized patients where, you know, therapy that



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1 isn't fully effective may result in worse patient  
2 outcomes, you are almost in this area where efficacy or  
3 lack of efficacy is starting to merge with safety, in  
4 essence, where you might have bad outcomes. And, you  
5 know, here, in this setting, you know, where the drug  
6 wasn't performing as well as it's comparator, you know,  
7 additional inquiries showed that in fact, you know,  
8 patients --

9 DR. HOPKINS: But, you are making a judgment  
10 already in all of your talk about accepting the  
11 efficacy on the basis of this global clinical  
12 assessment, you see?

13 DR. COX: Right. I mean -- well, let me just  
14 continue on. First of all, I think there is, you know,  
15 a biological reason why there are concerns about drug  
16 level in the lungs, so that's one issue to be mindful  
17 of. And then, beyond that too, you know, the question  
18 is, you know, the sensitivity to detect, you know,  
19 effects on less frequent outcomes, you know, such as  
20 mortality. So, I think, you know, in the setting of  
21 what, in essence is, you know, concern regarding  
22 efficacy that may lead to safety issues, I think folks

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1 do look at that type of information carefully and feel  
2 it's important to let people know about those sorts of  
3 issues so that people can make appropriate prescribing  
4 choices; and you know, if there is information that  
5 suggests that the drug may not be performing well,  
6 especially in a serious disease, to let people know  
7 that so that they wouldn't use the drug and run into  
8 problems.

9 DR. HOPKINS: Again, all of your --

10 DR. COX: We would let --

11 DR. HOPKINS: -- all of your statements are  
12 predicated upon accepting that global assessment, on  
13 some level.

14 DR. COX: Yeah. But, I think, you know, in  
15 the setting of something that, you know, does raise  
16 concerns when there is biologic plausibility, I think  
17 we have to be mindful of that. We may just have  
18 different opinions on that. Barry, do you want to  
19 comment at all?

20 DR. EISENSTEIN: Yeah, just briefly, but  
21 mostly in support of what Scott is saying. As I was  
22 trying to recall the exact criteria that we used to

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1 describe success failure in the cubicin/ceftriaxone  
2 community- acquired trial, mortality obviously was a  
3 top category for failure, but it also included  
4 significant drug- related adverse events requiring  
5 cessation of the drug. It also included a clear-cut  
6 demonstration of spread of infection, including  
7 empyema, the need for a ventilator, where the  
8 ventilator hadn't been used before; the need to switch  
9 to a new antimicrobial, which is an integrated decision  
10 that the patient is failing present therapy; and  
11 eventually then, at the test of cure, the inability to  
12 achieve pre-morbid feeling and function, which, when  
13 one thinks about it, is the ultimate goal of medical  
14 care. I support Scott's point that this is essentially  
15 what practicing physicians do, and also in the context  
16 of the Bayesian argument we were making before, this is  
17 essentially hundreds of years of medical knowledge and  
18 practice that's rolled into an integrated view of a  
19 patient. It is subjective in the sense that a  
20 physician is making these judgments, but I would argue  
21 that it's no more subjective than the PRO that the  
22 patient is filling out, and it's based on many

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1 objective measures, like you can diagnose an empyema on  
2 a chest x-ray. It's a fairly easy thing to categorize.

3 DR. COX: Bob?

4 DR. TEMPLE: Do I understand that in all of  
5 those measures Bayseian was inferior materially, or  
6 materially or significantly inferior, or what?

7 DR. EISENSTEIN: Yeah. It was the  
8 aggregation of those factors leading to failure that  
9 produced a failure rate -- the exact numbers were  
10 something like 90 percent of patients in the  
11 ceftriaxone arm succeeded. Roughly 70 percent of  
12 patients in the cubicin arm, who hadn't been on prior  
13 effective microbials, succeeded. There was a highly  
14 statistically significant difference. Importantly, to  
15 the point that we are making about the four or even  
16 six-hour rule we were saying earlier, the sub-  
17 population of the cubicin-treated individuals, who had  
18 achieved prior effective antibiotics, that is, that  
19 they had gotten their antibiotics within the four, six,  
20 or even eight-hour window, then randomized into the  
21 trial, given a 24-hour window to get enrolled, because  
22 it was thought that even up to 24 hours was not going

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1 to influence ultimate cure. It turned out that therapy  
2 within the first 24 hours, even though it ceased at  
3 that point, was enough to pull the cubicin arm into the  
4 exact same, in fact, slightly better on a numerical  
5 basis, 91 percent versus 89 percent, on the --

6 DR. TEMPLE: That's odd.

7 DR. EISENSTEIN: No, on the overall aspect of  
8 "success" failure.

9 DR. TEMPLE: So, it was only the untreated  
10 subset that had -- the not previously treated subset  
11 that had the disadvantage?

12 DR. EISENSTEIN: Correct. Correct. And,  
13 ironically, had we done the study in the United States  
14 alone we never would have seen that difference, because  
15 the standard of care in the United States is to require  
16 that.

17 DR. TEMPLE: Okay. So, my question is,  
18 what's disturbing about that outcome? Why are you  
19 bothered?

20 DR. HOPKINS: I'm not bothered. I think that  
21 it's a demonstration that a global clinical assessment  
22 is quite good, and the point is that the biologic

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1 plausibility was arrived at after the fact. In other  
2 words, the clinic taught us a very important piece of  
3 biology.

4 DR. EISENSTEIN: That was determined within  
5 redoing the animal models, finding that the initial  
6 animal model was improperly done. Ironically, a less  
7 intensive inflammatory necrotizing process enabled us  
8 to see that cubicin did not work in the animal model,  
9 and eventually the molecular biologic basis of  
10 surfactant binding in the alveolus was the explanation  
11 for the biological failure.

12 DR. TEMPLE: So, it sounds to me like, among  
13 other things, it tells you that in doing a study based  
14 entirely on survival you really better look into what  
15 the effect of the prior treatment is, try to control  
16 it, or at least monitor or get good data on it, or you  
17 will be misled, because everything will be looking more  
18 alike; a very relevant matter for the non-inferiority  
19 --

20 DR. HOPKINS: Absolutely. There are all  
21 sorts of lessons from that study.

22 DR. TEMPLE: Yeah.

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1 DR. HOPKINS: It was a great study. Just  
2 one, as the conversation has been going on and in  
3 response to Laurie's comments, I take it there are  
4 going to be a fair number of situations where you will  
5 not be forced to rely on non-inferiority markers,  
6 because all of the things you are talking about are  
7 what patients really care about and all that stuff.  
8 That doesn't matter unless you have historical data  
9 that tells you what the effect on those things is. You  
10 can't use it anyway, even if you'd like to, because  
11 it's not informative. So, all of these things seem to  
12 me to apply very well to cases where you are going to  
13 look for an earlier effect of one drug than another, or  
14 a better effect, or a similar effect on survival, but a  
15 better effect on something else; that's great, but it  
16 still won't get you out of the fix that you don't have  
17 any historical data on those things, or probably you  
18 don't anyway.

19 The other observation I would make is that  
20 some of the kinds of scales Laurie is talking about  
21 have one major advantage in that they are crafted so  
22 that you know that patients can interpret and respond

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1 to them; whereas, if you are talking about a physician  
2 globally, it probably depends on the quality of the  
3 physician and a whole bunch of other things. So, in  
4 some other settings, -- you know, in heart failure we  
5 have New York Heart Association classification that's  
6 made by the doctor, but there is a very well carefully  
7 developed scale of heart failure that, in many ways,  
8 seems to have greater provision than some of these  
9 other things. They are both relevant, but you get less  
10 noise.

11 DR. TEMPLE: Yeah. No. And, I agree with  
12 that, and again, one of the lessons I think from the  
13 cubicin study is that a very well-crafted global  
14 clinical outcome can be very informative. And, just  
15 from the description that we had here, that was not  
16 just, well the clinician thinks, you know, the patient  
17 is not doing well. There were a number of very well-  
18 defined endpoints there or measures that they took into  
19 consideration, and which could go back -- anyone could  
20 go back and see whether they were present or not.

21 DR. HOPKINS: Yeah. I don't think Laurie is  
22 against those. There are some clinician measures that



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1 are good.

2 DR. TEMPLE: I know.

3 DR. COX: Okay. John?

4 DR. QUINN: Yeah. I'm John Quinn. I'm an IV  
5 doc advisor. Can we get slide 16 back on please, from  
6 Judy's presentation, at least from the Biomarkers  
7 Consortium presentation? I wanted to make a couple of  
8 quick comments about that, and Joe is well equipped to  
9 comment on that too. Actually, Joe, back out -- it's  
10 the one that says -- that must have mutated, as she  
11 said -- the one that says project highlight cap and AB  
12 -- yeah, that's the one. So, the last bullet point on  
13 that slide says that this group is going to conduct  
14 retrospective analysis of data from several existing  
15 industry-sponsored clinical trials, and Pfizer and  
16 other multiple other sponsors in this room have  
17 participated in this ongoing work, and I wanted to just  
18 comment to people who weren't involved and it may be  
19 opaque. So, biomarker here is meant in the broadest  
20 possible sense. So, when I was first recruited into  
21 this group, I scratched my head and said, you know,  
22 where is the biomarker in skin infection or pneumonia?

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1 You know, I think biomarker, and as an IA doc I think  
2 about viral load and HIV disease or aisle six in a  
3 sepsis trial. So, in this sense, biomarker is meant to  
4 be very encompassing and including things you can  
5 measure, like fever and rapidity of cessation of  
6 spreading of skin infection. And, the intent really  
7 was to take these proposed NI guidelines looking at  
8 early events and see if they would actually work in a  
9 contemporary study, and would the contemporary studies  
10 look anything like the studies from the 1930s. And, a  
11 lot of work has been done, and a lot of work still has  
12 to be done, but I think it's fair to say, and I'd like  
13 Joe's opinion on this, that there are some kernels of  
14 information there that I think are helpful. It looks  
15 like in the skin studies, at least looking at the ones  
16 I am most familiar with from my data for linezolid  
17 versus vancomycin. The responders do respond quickly.  
18 So, looking at 48 or 72 hours for resolution of fever  
19 and cessation of spread or lesion looks like it really  
20 does work; it really is legit. And, the same is true  
21 in pneumonia, where the pneumonia data really looks  
22 like it validates the Snodgrass studies, and the

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1 Bullowa studies I think actually were the ones in  
2 pneumonia. So, I think there is reason to be  
3 optimistic that there will be more information coming  
4 out of this effort that will help to inform the two  
5 major questions put before the group, but, Joe, I'd  
6 like to hear what you think.

7 DR. TOERNER: Yeah. I think we have taken,  
8 or we have heard, in the work of the group, from the  
9 Foundation for the National Institutes of Health, we  
10 have seen snapshot pictures of those data, and there  
11 are proposals then to do further analyses, and one  
12 example of that is to look at not just cessation of the  
13 spread, but look at the proportion of patients who  
14 actually have a retraction of the size of their lesion,  
15 and that might be an important consideration moving  
16 forward, important to patient feels or functions; that  
17 they are actually witnessing their lesion size  
18 decreasing. That might be an important endpoint to  
19 consider moving forward. And, the same is true with,  
20 looking very quickly at the studies of pneumonia that  
21 the early endpoint it appears to be that there is some  
22 improvement noted among patients very early in the

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1 course of their disease. But, I was struck by Dr.  
2 Helen Boucher's talk, in that, you know, it's important  
3 for patients to know when they can be discharged from  
4 the hospital; when they can go back to work; and so I  
5 think part of the work then is to try to incorporate  
6 that into the design of a new endpoint so that you can  
7 be very comfortable with what's described in product  
8 labeling, of, you know, this is important for patients;  
9 that they are being discharged for home at this  
10 particular time point. And so, I think that work would  
11 be nice to flush out as time goes on, to tie that  
12 together into a regulatory endpoint, as well as an  
13 endpoint that's very important for patients and their  
14 providers.

15 DR. COX: Thanks, John and Joe. Okay, I'll  
16 go Laurie and then, I think, Helen next, if we could?  
17 So, Laurie?

18 MS. BURKE: Yeah. I want to go back to that  
19 subject of variability on the endpoint measure, and  
20 another one of the reasons why we are moving to symptom  
21 - - well-defined, well-developed symptom measures in  
22 some disease areas is because they can be designed so

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1 that the variability is much reduced compared to  
2 previous global, even well-defined global, well-  
3 partitioned and thought out globals, because -- and,  
4 there has been discussion in this CABP working group,  
5 the membership was displayed, that we shouldn't worry  
6 about the fact that we can't use this new measure in a  
7 non-inferiority trial because it's going to be so  
8 sensitive. We might be able show superiority to active  
9 treatment, and that could very easily be envisioned if  
10 we developed a measure to be very sensitive and  
11 specific. So, I just wanted to mention that.

12 Oh, and one other thing I wanted to mention  
13 that was brought up earlier is the multi-regulatory  
14 authority discussion that needs to take place, and we  
15 are very concerned about that too. We have an MOU with  
16 the EMA, and we are acting on that, and they have their  
17 on qualification process in place. And, of course,  
18 anybody who submits a qualification package to the FDA  
19 is going to submit it to the EMA at the same time, and  
20 we are discussing those between the two agencies and  
21 the people who do that, to make sure that we are on the  
22 same page. We have talked about a lot of these endpoint

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1 measurement issues there with that group, and so I  
2 think that, you know, we are trying very hard to be  
3 harmonized.

4 DR. COX: Thanks, Laurie. Helen?

5 DR. BOUCHER: So, the optimist in me wanted  
6 to talk about the other priority therapeutic areas for  
7 development of new primary efficacy endpoints, and you  
8 know, we are very hopeful that we are going to get to  
9 the point where we can think about really developing  
10 drugs for resistant gram negatives, and in that vein,  
11 some key indications might be complicated urinary tract  
12 infection and intra-abdominal infection where we see  
13 more gram negative pathogens playing a role. And so,  
14 along those lines, I had a question when Dr. Navarro  
15 was talking about whether the primary endpoint for  
16 complicated UTI has changed, because in the guidance  
17 it's a microbiologic endpoint, right? Its eradication  
18 of baseline pathogen at the five to nine-day test of  
19 cure, you know, from the urine. So, are we at a place  
20 where that's changed, or is that something people are  
21 ready to discuss?

22 DR. COX: So, as we work through, you know, a

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1 number of different disease processes and gone back and  
2 look at the literature, I mean, as you can tell, we  
3 have been through, you know, the respiratory tract  
4 indications and then moved on and worked on skin and  
5 hospital- acquired pneumonia ventilators, associated  
6 pneumonia where, you know, we expect to, you know, have  
7 draft guidance out in the next few months. And then,  
8 the next things to work on -- we obviously have more  
9 work to do in the area of community-acquired pneumonia,  
10 but complicated UTI is another area that we'll come  
11 back and look at a little bit more, and you know -- I  
12 mean, it is an area, you are correct, that historically  
13 folks have looked at the microbiologic eradication rate  
14 and complicated UTI. And, you know, my impression of  
15 this is that, you know, in UTI, you know clearance of a  
16 urine culture, you know, some time period after therapy  
17 has been completed is an important endpoint. I suspect  
18 that folks probably got to that because mostly  
19 everybody was asymptomatic by the time they got to that  
20 point in time. So, we'll take a look at things. We'll  
21 look at the information that's out there, you know, as  
22 to the role of also looking at clinical endpoint as

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1 part of, you know, the overall response to complicated  
2 urinary tract infection, but you know, that's a  
3 situation where at least my expectation would be that,  
4 you know, the reason that we got to the microbiologic  
5 evaluation was because largely that was probably the  
6 determinant factor, and then I would guess that, in  
7 fact, the clinical outcome was something that was  
8 probably, you know, happening at a very high rate, so  
9 it may not have had a huge impact. But, I think as we  
10 look at things we'll need to, you know, take into  
11 consideration what we, you know, are evaluating here  
12 and looking at what information we have about clinical  
13 outcomes and UTI also. So, a work in progress, more to  
14 follow.

15                   Yeah, Felix?

16                   MR. GYI: From somebody that feeds on the  
17 fringes of the knowledge pool that exists in this room.  
18 I wonder if I might share a couple of observations, you  
19 know. There seems to be a lot of very good work that's  
20 being done in terms groups, like what the Biomarkers'  
21 Consortium is doing, but I am reminded of how the  
22 electronic data capture system in the clinical trials



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1 environment has sort of grown up, and bear with me for  
2 just a moment. So, we have a number of EDC types of  
3 systems that seem to exist in a silo, and then all of a  
4 sudden some people have woken up and said, you know, we  
5 have the electronic medical records initiative; how do  
6 we wrap all of that around so that we can have some  
7 transparent sharing of data and the ability for us to  
8 do something good with this? And, at least from where  
9 I sit right now, there are a number of systems that are  
10 not talking to each other, and so while they may be  
11 individual silos of very efficient systems, in  
12 aggregate, we don't have a really well-defined way to  
13 communicate electronic medical records with clinical  
14 trials data and those types of things. So, my interest  
15 is in human subject protections and issues like privacy  
16 and confidentiality, and it seems as if you have a  
17 number of systems that are quite well thought through.  
18 The Alzheimer's initiative certainly must have had some  
19 good thinking about how we manage bio-specimens not  
20 only for primary use, but subsequent uses, including,  
21 you know, follow-up on the data analysis. That's the  
22 type of information, to me, that might seem worthwhile

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1 sharing with other communities, as FDA has different  
2 initiatives and different therapeutic areas that  
3 intersect with each other. For instance, at least in  
4 the circles of communication that have addressed some  
5 issues regarding privacy and confidentiality, people  
6 have asked what is the role of FDA's clinical  
7 trials.gov and the data that resides within that  
8 particular database? How do we have access to it and  
9 what do we do with it from a physician/practitioner  
10 perspective, as well as patient information  
11 perspective. And, I hear some of that type of  
12 discussion here with regard to the data elements that  
13 are being collected, and I wonder if there is an  
14 opportunity for us to have some discussion on a broader  
15 level and a higher level to try and wrap all of that  
16 together before it gets to be too many silos that  
17 cannot talk to each other.

18 DR. COX: So, Felix, help me understand a  
19 little bit more. So, what you are describing would, in  
20 essence, it would be some way of looking at data across  
21 trials, to get a better understanding of the natural  
22 history of treated disease and changes in patient

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1 symptoms and other parameters over time; is that what  
2 you are talking about?

3 MR. GYI: Well, it seems that that's part of  
4 the discussion that's been ongoing here, right? I  
5 mean, but the question is how do we do that seamlessly  
6 in compliance with both the regulations and ethical  
7 principals? And, some of that, while the scientific  
8 discussion is taking place, I haven't heard an overlay,  
9 and it's perhaps not the intent of a group like this to  
10 have that type of ethical discussion, but it seems to  
11 me that we probably ought to have that so that we don't  
12 get submarined down the road by somebody asking the  
13 question, how did you protect my data while you were  
14 doing all of this?

15 DR. COX: Right. Now, I'll just maybe make  
16 one general comment and welcome others who may want to  
17 comment on this, but the issue of standardized data  
18 sets, the organization CDISK and their efforts to try  
19 and standardized data, I think is because folks do  
20 recognize the potential power to be able to analyze  
21 such data. You are bringing up another important point  
22 that maybe you'll be able to help us with too, and some

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1 of this may be dealt with how the data is de-identified  
2 and those sorts of issues with regards to patient  
3 protection, so that the way the data is collected or  
4 the way that the data is made available to folks who  
5 may want to do other work, would it be made available  
6 to make sure that patient privacy and confidentiality  
7 are appropriately protected. I agree it is an important  
8 thing to be thinking about and make sure that it's  
9 being tended to so that there aren't surprises down the  
10 road.

11 DR. BALL: Ed, can I comment?

12 DR. COX: Please.

13 DR. BALL: I just wanted to say also, in  
14 answer to Felix's comment that we are going to be  
15 talking about that more tomorrow. So, it's a nest  
16 segue into the discussion tomorrow. We have David  
17 Ibersen-Hurst from CDISK, who will be talking about  
18 standards. And so, you all also will be talking from  
19 your perspective, and I wanted to emphasize that, you  
20 know, from a DSI perspective, we are looking at the  
21 kind of integration and it's a long-term goal, but  
22 we'll have more time for discussion of that tomorrow.

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1 DR. COX: Other comments? Scott?

2 DR. HOPKINS: Just going back to a comment  
3 that Laurie made, which was that we may come up with  
4 endpoints that were so good at measuring that we can  
5 make very fine distinctions between antibiotics. And,  
6 I tried to get across the notion in my talk that we may  
7 be able to make distinctions I a statistical sense that  
8 clinicians don't really care about and what would be  
9 the regulatory approach to that. But, going in the  
10 other direction, another thing that deserves I think at  
11 least a little bit of thought is that, in the discovery  
12 process within companies, these new endpoints will take  
13 on a life of their own, and the discovery process will  
14 be oriented towards compounds that do well at that  
15 particular endpoint. So, let's say fever is an  
16 endpoint that assumes supreme importance in the  
17 clinical trial process for whatever. So, Bob has  
18 already followed my line of thinking.

19 DR. TEMPLE: That's because I was thinking of  
20 the aspirin combo.

21 DR. HOPKINS: Right. Well, I mean, you can  
22 have that all in one compound with, you know, some

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1 macrolides too. So, I just raise that again as a  
2 caution about how we approach all of this; that we can  
3 have unintended consequences that -- particularly  
4 within big companies where these things again can take  
5 on a life of their own.

6 DR. COX: Thanks. Ellen.

7 DR. BOUCHER: Yeah. I would just add that I  
8 guess it hasn't been my understanding that the  
9 physician global assessment is redefined on each trial.  
10 I mean, the Guidances actually talk about what goes  
11 into that, right, in terms of death, discontinuation  
12 due to treatment-limiting adverse events, et cetera, et  
13 cetera. So, there actually is quite a bit of similarity  
14 in the things we are talking about based on the design  
15 of the trials that exist today. And, I just want to  
16 make sure I am not correct, but I didn't think that  
17 each new sponsor who came along with a pneumonia trial,  
18 for example, made up their own physician assessment of  
19 success?

20 DR. COX: So, you are right that the, you  
21 know, the specific sub-elements are pretty common, as  
22 far as, you know, if the patient needs additional

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1 antibiotic therapy; if the patient dies, you know,  
2 during the trial, and then you know, if the physician,  
3 you know, doesn't feel that the patient to cure, which  
4 is in essence is, you know, needs more therapy. So,  
5 yeah, I mean, there are similarities over the span of  
6 the trials. Laurie, you had a comment?

7 MS. BURKE: Right. Well, what I am talking  
8 about when I am talking about global assessments is  
9 that, to the extent that they are not well-defined, and  
10 you don't know really what the clinician is basing  
11 their rating on. So, if they are basing their rating  
12 on a very defined set of things and they have to give  
13 you the answers to all of that set because that's the  
14 set you think is important, that's not what I'm calling  
15 a physician global clinician rating, a clinician  
16 impression. That's a well-defined set of things that  
17 you are gathering, and that's really the basis of what  
18 we are trying to encourage in the Guidance that Elektra  
19 described; that you need to define what it is, make  
20 sure that -- and that also, the advantage here is,  
21 first of all, we know what we are measuring; we can  
22 interpret the score at the end of the day; and it

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1 reduces the variability around the measure so that you  
2 have a hope of actually being able to interpret the  
3 study results at the end of the day.

4 But, I also wanted to respond to your last  
5 comment about whether we are measuring something so  
6 finely that it's not clinically meaningful, and that,  
7 of course, is all a part of the development of an  
8 adequate measure. You wouldn't want to measure  
9 something that is so -- that is not clinically  
10 meaningful, that is a requirement of any instrument  
11 that we have.

12 DR. COX: It's not the measure itself. For  
13 instance, parameter X may be very clinically  
14 meaningful, but if we can measure that so precisely and  
15 so accurately and so forth that the distinctions that  
16 we can draw are meaningless.

17 MS. BURKE: Right, and that's what I am  
18 addressing.

19 DR. COX: Okay.

20 MS. BURKE: I mean, there have been -- I have  
21 probably been to a year's worth of conferences on this  
22 topic over the last decade, about what is a clinically



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1 meaningful difference, and that is a very -- and, the  
2 answer to that is built into the development of the  
3 measure. You can't take an instrument that you really  
4 don't know what you are measuring anyway and then try  
5 to decide what's clinically meaningful, because we  
6 don't even know what we are measuring. That's why we  
7 are starting with developing instruments well at the  
8 outset, where you have done the adequate research to  
9 define what the important content needs to be, then you  
10 have a better hope of being able to interpret and  
11 define that minimum change that's meaningful at the  
12 end.

13 DR. COX: Okay. Barry?

14 DR. EISENSTEIN: I've been enjoying the  
15 discussion, and it makes me wonder if some of the  
16 thinking, which is very appropriate and thoughtful, is,  
17 in part, related to porting in concepts from other  
18 therapeutic areas into infectious diseases, which might  
19 be unique. And, maybe I am stating the obvious, but  
20 let me just make a few points that one of the key  
21 features, of course, of antibiotics bacteria is that  
22 they are truly silver bullets that go in after targets

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1 that do not exist on the human cell. In contrast, the  
2 other therapeutic areas are going after human targets,  
3 and the ability to improve the kinetics abiding or the  
4 downturn effects or the off-target effects or the  
5 complex nature of the interaction, I am sure could be  
6 graded in very interesting ways that will lead to  
7 significant differences and outcome. By contrast, and  
8 I might be a little bit off her, but I'd like somebody  
9 to challenge this comment, and that is, as I have  
10 perused the antibiotic literature over the last 30 or  
11 40 years, typically you can boil down efficacy aspects  
12 to the susceptibility of the organism and the ability  
13 of the antimicrobial to get to the target in the body.  
14 And, essentially everything else from efficacy comes  
15 from that. There might be some subtle distinctions  
16 with certain diseases that bactericidal might be better  
17 than bacteriostatic; okay, but that's that typically  
18 the exception, not the rule. You can sometimes make  
19 arguments that certain antimicrobials perhaps don't  
20 lyse the cells or prevent the release of toxins. Okay,  
21 in certain areas that might have some meaning too that  
22 could be studied. What typically though drives

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1 decisions about antimicrobials, I believe, at the  
2 regulatory level and also the way physicians prescribe,  
3 are really more related to side effects, the safety  
4 issues, once you know that the antimicrobial gets to  
5 the target and the organism is susceptible. The  
6 distinction mostly then is on AE basis. So, when we get  
7 to talking about biomarkers, to Scott's point, that  
8 describe the speed by which the erythema goes away, for  
9 example, is that not overly determined in the  
10 standpoint you can measure it; you can get it down to  
11 statistical analysis; you might be able to show  
12 superiority; does it really matter; is it not  
13 meaningful; and are we therefore getting to be overly  
14 influenced by the other therapeutic areas that the FDA  
15 has to regulate?

16 DR. COX: Laurie?

17 MS. BURKE: I have a very quick response to  
18 that. That's why the Clinical Review Division is  
19 always involved in any clinical -- any development of a  
20 new endpoint. This isn't something that the  
21 measurement and the statisticians can do without the  
22 clinical insight, and that is -- that's part of --

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1 that's why our process, both with the Biomarker  
2 Consortium and with other people from the community,  
3 that have an idea for a project, we will not agree to  
4 collaborate in that qualification process without full  
5 support of the Medical Review Division that would then  
6 have the regulatory authority in that area.

7 DR. EISENSTEN: And, not only is that  
8 reassuring, but I should also have made another comment  
9 very similar to the one that John Quinn made earlier  
10 describing the FNIH process. I give great credit to  
11 the FDA to be using this process to try to get us to  
12 measurable markers. I think we are all frustrated now  
13 with the lack of good markers that measure the drug  
14 effect in a way that is reproducible. You get away  
15 from physician bias and error and the like. And, I do  
16 believe that the results of the FNIH is coming with at  
17 least interim practical, measurable and important  
18 validated, content validated endpoints, and it's a  
19 bridge until we get to further evaluation. But, I  
20 think Scott's point is still well-taken; we don't want  
21 to have these drive the concept of disease to the point  
22 that it's more because we can measure it than it really

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1 matters in terms of the actual disease.

2 DR. COX: Bob?

3 DR. TEMPLE: It does seem historically true  
4 that antibiotics have had fewer off-target effects than  
5 most other classes, but they are not completely free.  
6 They certainly have been nephro- and hepatotoxic. They  
7 create lots of allergy things, and when they are  
8 directed at viruses, who are sort of us, there has been  
9 all kinds of things. So, it is less worry, but it's not  
10 totally worry- free, I don't think.

11 DR. EISENSTEIN: And, that's what I meant by  
12 the adverse events. In no way am I suggesting that  
13 antimicrobials don't have them. They are very, in  
14 fact, variegate (ph) in that regard and unpredictable,  
15 which, to me, is one of the most important reasons for  
16 the phase three trials.

17 DR. COX: Laurie?

18 MS. BURKE: And, when you were describing the  
19 different types of antibiotic trials, I have to say  
20 that my entry with this endpoint development work in  
21 these divisions has been in a completely different  
22 area, and that's in the acute exacerbation of COPD,

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1 where you don't know what's happening with the bugs and  
2 we have to have a symptom measure, and that is a place  
3 where symptom measurement is critical.

4 DR. COX: Okay. John?

5 DR. FARLEY: Yeah. So, I am actually going  
6 to ask Katie and Sumati to address this, but we have  
7 discussed it internally a fair amount and they have  
8 years of review experience. And, just to kind of get  
9 this on the record, I think that, from what I am  
10 hearing is there is certainly some encouraging work  
11 looking at early endpoints, because we have a non-  
12 inferiority margin for those endpoints and there is  
13 quality of measurement. But also, there are other  
14 endpoints in the course of the review, secondary  
15 endpoints, that the FDA would look at, including, for  
16 example, cure at the end of treatment, and if there  
17 were disparities between those findings, I wonder if  
18 you could sort of give us a little insight into what  
19 might happen during the review process from such a  
20 product?

21 DR. NAMBIAR: Certainly, we have had several  
22 discussions about that, and I think when we first

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1 started discussing this topic, my thinking was if  
2 patients who sort of were responders early on but  
3 subsequently went on to not do so well that we would,  
4 in fact, classify them as failures. But, then I was  
5 told you couldn't do that from a statistical  
6 perspective, because your primary endpoint is the early  
7 endpoint and you have to make an assessment, so in fact  
8 you could not reclassify patients who have already been  
9 called responders. But, I think, as a clinician, to  
10 me, it's just as important that cure be sustained, so  
11 it really doesn't matter to me if somebody felt better  
12 at 48 to 72 hours, but by the time you finish treatment  
13 if you are a failure, I don't think I have learned  
14 much. So, I would have to go back to the phrase of  
15 it's a review issue, but I think that that will have to  
16 be looked at in detail now.

17 DR. COX: And, just another point, even when  
18 we looked at time point, you, know, after therapy had  
19 been completed, when the test of cure was X number of  
20 days after therapy had been completed, we oftentimes  
21 continued to follow patients thereafter and talked  
22 about the percentage of folks that had relapse. So,

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1 you know, this will still be something that's important  
2 to look at, because it really is just common sense if,  
3 in fact, you know, a high percentage of patients who  
4 have a response earlier on end up having problems down  
5 the road, that's always been important; that will still  
6 be important and something that, you know, we'll be  
7 interested in looking at. Bob?

8 DR. TEMPLE: Well, you could -- I'm not  
9 saying you should -- but, you could make the endpoint  
10 be early response without a relapse, if the  
11 biostatisticians would let you do that, if you thought  
12 it was the right thing to do.

13 DR. COX: Can you repeat that, Bob. I didn't  
14 hear early response with . . .

15 DR. TEMPLE: Well, you could say we are  
16 counting early responses, but we are only counting  
17 early responses that are not accompanied by a relapse  
18 later. I'm not saying do that, but if one thought that  
19 was the right thing to do, you could surely do it.

20 DR. COX: So, it sounds like another approach  
21 to essentially accomplishing the same goal?

22 DR. NAMBIAR: Can I make one other point?



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1 And, I think even in the old paradigm we were always  
2 assessing patients at early time points and calling  
3 them as cures or failures. Somewhere around the day  
4 two to day three markers, that's when clinicians made a  
5 decision about the need to alter therapy. So, I don't  
6 think it is something very dramatically different. So,  
7 I think, as Dr. Quinn mentioned, if, in fact, the data  
8 that we are looking at we are finding some correlation  
9 between early end points and later time points, I don't  
10 think should come as a big surprise, because that's  
11 what we have been doing in the past as well. The only  
12 additional failures that would probably come on, which  
13 are not really due to lack of drug efficacy, may be due  
14 to treatment emergent, adverse events or subsequent  
15 data, that's you know, discontinuations and things like  
16 that. But, truly from lack of the drug working, there  
17 should be correlation between what you see at an early  
18 time point and what you see at a later time point.

19 DR. COX: Thanks, Sumati. Other comments  
20 from the Panel or questions from the audience, comments  
21 from the audience? Have we arrived? Oh, Eileen? Go  
22 ahead.

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1 DR. NAVARRO: I actually had a question for  
2 our colleagues in the study endpoints and labeling  
3 division. I have heard about the concept that one can  
4 consider entering PROs, and I wondered whether you  
5 might like to comment about when that might be feasible  
6 and how people proceed with drug development when these  
7 instruments are not fully developed?

8 MS. BURKE: That is a very good question,  
9 because this happens all the time; that an instrument  
10 is under development and it's not ready to be  
11 qualified, but yet the clinical trials are ready to  
12 begin. So, it's a judgment call at the point in time  
13 where the instrument, you know, what stage the  
14 instrument development is at. And, of course, you have  
15 to put an instrument into a clinical trial before you  
16 really understand all the measurement properties of  
17 that instrument. So, there is some point where you  
18 just have to proceed with what you believe is adequate.  
19 And so, what we think is critical, and as you heard us  
20 describe from the Guidance, is that content validity is  
21 demonstrated, which means you have identified  
22 clinically the most important thing or set of things to

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1 measure in this clinical trial patient population, and  
2 you think that you are measuring them as well as you  
3 can. You have done that initial qualitative research  
4 with the patient population that is going to be  
5 enrolled; you know that if this measure has a good  
6 chance of being able to measure the thing that you are  
7 interested in. Once that has been established, then I  
8 think that the risk is much lower, even though we don't  
9 know the construct validity, we don't know full  
10 reliability, our ability to take change; but yet, if  
11 you can take that content valid instrument, put it into  
12 a phase two study to further establish those things so  
13 that you are ready for phase three, that's the ideal  
14 situation, but we know that that is not always the case  
15 and you are going to have to take a risk and  
16 incorporate it into phase three initially.

17 DR. COX: Thanks, Laurie. And, Jerry?

18 DR. SCHENTAG: Oh, yes, Schentag, Buffalo. I  
19 wonder if anyone who is doing the validation of  
20 biomarkers has given any thought to how frequently you  
21 need to sample things? Specifically, patients change a  
22 lot and they change very fast, and typically when we do

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1 clinical trials we do endpoint assessments or 30 days  
2 later and all the action happens early. When you look  
3 at those clinical trial databases then, to try to go  
4 back and validate the endpoint, you realize you don't  
5 have enough information to even take a stab at the time  
6 relationships. You might get a yes or no out of it,  
7 but you don't have anything for the time. So, I think  
8 part of the problem we have had arguing this over the  
9 years I think is related to the fact that we don't have  
10 a complete enough data set to do that. And, we are not  
11 going to get that in any of the efforts that I have  
12 just heard about today, because they are all either  
13 based on electronic health records where the, you know,  
14 in a lot of cases you are missing the progress notes,  
15 so you don't know what the clinicians were thinking, or  
16 they are based on clinical trials that we did back  
17 five, 10 years ago where we don't have enough sampling.  
18 So, what do we do about that? Do we have to start over  
19 prospectively?

20 DR. COX: So maybe just a general comment? I  
21 mean, you know, looking back at existing data can be a  
22 way to gain some insights, but your point is, is that

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1 if that data was not collected in a sufficiently  
2 granular fashion, it may not have the answers to what  
3 you need. And, it seems like if you don't have the  
4 answers to what you need from what you already have,  
5 then you probably do need to go out and get some more  
6 information to be able to explore things a little bit  
7 further.

8 MR. SCHENTAG: You know, I think that's what  
9 we have to go back to patient charts for, at least.

10 DR. COX: Yeah.

11 MR. SCHENTAG: I don't know if you have to  
12 start it prospectively, but retrospectively, the  
13 missing step that we are noticing, because we are  
14 trying to do this all the time now, is you have to  
15 actually go back to the charts.

16 DR. COX: Yeah. And, one other comment too  
17 could that if you are, you know, earlier on in clinical  
18 development and you are thinking about phase two, and  
19 there are some things that you would like to know with  
20 greater degree of granularity in order to be prepared  
21 for phase three, phase two might be another opportunity  
22 to try and be able to gather some more information --

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1 MR. SCHENTAG: Build a dam. Thank you.

2 DR. COX: -- as you are moving towards your  
3 phase three studies. Bob?

4 DR. TEMPLE: Laurie's people agonize about  
5 this all the time, sometimes when it's not quite that  
6 clear to me, it's essential, but, in this case, with  
7 people changing rapidly, you just plainly need to test  
8 them repeatedly or you'll miss what you are looking  
9 for. In other settings, you know, do you have to do it  
10 every month; is that too long, because they forgot what  
11 they are doing; are you trying to measure change from  
12 before or current status; all of those things come into  
13 these tests. But, in this one, it's hard to see why  
14 you wouldn't want to get it repeatedly.

15 MS. BURKE: And, you also absolutely have to  
16 have some input from patients with your instrument  
17 that's under development. You can't get it all from  
18 patient charts, I'm afraid. There has to be some  
19 qualitative work done prospectively.

20 DR. COX: At the microphone?

21 DR. RAYMOND: Yes. I am Stephen Raymond. I  
22 am with PhD Corporation, and over the course of the day

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1 it seems that there are two very different objectives  
2 where individuals are looking for help, who are  
3 treating patients and patients are looking to get a  
4 sense of what's going to happen to them when they take  
5 an anti- effective or an antimicrobial, and the FDA and  
6 the sponsors are primarily looking, what do I have to  
7 do to get my drug approved; what do I have to do to be  
8 sure that the medication is effective. And, I think  
9 that the objective of proving the discussion about the  
10 drug; is the drug effective, is something that really  
11 needs to be addressed by a very simple kind of trial  
12 that has a proof of efficacy in the form that we have  
13 been discussing, a percentage number of responders, a  
14 percentage number of cures. That sort of thing is very  
15 helpful at demonstrating that key question; yes, this  
16 is an effective drug. But, it isn't very informative  
17 with respect to whether or not the medication has more  
18 side effects than some other medication constitutes a  
19 greater patient burden; it gets the patient back to  
20 work earlier than another drug. Those are maybe  
21 secondary features when you are looking at qualifying a  
22 drug for efficacy, which was the treatment that we, or

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1 the main subject of today's conference.

2           So, to the point about measuring something  
3 that's occurring quickly, if you are watching a tumor  
4 grow or if you are watching a lesion or an infection  
5 diminish and you have areas of erythema measured in  
6 square millimeters and you just track it hour-by-hour,  
7 on the end of one basis that becomes completely  
8 compelling information. If you get a general  
9 impression two weeks later, did the lesion regress  
10 reasonably quickly without any clear impression of how  
11 quickly or anything, then you have much less valuable  
12 data, but you still have something. And, I think the  
13 whole -- my perspective of today is that there is a  
14 relationship between the kind of information that you  
15 captured and the kinds of things you can conclude from  
16 it. So, if you want to conclude that the drug is  
17 effective, capture something where it's a highly  
18 controlled randomized clinical trial with a simple  
19 endpoint that demonstrates that. And then if you want  
20 to get the full benefit from that trial, also collect  
21 some additional information that would expand upon the  
22 sorts of experiences that patients have who take the



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1 drug that would be a guide for those people who are  
2 going to prescribe it and who are going to experience  
3 it as patients.

4 DR. COX: Thank you. Matt?

5 MR. WIKLER: Thank you, Ed. Matt Wikler,  
6 IASO Pharma. I would just like to make a practical  
7 plea, I guess. I'm in the pharmaceutical industry. We  
8 try to develop new drugs. And, let me say first of  
9 all, I am fully supportive of finding better ways to  
10 evaluate patients, so my comment is not at all saying  
11 we shouldn't do this, because I think it is important  
12 to do that. Where we get into trouble is we are  
13 developing a drug, we get agreement where we design a  
14 study based upon the most recent knowledge of what's  
15 being looked for. It takes two years, two-and-a-half  
16 years, three years, to get the data down to the agency,  
17 and then the rules have changed. And, number one, it's  
18 frustrating, but, number two, I can tell you a lot of  
19 companies doing this now are small biotech companies.  
20 We have to go out and raise money from investors. And,  
21 I can tell you one of the big problems we have right  
22 now is people feel uncomfortable that we do not know

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1 what the rules are or how to develop drugs. So, I  
2 support the efforts. I think we need to go forward  
3 with them and I think we need to find the best way to  
4 evaluate these drugs, but I also think as we move  
5 towards that point that if we penalize folks developing  
6 drugs today, or say a year from now, as we are trying  
7 to develop things and we penalize them, it's going to  
8 do more harm in us getting drugs out to patients who  
9 need them and getting the capital actually to the small  
10 companies that's necessary to develop the drugs. Thank  
11 you.

12 DR. COX: All right. So, I mean, this issue  
13 has come up and it's come up a couple times in advisory  
14 committees in a general sense, and we recognize, you  
15 know, the difficulties here when, in fact, we learn  
16 something new about the biology of the disease that  
17 teaches us something that maybe we didn't fully  
18 appreciate before, or you know, end up in a situation  
19 where a clinical trial has been done that we now know  
20 really doesn't provide informative information, and  
21 it's a tremendously difficult situation for everybody.  
22 I mean, for the patients who have enrolled in the

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1 trial, and in fact, the trial didn't provide the type  
2 of information that we would, you know, need to have to  
3 be able to assess the drug safety and efficacy. You  
4 know, it's a situation that obviously we are trying to  
5 address now through the work of, you know, on updating  
6 guidance documents through the work of folks at FNIH,  
7 through the work of folks who have come to work shops,  
8 and we clearly recognize the importance of, you know,  
9 being able to get to pathways that will be durable and  
10 be informative and feasible and ethical. But, I  
11 appreciate and understand your point, and that is, is  
12 when a trial is initiated, conducted and then something  
13 new comes up that wasn't understood at the point in  
14 time that, you know, materially impacts on what can be  
15 concluded from the trial because we just didn't have  
16 the biology right or whatever the situation was, it is  
17 a difficult situation for everybody, so I appreciate  
18 your comment on that. Bob?

19 DR. TEMPLE: The opinions we give on whether  
20 a trial is okay or not okay; whether it's at end of  
21 phase two meeting or something else is in the category  
22 of advisory opinions, and we are urged legally to try

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1 to stick with those really hard and we do. But, if you  
2 now believe that the advice you gave would cause you to  
3 approve a drug whose effectiveness has not been  
4 documented, you really can't do that. It violates the  
5 law. It violates integrity. So, feeling terrible  
6 about it we will usually say sorry, we were wrong; you  
7 were wrong, we were wrong, we were all wrong. But,  
8 everybody hates that when it happens. I don't think  
9 that makes any difference to anybody, but we do.

10 DR. COX: Other comments?

11 MR. TOMAYKO: John Tomayko from Glaxo-  
12 SmithKline, just one related comment though. As we  
13 move towards gram negative indications and we are  
14 thinking about nosocomial pneumonia, I get the sense  
15 from some of my discussions with folks that mortality  
16 isn't always in 20 percent range, and that in order to  
17 try to design a trial with eligibility criteria to get  
18 that, that we might actually have to like start to  
19 think about the development of nuisance and organ  
20 failure and things that we used to use or we still use  
21 in defining populations for trials in sepsis and things  
22 along that line. And then there are a number of

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1 elements that were kind of touched on but not discussed  
2 very thoroughly, like making sure that you have the  
3 patients on the comparator arm with susceptible  
4 isolates and trying to estimate what that's going to  
5 look like, and then of course some of the challenges in  
6 getting the cultures and making sure that the qualified  
7 cultures are, you know, meeting the threshold of the  
8 eligibility criteria. And then finally, I don't know  
9 if it's worth talking about it, but I do want to  
10 mention that there has been this conversation about  
11 mortality that, if you do want to superiority in a  
12 population that has, like in a nested analysis of a  
13 population that does have resistant isolates, if your  
14 endpoint is mortality and they survive, even though  
15 they got failed early when the susceptibility paper  
16 came back, that was brought up in previous workshop  
17 that that patient still is going to be considered a  
18 success because their antibiotic got them to the point  
19 of failing.

20               So, the point I want to make is that there is  
21 a huge risk in doing something that hasn't been done  
22 with all of these variables and the costs have gone up

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1 enormously, and the unmet medical need for a gram-  
2 negative drug with pseudomonas activity with a  
3 resistant Enterobacteriaceae, it's in pneumonia, and  
4 I'm just concerned that even Big Pharma might not feel  
5 comfortable doing that study first, because it's a  
6 learning process.

7 DR. COX: Thanks for your comment. I mean,  
8 it is true. I mean, in a situation where there has not  
9 been somebody who has walked the pathway before you and  
10 established, you know, either the endpoint, the timing  
11 or assessment, the trial design, and shown exactly how  
12 it's going to work, it's certainly easier to do it, you  
13 know, after somebody else has gone forth. So, I  
14 recognize your point and the uncertainty involved in  
15 being essentially the first, you know, to move forward  
16 on a pathway that hasn't been used before where there  
17 may be questions about the endpoint and all. So, I  
18 appreciate your comment.

19 Other comments from folks? We are at 5:30.

20 (No audible comments).

21 DR. COX: Well, thank you all very much. We  
22 look forward to seeing folks tomorrow morning, and let

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1 me just look at the agenda here. We are starting  
2 tomorrow at 8:00 a.m., so we'll look forward to seeing  
3 you then. Thank you all and have a good night.

4 (Whereupon, the meeting is concluded).

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1 CERTIFICATE OF NOTARY PUBLIC

2 I, NATASHA KORNILOVA, the officer before whom  
3 the foregoing meeting was taken, do hereby certify  
4 that the testimony that appears in the foregoing pages  
5 was recorded by me and thereafter reduced to  
6 typewriting under my direction; that said meeting is a  
7 true record of the proceedings; that I am neither  
8 counsel for, related to, nor employed by and of the  
9 parties to the action in which this testimony was  
10 taken; and further, that I am not a relative or  
11 employee of any counsel or attorney employed by the  
12 parties hereto, nor financially or otherwise interested  
13 in the outcome of this action.

14

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20 My commission expires: October 1, 2011

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22

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NATASHA KORNILOVA  
Notary Public in and for the  
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