1 back to the other point though. If you **had** two
2 peripheral blood cultures of Staph. aureus, are you
3 going to implicate the catheter?
4 DR. RELLER: See, I'm not sure that I
5 would implicate the catheter if you gave me a
6 peripheral Staph. aureus. I would not be comfortable
7 ascribing a Staph. aureus infection to a peripheral
8 catheter if I have a single peripheral positive blood
9 culture and it came through the catheter and I was not
10 exceedingly careful to exclude all other things as
11 well because, in fact, in some studies that we've
12 done, presented, but not yet published, but at ASM,
13 that if you have a noncoagulase negative
14 Staphylococcus and you have a catheter tip that grows
15 a Staph. aureus or a Gram negative rod, and you, based
16 on that information, ascribe that infection to that
17 catheter, you are often on very dangerous grounds, and
18 in fact, you know, it may have started with the
19 catheter, but with the high risk of other sites of
20 infection having already become involved, that it's a
21 dangerous thing to simply accept that it's a catheter.
22 Take the catheter out short course therapy and forget
23 about it with Pseudomonas aeruginosa, enterobacter,
24 and Staph. aureus.
25 So actually I would feel, Bill, that I

1 would be very reluctant to put extra weight on the
2 importance of the catheter and linking it with the
3 catheter because I think actually in the non-coag.
4 negative Staph. you'd be misled, and on the coag.
5 negative Staph. you don't need it. I mean that's what
6 I think.
7 CHAIRMAN CRAIG: Dr. Mermel.
8 DR. MERMEL: I don't think you can have
9 your cake and eat it to. On the one hand, we're
10 requiring the pulse field gel with the absolute rigor
11 that these are true bloodstream infections and that
12 they're coming from the catheter.
13 Now we're saying that you have two blood
14 cultures for coag. negative Staph., and it's a
15 catheter related infection. Indeed, you don't even
16 have to culture the catheter.
17 I think we have to, if we're going to
18 stick to this very rigorous -- and thinking more about
19 it, I would agree with the pulse field gel. I think
20 hold the bar high. If we're going to get a new
21 product on the market, that's fine.
22 But I think we have to have the same rigor
23 to prove, for example, in the neutropenic, the short
24 cut syndrome patient that they're not translocating
25 from some other source.

1 I mean I think we all agree that many
2 primary blood stream infections, I think, which was
3 Dr. Craig's point, come from a catheter, but not all
4 of them do, and it obviously depends on the patient
5 population, the neonate or, again, the person who's
6 gotten a mucolytic agent.
7 So I think that we do need to -- I think
8 your idea of a hierarchy is important, but I think
9 that in that hierarchy we either need a culture of the
10 catheter or quantitative methods, and I guess we can
11 eventually discuss the time to positivity.
12 But I think just having a couple of
13 positive peripheral cultures in my mind isn't rigorous
14 enough, especially considering what we said ten
15 minutes ago about using molecular fingerprinting for
16 coag. negative Staph.
17 CHAIRMAN CRAIG: Dr. Archer.
18 DR. ARCHER: Let me just ask. I agree
19 with the criteria that Barth set for bacteremia. I
20 disagree, I guess, in that I think there needs to be
21 some measure if the catheter is infected.
22 My question is I tried to look up as many
23 of these articles as I could because I'm not directly
24 keeping up with this field, and the data on the three
25 to one to five to one quantitative culture being

1 catheter versus peripheral seems pretty shaky, sort of
2 like a lot of the hub data.
3 Dr. Mermel, maybe you can help me. Maybe
4 there's data I don't know about which helps define
5 this better.
6 DR. MERMEL: I think, and Sam probably has
7 a lot of experience at his institution, one of the
8 important things to know is that, as Barry Farr tried
9 to point out in his meta analysis, I believe all of
10 the data that's published with this methodology are
11 long term catheters.
12 Now, that's not to say that it wouldn't
13 work with short term catheters. Intuitively, the
14 problem with that, however, intuitively is that we
15 believe that the longer the catheters are in, the
16 greater the risk the hub may be a source of
17 bloodstream infection, and therefore, if you're
18 obviously drawing these blood cultures through the
19 hub, you're going to have a bigger bioburden and have
20 the higher quantitative cultures.
21 With short term catheters there may be
22 more -- a greater role of the skin and a lesser
23 sensitivity with quantitative methods.
24 So we just don't know, however, in the
25 average ICU population with a short term triple lumen

1 catheter the sensitivity and specificity. I think
2 Barry tried to point that out, Dr. Farr, in his meta
3 analysis, that we don't have that sort of data in this
4 patient population.
5 DR. ARCHER: Right. Well, that was the
6 problem with the meta analysis, that he fully agreed.
7 None of the studies were comparable, and so really
8 doing the meta analysis is almost -- you could argue
9 about the exercise, but in any of these one individual
10 studies, and there's only a couple even that he quoted
11 that looked at quantitation either of the hub or
12 catheter cultures versus peripheral, and in no one
13 study was there compelling evidence that this was
14 really going to differentiate one from the other.
15 DR. MERMEL: Well, I'm not so sure. I
16 think actually the opposite. I think actually the
17 data is mounting with the time to positivity and the
18 quantitative methods that we're talking about, you
19 know, a difference in the bioburden of organisms and
20 how quickly they grow or the quantity of them in the
21 microbiology lab when the catheter is infected, and I
22 think it's almost like a bioassay in terms of, you
23 know, the time to positivity in this method.
24 And I think most of the studies have known
25 -- 1 think where there's some squeakiness in the wheel

1 is should we use three to one, should we use five to
2 one, you know, those sorts of arguments.
3 Some people have even suggested that if
4 you have more than 100 colonies just in a catheter
5 drawn culture, that that enough is alone. Certainly
6 that's even on shakier grounds, I believe.
7 But I think greater than five to one makes
8 sense scientifically. I think there is an argument in
9 terms of the weakness in not having a lot of data,
10 very little or no published data with short term
11 catheters, but I wouldn't use that as a reason not to
12 include this criteria. I think we could argue about
13 it should be five to one or four to one.
14 DR. ARCHER: But short term catheters,
15 you're going to be able to take the catheter out.
16 DR. MERMEL: That's right.
17 DR. ARCHER: And then you can do all kinds
18 of different quantitative studies for which there's a
19 lot more data. We're talking about leaving catheters
20 in and trying to document the catheter as the source,
21 and you've really only got quantitative hub and
22 quantitative drawing blood back through the catheter
23 as the whole two methods, or maybe infusate as well,
24 to try to say that this is a catheter related
25 infection, right?

1 DR. MERMEL: Right, or, well, also there's
2 the predictive value of the skin, but I think for
3 those long term catheters, I'd feel comfortable as
4 long as we agreed upon a certain definition where the
5 cutoff should be; I'm happy with quantitative
6 cultures.
7 CHAIRMAN CRAIG: Dr. Isaam?
8 DR. RAAD: Yes. There are five studies
9 which strongly suggest that the ratio of greater than
10 ten to one is highly suggestive that the catheter is
11 the source. There is one study that sort of brings it
12 down to five to one. I don't feel comfortable in
13 going to three to one. There might be some reference,
14 but I think this is kind of becoming too flexible, and
15 then we're sort of -- and it all kind of postulates
16 that there is in the lumen of the catheter, there is
17 probably at least fivefold the number of colonies than
18 what you're getting from peripheral blood, suggesting
19 that the source in long term catheters, including
20 tunnels and ports, is the catheter itself.
21 So in long term catheters where you cannot
22 remove the catheter, you need some evidence,
23 microbiologic evidence to point to the catheter as
24 being the source, and hence you have to rely short of
25 differential to positivity time on simultaneous

1 quantitative blood cultures.

2 The issue is -- the problem is that both
3 catheter cultures and quantitative blood cultures, the
4 results come back later on, 96 hours after the onset
5 of fever, and in the real world what happens is even
6 if you're going to remove the catheter, the culture
7 results going to come back 72 or 96 hours after the
8 onset of fever.

9 If you do quantitative blood cultures at
10 our institution, which we routinely do them, they're
11 labor intensive, and again, the results come back 96
12 hours later. By this time, the patient has been in
13 some sort of antibiotic if this is a real infection.

14 So in the real world if you're going to
15 wait until the results of these quantitative catheter
16 cultures or blood cultures are going to come back to
17 include the patient on a study, there will not be any
18 patient to be included on the study. These patients
19 will have been on some sort of antibiotic for more
20 than 24 hours or more than 48 hours.

21 So this would be a great guidance, but it
22 will not -- there wouldn't be any study, any patients
23 to study really. So one has to keep this in mind.
24 Unless we have differential positivity time or unless
25 we are able to include highly suspected cases, someone

1 with a Staph. aureus bloodstream infection, a
2 peripheral blood culture with Staph. aureus, has a CVC
3 in place, have inflammation at the site; there is no
4 other apparent source. I mean this is catheter
5 related bloodstream infection until proven otherwise.
6 And this does correlate ultimately with a
7 quantitative catheter cultures or blood cultures. So
8 there should be some include criteria. Two positive
9 Staph. epi. infections, the same antibiogram, there is
10 no other apparent source; the patient has a central
11 venous catheter. These could be included, and then
12 there would be restriction microbiology criteria for
13 evaluability, to determine evaluability, but not
14 inclusion, and this is the point I would like to make.
15 CHAIRMAN CRAIG: Yes, Dr. Ross.
16 DR. ROSS: Just to clarify, I think Dr.
17 Raad raises an extremely important point that we're
18 fully in agreement with. I think it simply would not
19 be workable to say you have to have a positive culture
20 result in hand before enrolling these patients. I
21 think the intent is that patients be enrollable on the
22 basis of clinical criteria alone, and then at the end
23 of the day in terms of the evaluability be assessed,
24 but I absolutely agree with you. I think you will
25 lend up with no enrolled patients if you were to wait

1 for a positive culture.

2 CHAIRMAN CRAIG: Now, I thought when we

3 talked about this issue before and the committee sort

4 of reviewed it that what we thought was that there

5 should be at least two positive blood cultures, but

6 that we didn't feel that they necessarily had to be

7 both peripheral, but that one could come through the

8 catheter if it had a large enough number to implicate

9 the catheter.

10 And I think I agree with Barth's thing

11 that two blood cultures are sort of necessary, but

12 what I do disagree with him is that I would feel

13 comfortable with just two peripheral. I think there's

14 got to be some way since we're trying to be strict and

15 trying to really be sure that we're dealing with

16 catheter related infection that we have some way of

17 still connecting the infection to the catheter.

18 So I would want to have that stipulation

19 as well either by having a higher number coming from

20 the catheter blood culture or if the catheter is

21 removed, getting it there.

22 I'm less confident though with hub

23 cultures and some of those others farther down the

24 line.

25 Dr. Murray.

1 DR. MURRAY: Yeah, just to say for the
2 record that I agree complete with what Bill said, and
3 I think Gordon said the same thing.
4 DR. WEINSTEIN: Bill.
5 CHAIRMAN CRAIG: Yes, Dr. Weinstein.
6 DR. WEINSTEIN: As a practical matter, the
7 number of laboratories in the United States that are
8 currently do or may be able to do quantitative blood
9 cultures is exceedingly small. So that if that is a
10 criterion, and it may be a reasonable criterion to
11 use, you're not going to be able to find many
12 laboratories that are going to be able to support that
13 kind of a clinical study.
14 CHAIRMAN CRAIG: Dr. Mermel.
15 DR. MERMEL: However, I think we have to
16 realize that's just in that situation where they've
17 not removed the catheter, and then that also begs the
18 question then of are we going to accept time to
19 positivity as an inclusion criteria knowing that 95
20 percent of the labs don't have quantitative methods.
21 CHAIRMAN CRAIG: Dr. Reller.
22 DR. RELLER: I'm glad Dr. Mermel came back
23 to the quantitation because I wanted to address that
24 or the time to positivity.
25 If one is looking at a ratio, whether it's

1 four, five, or ten, it would be absolutely critical to
2 make sure that the blood from the catheter and
3 peripheral were cultured in the same media because the
4 media differences far outweigh the time differences or
5 outweigh the time differences that people have spoken
6 to.
7 And then one goes to the physiology. I am
8 exceedinglyuneasywithquantitation as a differential
9 -- excuse me -- with time to positivity as a
10 differential tool. How often do these organisms
11 replicate? Fifteen minutes, 30 minutes? I mean we're
12 talking about what might be one being four and then
13 whatever you start with similarly going up in good
14 media and under incubation.
15 The replication of the organisms and the
16 quantitative differences are not within the time
17 frames that would enable, I think, a reliable
18 differentiation in terms of assuming because something
19 grows faster that there's that precise a relationship
20 with quanti -- I just don't believe that. It doesn't
21 make any sense microbiologically.
22 Dr. Murray has mentioned maybe in the
23 research laboratory, but physiologically,
24 microbiologically it doesn't make sense to me, and I
25 would avoid that one. It's, I think, dangerous. It's

1 a dangerous quagmire to get into.

2 The absolute -- when we discussed this
3 last year, actually we started out with two peripheral
4 blood cultures and then loosened up to include ones
5 through the catheter because the standard party line
6 that used to be true was that people shouldn't get
7 cultures through the catheter. Some laboratories
8 wouldn't accept them.

9 The reality is that we can't do that
10 anymore because, one, we don't know where they're
11 drawn from, and that may be all that we get,
12 particularly in premature or neonates. So it becomes
13 exceedingly important to have ways of telling whether
14 things are real are not.

15 And there's been a lot of work done on
16 that, that they have to be close in time. They have
17 to be pulse field, for example, in premature or
18 neonates with even cultures that are multiply positive
19 with coag. negative Staph. over days. If you look at
20 positive day one, day three, they're often different
21 by pulse field as opposed to having them all at the
22 same pulse field close in time of being supportive of
23 real bacteremia.

24 so that if one then looks at the
25 insensitivity of the roll technique where you would be

1 missing by numbers that Leonard and Dr. Raad gave
2 earlier of maybe only 70 percent sensitivity with the
3 great than 5 colony forming units, Leonard?
4 DR. MERMEL: It's less than that. It is
5 a little bit less than that.
6 DR. RELLER: At best.
7 DR. MERMEL: Yeah.
8 DR. RELLER: And I think most people here
9 would recognize of all of the techniques,
10 quantitative, semi-quantitative, differential
11 quantitation through catheter, et cetera, I mean, most
12 people would accept not that it's necessarily the most
13 sensitive; it's the most reproducible, the most
14 available, and the one most often used.
15 So if you've got a technique that it's at
16 best 70 percent sensitivity, I see the potential for
17 exclusion of patients who really have catheter related
18 bacteremia, where they've got the clinical criteria;
19 they've got two peripheral blood cultures that grow a
20 coagulase negative Staphylococcus that's going to
21 constitute the vast -- I mean, the majority, 70, 80
22 percent of these are going to be with coagulase
23 negative Staphylococcus, and you don't have any other
24 site, no prostheses, et cetera. I think it would be
25 unreasonable when we're searching for numbers to

1 necessarily a priori exclude.

2 I have no problem with doing a

3 quantitative, a semi-quantitative culture of the cath.

4 tip if it's removed, but given the ambiguities of

5 quantitation relative to peripheral, and to me the

6 uselessness of time to positivity and the lack of

7 availability in clinical laboratories of quantitative

8 methods that have to be done at the time of

9 enrollment, you can't do it after the fact like you

10 can pulse field gel electrophoresis.

11 I just think that with the primary

12 emphasis on bloodstream infection, that one can fairly

13 categorize this 30, 40 percent of patients with

14 coagulase negative Staphylococci who have two

15 peripherals and no other source, and the patient gets

16 treated and responds. I think there are ways to deal

17 with this.

18 CHAIRMAN CRAIG: Dr. Archer.

19 DR. ARCHER: Just one question for Dr.

20 Mermel again. Do antibiotic and anti-infective

21 impregnated catheters affect your ability to recover

22 organisms from or through the catheter?

23 DR. MERMEL: Sam could also speak to this.

24 There was an article in Journal of

25 Clinical Micro., because I had reviewed it a few years

1 ago, that raised that possibility that with some
2 intraluminally covered -- with some antimicrobial
3 agent, catheters drawing a blood culture through may
4 have -- I can't remember who the author was. I don't
5 know if Barth --
6 DR. RAAD: Schmidt is it?
7 DR. MERMEL: I think so. That's right.
8 The Cleveland Clinic, I think, group, suggested that
9 that was a possibility.
10 I've also been concerned about that, say,
11 with heparin bonded catheters they use in children,
12 with umbilical catheters where they're bonded with
13 benzoconium, and we know that initially when those
14 catheters -- if you draw blood through a heparin
15 bonded catheter that's got the benzoconium in it, that
16 adversely -- that impacts on potassium measurements.
17 Using the Kodak ectocam system can cause false, pseudo
18 hyperkalemia, and then they go and treat people and
19 they actually have normal potassiums, and you get this
20 big bolus effect as you're drawing blood through a
21 freshly inserted heparin bonded catheter with
22 benzoconium.
23 So I think the possibility does exist.
24 DR. ARCHER: That would certainly affect
25 time to positivity if you got some inhibition growth

1 early on because of that.

2 DR. MERMEL: I would agree that that would

3 seem very plausible.

4 DR. RAAD: I think the time to positivity

5 should exclude patients with the impregnated

6 catheters, whether antibiotics or antiseptic. But

7 going back to what Dr. Reller said, and I strongly

8 agree, I think there is an entity. Given the fact

9 that our quantitative culture methods are somehow

10 limited, whether the semi-quantitation, even the

11 sonication, even the quantitative blood culture

12 methods, we have to give room to this entity of

13 probable catheter related bloodstream infection that

14 does include patients with true bacteremias, including

15 Staph. epi. and certainly Staph. aureus, no other

16 apparent source, probably catheter site inflammation,

17 and these are probable catheter related bloodstream

18 infections, even the absence of catheter site

19 inflammation.

20 That has to be part of the intent to treat

21 analysis, and then in the specific analysis of

22 evaluable definite cases, there would be the ones with

23 definite microbiologic and quantitative data, whether

24 quantitative catheter cultures or differential

25 quantitative blood cultures.

1 DR. MERMEL: Can I ask for a
2 clarification? Sam, you're saying that you would
3 include those patients. It's like probable. What
4 would you do though when the rubber hits the road at
5 the end in terms of definite, and they just have two
6 peripheral cultures?
7 DR. RAAD: I think these probable cases
8 should be part of the intent to treat. I mean this is
9 what intent to treat is about. If you exclude them,
10 you're really biasing the studies.
11 But then you might want to do a
12 subanalysis for the definite cases or ones that you
13 might want to call evaluable.
14 The other issue is with the Staph. aureus.
15 Now, all of us agree here that Staph. epi. you would
16 like to see at least two positive blood cultures, but
17 Staph, aureus -- and it all depends on the fact
18 whether the clinician was expecting endocarditis at
19 that point or not, and remember this is a febrile
20 patient that might have had one blood culture draw and
21 has a Staph. aureus and later on you remove the
22 catheter and the catheter is culture positive with
23 high colony count on the catheter tip for Staph.
24 aureus.
25 This is catheter related Staph. aureus

1 bloodstream infection even if you don't have two
2 cultures. so to call this at the end being
3 inevaluable because you wanted two peripheral positive
4 blood cultures for Staph. aureus and in addition to a
5 catheter culture for Staph. aureus would be too
6 excessive.
7 I think for Staph. aureus, it should be
8 treated differently than Staph. epi. With Staph.
9 aureus, I think most people would agree that one
10 positive blood culture in the setting of clinical
11 sepsis and a positive catheter tip culture or
12 intravascular segment would certainly speak of a true
13 catheter related bloodstream infection for Staph.
14 aureus.
15 CHAIRMAN CRAIG: Well, can we get back to
16 the criteria? At least I've heard Barth reemphasize
17 what we had talked about before of having two positive
18 blood cultures, and I've heard some comments from
19 other people that they felt that that was desirable,
20 too.
21 Is that, again, what we want to emphasize,
22 that we should have at least two positive blood
23 cultures?
24 Now, to implicate the catheter, the
25 question is: is that all we're going to require, is

1 just two positive blood cultures, or do people want
2 more to try and implicate the catheter?
3 My own feeling was that, yes, I think we
4 still need to implicate the catheter. I mean, I had
5 personal experience with patients with VRE at our
6 institution where I've had positive blood cultures
7 with VRE from peripheral sites, but taking out the
8 catheter we can't find the organism there at all, and
9 I have a positive rectal culture. So I'm sure it's
10 probably translocation from the gut.
11 so I think there needs to be some
12 connection to the catheter so that if one of the
13 cultures was drawn through the catheter and you had a
14 high number, that would be a way of implicating it,
15 and then if the catheter is removed, that would be
16 another way of implicating it.
17 But I have great difficulty with some of
18 the other criteria.
19 Yes.
20 DR. NORDEN: I think you just changed a
21 little bit from what you had said earlier. I mean, I
22 think a blood culture drawn through the catheter, if
23 it's not quantitated, is no different than a
24 peripheral culture. It's still a blood culture.
25 CHAIRMAN CRAIG: Yes.

1 DR. NORDEN: Well, this time you added
2 quantitation.
3 CHAIRMAN CRAIG: No. What I'm saying is
4 that you need some way of implicating the catheter.
5 DR. NORDEN: I agree.
6 CHAIRMAN CRAIG: If you draw two blood
7 cultures and you draw one through the catheter, it
8 would still be okay if the catheter is removed and you
9 met the criteria for implicating the catheter by way
10 of the roll test.
11 DR. NORDEN: Right.
12 CHAIRMAN CRAIG: On the other hand, if the
13 catheter was not being removed and you weren't going
14 to be able to get that and you had two cultures and
15 one was drawn through the catheter, the only way to
16 really implicate the catheter then would be from
17 quantitation.
18 DR. NORDEN: Okay. I don't disagree with
19 that.
20 DR. ARCHER: It seems to me that the best
21 way to handle this might be to have the sponsor
22 include as many tests as possible when the catheter is
23 not removed or even when it is to try to implicate the
24 catheter, and we might be able to collect some data
25 actually on the basis of the studies that are done,

1 whether these methods actually predict catheter
2 related infections and what the outcome is.
3 Maybe more than one should be required of
4 sponsors in order to try to answer some of these
5 questions.
6 I have another FDA related question. If,
7 for instance, a company does studies with catheter
8 related bloodstream infections and, say, has 20 Staph.
9 aureus infections and in ten of those or 15 of those,
10 the catheter is removed, the patients do well, ten
11 days' treatment; do they then get an indication in the
12 package insert for Staph. aureus bacteremia, or will
13 it have to say catheter related Staph. aureus
14 bacteremia where the catheter comes out?
15 DR. CHIKAMI: I'm not sure I can address
16 the numbers issue, but you raised the issue about how
17 the study was actually done. That is, in the course
18 of the study if the catheter was removed as an
19 important point in management, and I think we'd have
20 to think about it. It's an issue we may bring to the
21 committee, but in fact, there are other precedents
22 where important management issues in the course of a
23 clinical trial have been described in the label in the
24 clinical study section if we feel and there is
25 scientific evidence to support that whatever that

1 management strategy was was important. We think it's
2 important for the use of that product and in its
3 effectiveness and its safe use.
4 CHAIRMAN CRAIG: Dr. Mermel.
5 DR. MERMEL: I think it's an extremely
6 important point because there are studies that have
7 shown that with Candida and Staph. aureus not removing
8 the catheter is an independent risk factor for death.
9 So now I know death isn't the sort of
10 thing that's an endpoint, but it is going to --
11 leaving the catheter in with Staph. aureus or Candida
12 is going to increase independently the risk of death
13 of the patient and, you know, obviously a bad outcome,
14 and I think that distinction in terms of analysis is
15 going to be extremely important.
16 How it is in the package insert I don't
17 know, but I think in the final analysis it's going to
18 be very important because of that very compelling data
19 whether or not the device has been removed or not as
20 part of treatment.
21 CHAIRMAN CRAIG: Dr. Murray.
22 DR. MURRAY: Yeah, because i was going to
23 make that point, too. I have to assume that any
24 study, any evaluation, you're not going to be looking
25 at the guys who had the catheter removed mixed in with

1 the guys that hide the catheter left in. I mean those
2 are two very distinct patient populations.
3 And although they may all come into the
4 same entry criteria or get admitted into the study and
5 put on therapy, surely the analysis can't have them
6 mixed together because I think those are apples and
7 oranges completely.
8 And while I agree that the two positive
9 blood cultures as a criteria, I also sort of agree
10 with Sam that if it's Staph. aureus, so the fever went
11 to 104, you drew a blood culture, took out the line,
12 cultured the cath. tip and there were, you know, 50
13 Staph. aureus on the cath. tip, but you lost the
14 opportunity to get another blood culture. I think the
15 Staph. aureus kind of would tend to agree with in that
16 instance that one might be sufficient.
17 Now I want to make one other comment.
18 What about these Staph. epis. where the catheter has
19 been removed? And so I'm really sort of throwing this
20 out to the pharmaceutical industry. Maybe there is a
21 way to get some information there.
22 So at 48 hours you find out it's Staph.
23 epi. The patient has now been on therapy for 48
24 hours. The catheter was removed. Perhaps we could
25 consider or encourage the companies to consider having

1 an arm that when that was the case, the therapy either
2 stops at 48 hours if the patient is doing well or at
3 72, and otherwise they continue on with what was the
4 preset therapy.
5 Because I think we may end up treating a
6 lot of people with Staph. epi. bacteremias whose
7 catheters were removed for seven to ten days, and that
8 tells us nothing. And there may be a way to
9 incorporate into this having a separate part of the
10 study for those where it's removed and you find out
11 it's Staph. epi. cutting therapy short, and find out
12 if two days is equal to seven. Then that's good
13 information, getting closer to zero all the time.
14 CHAIRMAN CRAIG: Yes, Dr. Mermel.
15 DR. MERMEL: I think also, Barbara, you'd
16 make this a non-neutropenic, and also I think I would
17 also echo Dr. Raad's comments with regards to a single
18 positive blood culture for Staph. aureus and also add
19 Candida.
20 CHAIRMAN CRAIG: There's one other
21 scenario here that I wanted to see what the people
22 thought, is when we do have entry site exudate, and as
23 was suggested by Dr. Archer, that a Gram stain
24 definitely looks like there's purulence there, and you
25 see some organism there; that if you had a positive

1 culture there and two blood culture positives and they
2 were all the same organism, that you would consider
3 that to be a catheter related infection.
4 So we could have three ways then of
5 implicating the catheter: by having a higher number
6 in the culture through the catheter or for the blood
7 culture through the catheter; by rolling it; and by if
8 there happens to be an exudate that is Gram stain
9 positive and also then recovers the same organism.
10 What do people feel about the catheter hub
11 and the infusate? Should we just suggest that
12 companies would be encouraged to collect such data;
13 that it may be helpful, but at this point in time
14 we're uncertain about the sensitivity and specificity
15 of those tests?
16 Okay. Well, that takes care of at least
17 the initial bacteria. Yes, Dr. Parsonnet.
18 DR. PARSONNET: I just wanted to make one
19 comment, which is that throughout this discussion it
20 seems like we've just massive increased the complexity
21 of the studies that are being done to the point where
22 we've talked about stratifying by duration of therapy,
23 type of catheter, the organism involved, whether the
24 catheter is retained or removed, ways of implicating
25 the catheter, probable versus definite infections, to

1 the point where I'm not sure these studies are going
2 to be feasible to look at all of these various things,
3 and it may be that we need to prioritize what things
4 are most important.
5 DR. MURRAY: I think that reflects the
6 fact that we're not sure they are feasible in some
7 ways. I mean it is very difficult. There's so much
8 mixed out there, and that's probably why there is no
9 indication right now it's extremely complex, and every
10 time we ask again we sort of waffle.
11 DR. PARSONNET: I think that's the point.
12 These studies haven't been done very well in the past
13 for a reason, which is that they are extremely hard,a
14 nd we're throwing out all of these criteria, but it's
15 not clear to me, especially given the sample size
16 calculations that we heard previously that by
17 including all of these things we're just making these
18 sorts of studies completely -- we're just showing that
19 they're going to be completely impossible to do to the
20 degree that we'd like to see them done.
21 DR. ARCHER: But I think that the point
22 has been made several times about you include a lot of
23 people in the studies and then you look at how the
24 data falls out, and maybe a lot of this will have to
25 be done post hoc, and you may not exclude everybody on

1 the basis of these criteria, but you need to collect
2 the data, as much data as possible.
3 And I think the stratification, I mean
4 it's going to be a tough job for the FDA once all the
5 data come in to decide what qualifies and what
6 doesn't, but I think if you collect the data, then I
7 think you might be able to arrive at some conclusions.
8 CHAIRMAN CRAIG: I think the hardest thing
9 is the catheter removal, and I agree, as David said
10 and as it says in here, the guidelines, is that the
11 companies have to have some set way of dealing with it
12 so that it's standard throughout the protocol of how
13 it's going to be looked at.
14 Because that's such, in my mind, a big
15 variable in what one's going to see in terms of the
16 outcome that that really needs to be down in print and
17 standardized, and it's going to happen exactly as it
18 says.
19 DR. MERMEL: I just want to say the time
20 is ripe to do the studies. We know life is difficult
21 and it's going to be complex, but looking at studying
22 thousands and thousands of patients for heart disease
23 and oncology and yet we can't tell a physician how to
24 treat their patient. I mean anyone who's taken care
25 of anybody in a hospital over a few days is going to

1 have a patient with a bloodstream infection, and if
2 it's related to a catheter, we can't tell them
3 anything.
4 And so something that's part and parcel
5 with daily care of patients, it is complex, and I
6 think we'll just have post hoc analysis and keep track
7 of whether or not the patient got an echo cardiogram
8 up front and whether or not the catheter is removed.
9 There's going to be a lot of complexities,
10 but I certainly wouldn't discourage industry from
11 pushing ahead and trying to answer some of the most
12 basic, fundamental questions in taking care of
13 patients that are hospitalized and in home care that
14 are totally unanswered.
15 CHAIRMAN CRAIG: Okay. The other question
16 I think we need to clearly address that we've talked
17 about already is the test of cure cultures, and
18 questions of whether they're necessary, whether
19 they're necessary for certain organisms and not for
20 others. I'd like to hear some comments from
21 participants.
22 Dr. Archer.
23 DR. ARCHER: I agree 100 percent with what
24 Dr. Raad said. I don't think test of cure for any
25 organism, if the patient is doing well, feeling well,

1 is going to yield anything but a bunch of contaminants
2 that's going to make the study results difficult to
3 interpret -- in adults.
4 CHAIRMAN CRAIG: Could I just ask --
5 (Laughter.)
6 CHAIRMAN CRAIG: Could I ask our
7 consultants what the data would say on catheters that
8 are left in, that with organisms such as coagulase
9 negative Staph., if there's any usefulness there later
10 on? Do those catheters sometimes continue to give
11 positive blood cultures without fever symptoms, the
12 other things going on?
13 DR. MERMEL: Two points. The test of
14 cure, I think, Sam might have touched upon the fact
15 that -- Gordon, would you feel there's more compelling
16 evidence to do it if it were something like Staph.
17 aureus? Still no.
18 DR. ARCHER: Can you imagine a patient
19 with Staph. aureus bacteremia who's asymptomatic?
20 DR. MERMEL: No, no, no. In terms of --
21 well, I've seen it. Yeah, I've actually seen cases.
22 Yeah, I actually have, yeah. But --
23 DR. ARCHER: Well, possibly if the
24 catheter is left in, in a patient with Staph. aureus
25 bacteremia, you might want to get some test of cure,

1 but otherwise if the patient is doing well, I think
2 you have all these other ways of assessing.
3 You're not likely to get Staph. aureus
4 contamination. So that's less of a -- but it's one
5 more test to do that's probably going to yield you
6 minimal information.
7 DR. MERMEL: Well, I'm just sure. I just
8 think the Staph. aureus is just so much more
9 pathogenic. I just -- I usually, when that's the only
10 Staph. aureus bacteremia, routinely, irrespective of
11 the source, recommend repeat blood cultures after I've
12 stopped therapy. That's just the way I was trained to
13 practice by people like Dr. Craig.
14 Regarding the catheter in, Dr. Raad has
15 data showing that there's a threefold, if I'm quoting
16 correctly, higher risk of repeated bloodstream
17 infection with coag. negative Staph. if you leave the
18 catheter in, although I don't know, Sam, how many of
19 those people -- what their clinical symptoms were at
20 that time in terms of were any of those people, you
21 know, not meeting the criteria we're using.
22 DR. RAAD: Yeah, there was patients who
23 had the catheter left in with Staph. epi., but they
24 had real Staph. epi. bacteremias. There were 20
25 percent chance higher of relapse versus those that had

1 their catheters removed.

2 But all of those that had a recurrence

3 came back with, again, clinical manifestations of

4 infection, including fever. So that's why I'm making

5 the argument that if patient is doing well, there is

6 no need to do the blood cultures certainly with Staph.

7 aureus unless with the Staph. aureus you have

8 something to mask the infection: an elderly patient,

9 a renal failure patient, or a patient on steroids.

10 DR. MERMEL: Yeah, I think those are

11 important.

12 DR. RAAD: And Candida.

13 DR. MERMEL: Clinically I've seen patients

14 with Staph. aureus bacteremia without much fever in

15 those sorts of subgroups.

16 CHAIRMAN CRAIG: Yes, Dr. Donowitz.

17 DR. DONOWITZ: I think there's test of

18 cure weeks after you've stopped therapy or days after

19 you've stopped therapy, but I also think that there

20 should be some criterion during the infection in terms

21 of daily cultures until negative, which should be

22 fairly specific, and that way you're talking about

23 efficacy of therapy in the middle of your diagnostic

24 period.

25 Routinely I would advocate that. We don't

1 routinely, Gordon, much to your surprise do any test
2 of cure in kids because, again, if they enter with
3 symptoms and they recur, they recur with the same
4 symptoms.
5 DR. ARCHER: I think for Staph. aureus, in
6 particular, multiple blood cultures after starting
7 therapy is very important. For instance, if you do
8 those with naphcillin (phonetic) versus vancomycin,
9 there's a clear difference in time to eradication of
10 bacteremia with vancomycin versus naphcillin, and it
11 might be another way of evaluating drugs, one versus
12 another, in comparative studies.
13 DR. WEINSTEIN: But, Gordon, given that a
14 large percentage of hospital acquired Staph. aureus
15 bacteremia, many of which may be associated with
16 catheter, are going to be caused by methicillin
17 resistant strains and vancomycin kills slowly, and it
18 may take a week to clear the bacteremia, it probably
19 doesn't make a lot of sense to repeat blood cultures
20 after 48 or 72 hours when you know that a fair number
21 of those patients are going to continue to be
22 bacteremic. It's going to take longer to clear the
23 bacteremia.
24 DR. ARCHER: True, but there's a range.
25 Some may; some may not, and once again, if you're

1 doing it as a comparator, and you comparator is
2 vancomycin against whatever your drug is, then you
3 want to show that it does better than vancomycin in
4 terms of clearing the blood, and I think that's a
5 useful kind of a test to get in those situations.
6 CHAIRMAN CRAIG: Something that you'd put
7 in there to suggest people to do or something that you
8 would require people to do?
9 DR. ARCHER: Once again, I th.ink if a
10 company wants to prove that its drug is better or
11 equal to, they want as many parameters as possible for
12 evaluating drug efficacy, and that's just one. I mean
13 it would seem to be in their benefit to get those
14 kinds of studies.
15 CHAIRMAN CRAIG: Dr. Murray.
16 DR. MURRAY: I think it's of interest, but
17 I think without knowing that the rapidity with which
18 a blood culture becomes negative under therapy in
19 these settings, that that has anything to do with
20 ultimate outcome, it's kind of a slippery slope to
21 make it a requirement.
22 DR. MERMEL: But again, Sam has data with
23 Staph. aureus bacteremia suggesting that if after
24 three days of initiating appropriate therapy they
25 still have bacteremia, that those patients are very

1 different than those in which it resolves within three
2 days and are those much more likely to have metastatic
3 foci.
4 So if you didn't follow that criteria and
5 then you had a higher failure rate with Staph. aureus
6 bacteremia and you didn't know that those patients
7 were bacteremic for several days, you might think it's
8 a drug effect where in actuality they seeded those
9 sites early on in the infection.
10 So I think with Staph. aureus, again, that
11 getting multiple cultures is very important in looking
12 at efficacy because you tease apart those that seeded
13 foci as compared to drug efficacy.
14 CHAIRMAN CRAIG: yes.
15 DR. CHIKAMI: I think that's an important
16 issue because as the guidance is written now, there
17 are early evaluations based primarily on evaluating
18 the clinical course. There have not been built into
19 it recommendations related to this issue of following
20 the microbiologic response and how important that may
21 be.
22 Again, it may be organism specific.
23 That's the sort of complexity that we'd have to think
24 about in how to sort of provide that sort of guidance.
25 DR. MERMEL: I think many clinicians or at

1 least myself, if someone's got high grade continued
2 bloodstream infection, I treat them for a long course.
3 I treat them as if they have a endovascular focus of
4 infection, even if they had a TEE, for example, and it
5 was negative. If I see someone with Staph. aureus and
6 I think it came from a line, pulled out the line,
7 initiated therapy, four days later they still have
8 positive blood cultures, in my care of patients they
9 get a month of therapy as if they have an endovascular
10 focus of infection.
11 So I think it's very important with Staph.
12 aureus to know that, have that data.
13 CHAIRMAN CRAIG: Is that based just on the
14 blood culture or is that based -- are the patients
15 clinically sick as well?
16 DR. MERMEL: I think oftentimes they're
17 sick as well, and it doesn't have to be -- you know,
18 they could have septic thrombophlebitis, for example,
19 but they've got continuous bloodstream infection.
20 Isn't that our definition of an endovascular
21 infection?
22 CHAIRMAN CRAIG: Yeah, but, I mean, the
23 question that I think they were trying to get is we've
24 been talking before about clinical and now we're
25 talking about microbiologic. Is there something

1 unique about it that's not picked up by clinical
2 observation?
3 DR. **MERMEL:** I don't know if we have the
4 data.
5 DR. **ARCHER:** These might be sick patients
6 who are ill for other reasons, and it's one more thing
7 to follow. They may not deffervesce immediately in
8 terms of whatever their symptoms are, but if they
9 clear their bloodstream very quickly, then I think
10 that's one more parameter that can be used to follow
11 them versus not.
12 And, once again, you've got a lot of
13 patients with a lot of different things, but you've
14 got them randomized to two different drug regiments,
15 or Drug A/Drug B, and you tease all of this out, I
16 think, at the end looking at all of it, rapidity to
17 clearance, metastatic foci, and so forth with each
18 individual drug, but there will be a lot of data
19 gathered in the meantime that we don't have now.
20 CHAIRMAN **CRAIG:** Okay. Any other comments
21 on that?
22 So I think the general consensus from here
23 was that blood cultures when somebody's doing fine are
24 not needed, but if they still have symptoms at the
25 time, then we would.

1 **DR. CHIKAMI:** And just to clarify that
2 point, these are in situations also where the catheter
3 was left in place. The feeling is that those patients
4 who are likely to have relapsed would relapse with
5 symptoms.
6 **CHAIRMAN CRAIG:** Well, I mean, at least
7 that's what I thought Dr. Raad said. Is that correct?
8 Dr. Danner's experience?
9 DR. DANNER: When a catheter is left in
10 place, I would favor cultures even if someone is not
11 febrile, and the reason for that is that you may have
12 decreased the amount of colonization, but not
13 completely cleared the catheter. You might pick that
14 up with a blood culture, but not see it clinically.
15 And it also depends a little bit on how
16 the catheter is being used at that time. If the
17 catheter is just being locked and not otherwise used,
18 you may not know that the catheter has a problem based
19 on clinical symptoms until the person comes in for
20 another course of chemotherapy or some other
21 intervention and it's hooked up to an IV and you run
22 stuff through it, and then they get a shaking chill
23 and have another event.
24 So as a test of cure to show that you at
25 least can no longer detect that that catheter is

1 colonized with the same infection, in the situation
2 where the catheter is left in place I would draw a
3 culture through it.
4 DR. ARCHER: But what if you got a
5 positive culture from the catheter and a negative
6 peripheral culture in a patient who is doing well?
7 Would that be a failure of therapy?
8 DR. DANNER: If it's the same organism,
9 you know, that you had two weeks ago, yeah, I think
10 that is probably, and what will happen likely with
11 that catheter is that eventually there'll be a
12 relapse, but it may happen down the road.
13 CHAIRMAN CRAIG: I guess my concern still
14 is what are we treating. Is this an infection we're
15 treating or is this a catheter we're treating?
16 DR. DANNER: I thought when you're trying
17 to treat an indwelling catheter that you're leaving in
18 place that you're clearing the catheter related
19 infection, but you're also decolonizing that catheter,
20 and if you haven't decolonized the catheter, then
21 that's a failure of your treatment.
22 DR. ARCHER: I think Dr. Raad would say
23 that you've got organisms buried deep in biofilms in
24 catheters after successful therapy that you could
25 probably recover in most cases if you looked hard

1 enough.

2 DR. RAAD: Yes. It's extremely difficult
3 to decolonize catheters even with long term therapy
4 because of the organisms being imbedded in biofilm and
5 being resistant to antimicrobial agents in the setting
6 of biofilm. So a positive blood culture through a CVC
7 might not be very helpful, certainly for Staph.
8 epidermidis bloodstream infections.

9 For Staph. aureus, I see where the
10 cautiousness clinically and you want to make sure that
11 this is negative, but, again, if this is positive
12 through the CVC and a catheter is left in and the
13 peripheral vein is negative and there is no evidence,
14 no clinical manifestations of infection, what do you
15 call hits, a hub colonization? Is it failure of
16 therapy?

17 So why to do a blood culture which is not
18 going to be helpful or meaningful? And for Staph.
19 aureus infections, the data in the literature is in
20 favor of removing the catheter if this is true
21 catheter related bloodstream infection, and so these
22 catheters should not be left in place.

23 There is no attempt to use antibiotic lock
24 therapy for long term catheters and so on, but I
25 certainly will not kind of propagate using blood

1 cultures through CVC for Staph. epidermidis if the
2 patient is doing fine. For Staph. aureus I see where
3 you're concerned.
4 DR. DANNER: Well, also other organisms.
5 I mean enteric Gram negatives and things. I mean if
6 that's still in that catheter, it's going to come back
7 eventually, particularly if the patient with that
8 catheter is going to go through another cycle of
9 chemotherapy and become neutropenic again and things.
10 I wouldn't leave the catheter in. I think
11 that's a failure of trying to clear the catheter.
12 It's still infected.
13 DR. RAAD: Yeah, but we're not evaluating
14 actually whether we're able to decontaminate the
15 catheter. We're evaluating whether we're able with
16 follow-up to cure the patient, and the issue --
17 DR. DANNER: Well, it's not a cure if you
18 make the patient neutropenic two weeks later and they
19 then are bacteremic with the same organism because
20 you've stopped the antibiotics and the organism is
21 still on the catheter and it's now regrown and you're
22 infusing stuff through the catheter and they're still
23 infected.
24 CHAIRMAN CRAIG: Yes, Dr. Norden.
25 DR. NORDEN: I'd like to respond to that,

1 Bob. I think that really we have to define what we're
2 trying to do in the study. The study is trying to
3 treat catheter related bacteremia, and you need one
4 endpoint for that.
5 The clinical outcome as you talk about two
6 weeks down the road or four weeks down the road, when
7 the patient gets another episode of neutropenia is
8 something that as clinicians we're going to be unhappy
9 about, but I don't think, you know, it's something you
10 can ask of an antibiotic or that you'd decolonize, as
11 Dr. Raad has said, the catheter.
12 So I think you have to say this is my
13 endpoint. The endpoint is clearing bacteremia, and
14 you stop there, and that's a success.
15 DR. DANNER: Well, Carl, maybe we practice
16 different, but to me, you know, just like with a
17 urinary tract infection, if you want to know you
18 cleared it, you then have clean urine and you're not
19 still growing the organism and you don't still have
20 white cells there.
21 You know, these patients are very complex.
22 A lot of them are on steroids. A lot of them are
23 elderly. A lot of them have reasons not to
24 necessarily have clinical signs, particularly if
25 you've decreased the amount of organisms in the

1 catheter during the course but not cleared it, and if
2 you are otherwise not using the catheter in the same
3 way and you've just locked it, and it's not currently
4 being used for infusion because your antibiotics have
5 stopped and they're not getting a course of
6 chemotherapy, and to me you need to know that the
7 catheter was cleared of the infection.

8 And the way to do that is to draw a
9 culture through it.

10 DR. NORDEN: I don't think it's a matter
11 of practicing differently. I suspect we probably take
12 care of patients very much the same. I think that
13 what I'm trying to say though is that this is a drug
14 trial that you're now doing, and you have a right to
15 set up any criterion that you think is valid as an
16 endpoint.

17 And if the criterion you decide is
18 clearing of bacteremia and everybody agrees that
19 that's okay, then that's what you use.

20 I mean, I think you're absolutely right
21 about urinary tract infection. You do the same thing
22 with osteomyelitis. You'd like a bone biopsy to be
23 sterile, but when you treat pneumonia, you don't
24 actually look to see if you clear the sputum. I mean
25 you don't always do that.

1 CHAIRMAN CRAIG: I mean you're actually
2 talking about a surrogate for decolonization of the
3 catheter. I mean the only way to really be sure that
4 it's decolonized would be to completely remove it,
5 scrape everything off you could from the inside and
6 culture it to be sure that it didn't have any
7 organisms, and that's not going to happen.
8 DR. DANNER: Well, I don't think you have
9 to be short that level, but at least to know that you
10 still don't have positive cultures, and when you hook
11 up to that catheter, you know, if you hook into the
12 catheter and you draw blood out and there's bacteria
13 in it, when you hook into the catheter and infuse
14 things in, there's bacteria in that also.
15 DR. ARCHER: But, Bob, 90 percent of the
16 catheters that are going to be left in are going to be
17 left in for Staph. epi. and coag. negative Staph.,
18 right?
19 DR. DANNER: Staph. epi., I think, is a
20 different issue.
21 DR. ARCHER: Okay. Well, I think that is
22 the issue. I think most of us would agree if you have
23 to leave the catheter in and the patient had
24 Pseudomonas, enterobacter, or Staph. aureus, then I
25 think you're right. You would want to be careful, and

1 maybe you'd want to culture the catheter again.

2 But most of the time those catheters are
3 going to be pulled even if it's a central catheter for
4 those kinds of bacteremia related to catheter.

5 DR. DANNER: Yeah, enterobacteriaceae, I
6 mean, people treat those, I mean, for the permanent
7 catheters. They attempt to clear the catheter and
8 treat that.

9 DR. ARCHER: And your experience is those
10 relapse?

11 DR. DANNER: Some of them do. Some of
12 them clear, and some of them relapse, and I would like
13 to have the culture.

14 If you keep in the criteria where you're
15 following up long term enough, then I think the
16 catheters that are still colonized and have not been
17 cleared adequately if your follow-up is long enough,
18 those people who are going to have a problem will
19 relapse and you'll pick it up.

20 But you certainly then need to have the
21 later follow-up in there.

22 DR. RAAD: But then the antimicrobial
23 agent will not be able to decolonize the catheter.
24 In these situations what you need to do is be more
25 concerned about removal of the catheter, which is a

1 management issue.

2 To expect that the antimicrobial agent in

3 the case of some of the organisms, such as

4 stenotophomonus multiphilia (phonetic) or some of the

5 other agents will decolonize the catheter, and to call

6 this that this is failure because a positive blood

7 culture through the CVC in a patient who is doing well

8 is positive reflects failure of the antimicrobial

9 agent is --

10 DR. DANNER: Well, I don't know. I mean

11 you have somebody that got an E. coli infection of

12 their catheter. You treat them with antibiotics.

13 Subsequent cultures through the catheter are negative.

14 Three months later they have fevers. You're drawing

15 other cultures. You don't recover that same E. coli.

16 So I think those catheters are, in fact,

17 decolonized. They no longer have the E. coli on them.

18 CHAIRMAN CRAIG: We need to --

19 DR. MERMEL: Could we resolve that issue,

20 however? Instead of requiring a blood culture through

21 the catheter, for patients whose catheters are left in

22 place have longer follow-up so that if there is a

23 bacteremia it could be recorded because then it's

24 clinically meaning. The patient has a true

25 bloodstream infection, you know, six weeks after --

1 DR. DANNER: Six weeks after if it
2 relapses with the same organism. Then that's a
3 failure, and yes, if you had a longer follow-up you
4 could address it the same way.
5 I myself, I mean, after I finish the
6 antibiotics, you know, not for all organisms, but for
7 a substantial number of organisms, I'll repeat
8 cultures through the catheter and make sure I cleared
9 the organism from the catheter.
10 But long enough follow-up would address
11 the same issue.
12 CHAIRMAN CRAIG: Okay. Dr. Reller.
13 DR. RELLER: I wonder if one way out of
14 this controversy, given the diversity of the
15 organisms, some catheters coming out and some not, and
16 I think it's in accord with clinical practice, that if
17 a patient is not doing well, implicit in these
18 guidelines is a delineation of the factors for
19 documentation of whether the catheter was removed or
20 not, and what the criteria for removal of the catheter
21 are.
22 So that if a patient who has an organism
23 that's an aureus or a Candida, most people are going
24 to remove the catheter if they can straight away.
25 Some, if it's a vital lifeline, are going to try to

1 get by without moving the catheter, but if the patient
2 is not doing well, they're going to get blood cultures
3 and if positive, then the pressure is really on to
4 remove the catheter.
5 So if we had it in that the patient was
6 doing well, whether the catheter was removed or not,
7 and most of the time this is going to be with
8 coagulase negative Staphylococci, which would be one
9 of the goals in developing a drug is to be able to
10 save more catheters to get through whatever they
11 needed the catheter for in the first place.
12 So if a patient is not doing well and the
13 catheter is going to be removed and blood cultures are
14 obtained, that that be required, that those data be
15 captured, but that getting blood cultures at two,
16 three, five days on every patient regardless is not.
17 It's neither necessary, nor, in fact, depending on the
18 antibiotic and the organismnecessarilyinterpretable.
19 But at the end of therapy, presumably if
20 you're treating catheter related infection, it's going
21 to be a short course. Whether short is five days,
22 seven days, or ten days, it's going to be delineated
23 in a given protocol for a given agent, and I would
24 think that after completion of therapy, at some time
25 after that, that that's the follow-up blood culture

1 that I'm interest in, and interest in for two or three
2 reasons.
3 One is that if this patient had a catheter
4 related infection that was caused by Staph. aureus or
5 Candida, even with removal of the catheter, I am
6 always nervous, and it may be subtle in the dialysis
7 patient, et cetera. For the purposes of a clinical
8 trial, if you're saying this is a simple one, it may
9 be a bad organism but it's simple. We remove the
10 catheter; they got a short course of therapy. To
11 document that after therapy is stopped I think would
12 be very important.
13 They might pop up with osteomyelitis six
14 weeks down the -- but you would say three or four days
15 after completion of therapy with a bad organism and
16 catheter removed that that patients did not have
17 bacteremia, which was a necessary criterion for
18 evaluability on entry.
19 For the patients with the you might say
20 easier organism, the coag. negative Staph and the
21 catheter was left in place, even without symptoms, I
22 am very interested for the purposes of study in
23 showing that after the therapy is stopped because of
24 biofilm, et cetera, that that thing is not popping
25 back up right away.

1 One could argue about whether it would be
2 worthwhile looking further down the line, but I think
3 there needs to be -- we put a lot of emphasis, and I
4 think appropriately, on the primacy of microbiological
5 criteria for evaluation, that they actually have a
6 bloodstream infection related to the catheter, but I
7 think afterwards whether removed for the bad organisms
8 or left in for the easier organism, that it would be
9 important to document that they no longer have
10 bacteremia.
11 I'm not interested in between if they're
12 doing well, but I am interested at the conclusion of
13 therapy.
14 CHAIRMAN CRAIG: But you're going to
15 require a peripheral one then, right?
16 DR. RELLER: Yes, or I mean it could be --
17 well, I mean, if the catheter -- it has to be a
18 peripheral if the catheter is gone, for those that had
19 it removed for --
20 CHAIRMAN CRAIG: No, but I'm talking about
21 the catheter still being in place.
22 DR. RELLER: With the catheter still in
23 place, I mean, what I'd really like to have, Bill, at
24 the conclusion of therapy is one through the catheter
25 and one peripheral, for the catheters which are left

1 in place, which is most of the time going to be for
2 coag. negative Staph., because then I think you would
3 really get the information that you want that this
4 patient got Antibiotic X. They had a bacteremia
5 related to the catheter. They got a short course of
6 therapy, and the antibiotic works, and after stopping
7 therapy what was positive before and peripherally is
8 no longer there. That would be the best situation.
9 CHAIRMAN CRAIG: I guess my problem is I
10 think we've identified a population in the beginning
11 with our entry criteria of people that are going to
12 respond with fever and signs and symptoms. So we're
13 not talking about patients on steroids, patients with
14 renal disease. We're talking about people that can
15 respond to infection with signs of infection.
16 So in somebody that's doing perfectly well
17 at the end of therapy, I have great difficulty in
18 understanding why we need to do a blood culture in
19 that population.
20 Now, if you want to have as a second
21 indication for approval of the drug that it can
22 decolonize the catheter and the catheter is left in,
23 then I think it's perfectly fine to go ahead and get
24 a blood culture, but I don't think that has anything
25 to do with treating catheter related bloodstream

1 infection. It has to do with decolonizing the
2 catheter, which I think can be a second endpoint.
3 Someone could look at both of them, but I
4 don't think that they're related. Sure, if you don't
5 decolonize the catheter several times down the line
6 the patient may again get a secondary infection, but
7 I'm not sure that that has anything to do with the
8 ability of the drug to treat the infection.
9 DR. DANNER: I think we're looking though
10 at different diseases. I mean if you have a temporary
11 catheter in, a peripheral IV or a temporary central
12 catheter, those catheters when they're infected are
13 removed. You don't try to treat them in situ, and
14 your goal is, therefore, different.
15 You're removing the catheter, and then
16 you're trying to mop up whatever bacteremia or, you
17 know, sites that have been seeded or whatever with
18 your antibiotics.
19 There's another very large set of patients
20 that are being included in this type of trial, which
21 is a very different disease in a different set of
22 patients where you have a permanent catheter in that
23 has become colonized and has, through its becoming
24 colonized, caused an infection.
25 These catheters are not supposed to be

1 colonized with bacteria. It's not like some other
2 devices or medical devices where they're in non-
3 sterile sites. Intravascular catheters aren't
4 supposed to be colonized with bacteria, and your goal
5 there to me is to either decolonize them in treating
6 the infection; it's part of the thing you're using the
7 antibiotics for, or it's at least to knock down the
8 colony counts so much so that the remaining bacteria
9 are all locked in glycochalates and other things, and
10 it's not going to get back out and cause another
11 infection.

12 They're really two different entities.

13 CHAIRMAN CRAIG: But you're going to
14 change the study design. I mean any company that
15 wants to try and get an indication for the drug then
16 isn't going to look at long term catheters. You're
17 not going to get the data on long term catheters.
18 You're going after the short term because if you're
19 going to get a blood cu ture at the end and call that
20 as part of a failure of the therapy, then why look at
21 that population?

22 DR. DANNER You don't have to be any
23 better --

24 CHAIRMAN CRAIG: I think it's a secondary
25 endpoint that applies only to catheters that are

1 there, that the primary endpoint, which is the
2 clinical response and the ability to clear the
3 bacteremia that was related to the infection is the
4 primary thing.
5 There I think you can combine the data
6 from those that have the catheter removed in addition
7 to those that have the catheter staying in, but when
8 it comes to the ability as a secondary thing to be
9 able to clear the catheter, that should be a secondary
10 endpoint, and if you fail there, that's one of the
11 secondary things you're unable to do, but it shouldn't
12 result in you being a failure for the treatment of the
13 infection.
14 DR. DANNER Your goal when you treat a
15 catheter infection in situ and leave the catheter in
16 is to clear the infection and to clear that catheter
17 so that you can continue to use it and leave it in
18 place.
19 The study drug will not be put under any
20 higher burden than the comparator. The comparator
21 will also be -- that's a more difficult situation.
22 There's no doubt about it. If you remove the
23 catheter, your ability to clear these infections with
24 or without antibiotics is dramatically improved, but
25 the comparator is going to be put under the same

1 burden and criteria.

2 So, yeah, your failure rate will be

3 higher, and you will have some of those catheters you

4 leave in situ where they remain heavily colonized, and

5 you briefly clear the bacteremia, but then it recurs

6 and the person gets sick again, and you know then that

7 you have to remove the catheter.

8 Also, some of those people will fail to

9 clear the original infection, and the catheters will

10 come out in 48 or 72 hours because of persistent

11 fever, which a lot of people will use as criteria.

12 The comparator has the same -- you know,

13 that's why you have a comparator. Is the new drug

14 that you're looking at, is it equivalent to

15 conventional therapy?

16 **CHAIRMAN CRAIG:** Yeah, but with the

17 requirement of ten percent difference, I think at

18 least what I would see happening is it would be much

19 better to look at it in a population where you're

20 going to have very good results than looking at it in

21 a population where you're going to have a lower

22 response.

23 And so what would drive it then would be

24 where you would expect to get your good response, and

25 that was those where the catheters would be removed.

1 And so my way of designing the trial then
2 would be only look at those which the catheter is
3 removed.
4 On the other hand, if it's a secondary
5 endpoint and it's being looked at as a secondary
6 endpoint, as a separate thing, I have no trouble with
7 that. I agree that it is something that should be
8 looked at, and what you'd like with any drug is not
9 only to be able to treat the infection, but also to
10 eliminate colonization as a secondary endpoint, and
11 those to me are two different things that you're
12 asking the drug to be done, and they should be listed
13 in the criteria as two separate things.
14 But to fail on one and say, therefore, you
15 fail overall on everything, I think, is incorrect.
16 Dr. O'Fallon.
17 DR. O'FALLON: I'm very much behind what
18 you're saying. What bothers me is that there really
19 are two things going on here. One of them is how best
20 to treat the patient. No question about that.
21 But these studies are being done as to how
22 to assess the effectiveness of the therapy. We want
23 to know whether this is an effective therapy, and so
24 what we're really looking for are two different
25 things. One of them is can it clear the bugs, not

1 being a doc. Can it really get rid of it? That's
2 what they really want to know and we want to know, as
3 to whether this stuff is any good.
4 I keep hearing that the can't clear, you
5 can't expect it to clear the catheter, but I mean, as
6 a second endpoint. So it seems to me that's another
7 endpoint, but they're basically trying to figure out
8 whether this is effective in clearing bugs.
9 CHAIRMAN CRAIG: Yes. Dr. Reller.
10 DR. RAAD: I just wanted to say current
11 antimicrobials are not able to decolonize catheters
12 because of the dynamics of the whole environment of
13 biofilm.
14 We published in the JID, the Journal of
15 Infectious Disease, in 1993 a study on 354 catheters
16 from patients who were treated with antimicrobial
17 therapy, some of them for a long time period.
18 Colonization was almost universal, even after
19 treatment with vancomycin, and Ornafsen and Tenny had
20 the same data from, again, University of Maryland.
21 so for these long term catheters,
22 colonization is almost universal, and even with
23 treatment you're not able to decolonize these
24 catheters. You might kill some of the free floating
25 organisms for a short while, but ultimately these

1 organisms in biofilm would creep back again.

2 And hence to kind of expect -- this would
3 be ideal as another endpoint to look for an agent that
4 would decolonize catheters, but at this point we don't
5 have antimicrobials that are able to achieve this
6 endpoint, and this might be an interesting study
7 towards this specific endpoint, which would be quite
8 desirable.

9 And I think it's not going to be achieved
10 by an antimicrobial alone. You'll probably need
11 something else to break the biofilm.

12 CHAIRMAN CRAIG: Dr. Reller.

13 DR. RELLER: Some, perhaps many, of these
14 patients after initiation of therapy for presumed and
15 subsequently documented by criteria outlined catheter
16 related bloodstream infection, especially with
17 coagulation negative Staphylococci because it's so
18 common, won't get well because they've got other
19 things going on.

20 And then there's no objective assessment
21 about clearing what was documented to be present. I'm
22 uneasy. What you're suggesting, Bill, is that a
23 patient --

24 CHAIRMAN CRAIG: No, we said before --

25 DR. RELLER: -- could be clinically

1 well --

2 CHAIRMAN CRAIG: We said that if the
3 patient was not doing well we felt that follow-up
4 cultures were indicated in those patients. I'm
5 talking about somebody at the end of therapy that is
6 afebrile, doing well, and we decided at the beginning
7 in our entry criteria that we identified patients that
8 can respond to infection with signs of infection.

9 My feeling in that population is I'm not
10 going to yield anything at the test of cure, at the
11 end if they're doing well in terms of getting blood
12 cultures at that time.

13 DR. RELLER: Let me come to the bottom
14 line, Bill. Let's take two patients, not whether it
15 should be done or not, but this is what is actually
16 done in the study that I'm evaluating.

17 I have a patient who is clinically doing
18 well, had coag. negative Staph., got seven days of
19 therapy. Three days later they're still doing well.
20 I obtain a blood culture, and through the line and
21 peripherally, and they're both positive for coag.
22 negative Staphylococcus. It's the same one that was
23 there before.

24 Now I have a patient, another patient, who
25 is not perfectly well clinically, had coagulase

1 negative Staphylococcus from the two sites earlier,
2 and three days after stopping therapy, they're not
3 perfectly well, but their cultures are negative.
4 Who's the failure and who's the success?
5 CHAIRMAN CRAIG: Based on -- you said the
6 first one clinically --
7 DR. RELLER: The first one clinically
8 well, but their cultures are still positive. The
9 catheter was left in place for coag. negative Staph.
10 CHAIRMAN CRAIG: Yeah.
11 DR. RELLER: The other one was clinically
12 not well, complicated patient. They've got, you know,
13 congestive failure, other things, and they had coag.
14 negative Staph.
15 CHAIRMAN CRAIG: But, again, the initial
16 fever and everything was --
17 DR. RELLER: No, these patients were the
18 same at the start, the same at the start.
19 CHAIRMAN CRAIG: Yeah.
20 DR. RELLER: One appeared to get well and
21 their blood cultures are still positive. The other
22 one was not well, whether owing to the infection or
23 not, was not -- everything didn't go away.
24 CHAIRMAN CRAIG: That would be a clinical
25 failure, and it would probably end up as a -- since

1 you did do blood cultures, as a microbiologic success.

2 DR. RELLER: Okay.

3 DR. ARCHER: But, Barth, the first case

4 isn't going to occur. The data are that those

5 patients who don't clear the blood will be

6 symptomatic. That's the point.

7 DR. RELLER: See, I don't believe that.

8 DR. ARCHER: Dr. Raad presented data that

9 if the patients didn't have another reason, if they

10 cleared the blood and they became asymptomatic, fever

11 went away quickly, stopped therapy, they still were

12 fine; the chance of recovering organisms from both

13 those sites are exceedingly small. I don't know what

14 the exact numbers were, but very small.

15 DR. RELLER: I thought people with coag.

16 negative Staphylococcal bloodstream infection with

17 coag. negative Staph. treated with the catheter left

18 in place, that the failure rate was in the order of

19 30, 40 percent.

20 DR. MERMEL: It depends on how you look at

21 the data. I think what Sam showed -- I guess Sam's

22 still here -- is that there was a higher rate of

23 relapse, but in terms of looking at fever, you know,

24 over the days ahead leaving the catheter in, I don't

25 think there was a difference.

1 MR. RAAD: There was a 20 percent relapse
2 rate, but all of those had clinical manifestations of
3 infections. So, again, that's a small number. Twenty
4 percent came back with Staph. epi., multiple blood
5 cultures, but all of them had clinical manifestations
6 of infection.
7 I'm not aware -- if somebody had a real
a infection if it's catheter related, if they manifest
9 it in the first place, they should manifest with it
10 later on within the four to eight weeks' follow-up.
11 I don't see why they would not be able to manifest
12 with that kind of -- with the infection.
13 CHAIRMAN CRAIG: Well, Gary, I don't think
14 we're going to come up with a consensus on this --
15 (Laughter.)
16 CHAIRMAN CRAIG: -- last issue. I think
17 there's some that feel that repeats are not needed
18 even when the catheter is left in place, and there are
19 some that feel that when the catheter is left in
20 place, repeats are needed.
21 The possibility of having it **be** a
22 secondary objective in places where the catheter is
23 left in place, to have the organism removed, I'm just
24 not sure unless you want us to give you a vote as to
25 how we would do on it. I think it's not a consensus

1 among the group.

2 DR. CHIKAMI Well, and I think that if

3 committee members and certainly members of the

4 audience, and as I said, this is a draft document

5 which will be published in the Federal Register for

6 comments, and this is clearly a controversial issue

7 that we'll expect to get further comments on and try

8 to come to some resolution.

9 CHAIRMANCRAIG: Okay. Any last comments

10 that anybody wants to make?

11 If not, we'll break for lunch and we'll

12 start what, one o'clock or five after?

13 DR. RELLER: Bill.

14 CHAIRMAN CRAIG: Yes.

15 DR. RELLER: One o'clock, please.

16 CHAIRMAN CRAIG: One o'clock.

17 (Whereupon, at 12:05 p.m., the meeting was

18 recessed for lunch, to reconvene at 1 :00 p.m., the

19 same day.)

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

2 (1:00 p.m.)

3 DR. RELLER: Good afternoon. I'm Barth
4 Reller, at Duke University Medical Center, and the
5 acting chairman for this afternoon session. I'd like
6 to call the meeting to order and begin with the
7 conflict of interest statement by Rhonda Stover.

a DR. STOVER: The following announcement
9 addresses the issue of conflict of interest with
10 regard to this meeting and is made a part of the
11 record to preclude even the appearance of such at this
12 meeting.

13 Based on the submitted agenda for the
14 meeting and all financial interests reported by the
15 committee participants, it has been determined that
16 all interests in firms regulated by the Center for
17 Drug Evaluation Research which have been reported by
18 the participants present no potential for an
19 appearance of a conflict of interest at this meeting
20 with the following exceptions.

21 Dr. William Craig and Dr. Gordon Archer
22 are excluded from participating in today's discussion
23 and vote concerning Levaquin.

24 In addition, in accordance with 18 United
25 States Code 2.8(b), full waivers have been granted to

1 Dr. Robert Danner, Dr. Carl Norden, Dr. Julie
2 Parsonnet, and Dr. Keith Rodvold.
3 A copy of these waiver statements may be
4 obtained by submitting a written request to the
5 Agency's Freedom of Information Office, Room 12A30 of
6 the Parklawn building.
7 In addition, we would like to note that in
a 1996, Dr. Rodvold consulted with Johnson & Johnson
9 regarding levofloxacin. Further, he has had interests
10 in Eli Lilly, Rhone-Poulenc Rorer, Bayer Corporation,
11 and Bristol-Myers Squibb unrelated to their competing
12 products.
13 Although these interests do not constitute
14 a financial interest in the particular matter within
15 the meaning of 18 United States Code 2.8, they could
16 create the appearance of a conflict. However, it has
17 beendetermined, notwithstanding these interests, that
18 it is in the agency's best interest to have Dr.
19 Rodvold participate in the committee discussions
20 concerning Levaquin.
21 Further, several of our committee members
22 have had interests related to Levaquin that we believe
23 should be disclosed. FDA believes that it is
24 important to acknowledge these participants'
25 involvement so that their participation can be

1 objectively evaluated.

2 Dr. Carl Norden previously served as a
3 consultant for Ortho-McNeil concerning levofloxacin
4 for different indications.

5 Dr. Rodvold previously participated in a
6 pharmacokinetic study of levofloxacin and
7 ciprofloxacin in a lung penetration of levofloxacin
a and trovafloxacin sponsored by Ortho-McNeil.

9 In the event that these discussions
10 involve any other products or firms not already on the
11 agenda in which an FDA participant has a financial
12 interest, the participants are aware of the need to
13 exclude themselves from such involvement, and their
14 exclusion will be noted for the record.

15 With respect to all other participants, we
16 ask in the interest of fairness that they address any
17 current or previous financial involvement with any
18 firm whose products they may wish to comment upon.

19 DR. RELLER: Thank you, Rhonda.

20 I'd next like to have -- even though some
21 were present this morning, we have new consultants for
22 this afternoon -- to next have each of the members and
23 consultants for the advisory committee meeting to
24 identify themselves.

25 Please.

1 DR. O'FALLON: Judith O'Fallon,
2 Biostatistics, Mayo Cancer -- May Clinic.
3 DR. RODVOLD Keith Rodvold, Colleges of
4 Pharmacy and Medicine, University of Illinois at
5 Chicago.
6 DR. CHRISTIE-SAMUELS: Celia Christie,
7 Department of Child Health, University Hospital of the
8 West Indes, Jamaica.
9 DR. SOPER David Soper, Medical
10 University of South Carolina.
11 DR. DANNER: Bob Danner, Critical Care
12 Medicine Department, NIH.
13 DR. STOVER: Rhonda Stover, FDA.
14 DR. RELLER: Julie.
15 DR. PARSONNET: Julie Parsonnet, Division
16 of Infectious Diseases, Stanford University.
17 DR. NORDEN: Carl Norden, Infectious
18 Disease, Cooper Hospital, University of New Jersey
19 Medical School.
20 DR. BATTINELLI: Dave Battinelli, Vice
21 Chairman, Education, Boston University School of
22 Medicine.
23 DR. WHITNEY: Cindy Whitney, CDC, Atlanta.
24 DR. COX: Edward Cox, Medical Officer,
25 FDA.

1 DR. HOPKINS: Bob Hopkins, Medical Team
2 Leader, FDA.
3 DR. GOLDBERGER: Mark Goldberger, the
4 Director of the Division of Special Pathogens.
5 DR. KWEDER: I'm Sandra Kweder. I'm the
6 Acting Director of Office of Drug Evaluation IV.
7 DR. RELLER: Thank you.
8 Next on our agenda is our open public
9 hearing. Are there any comments that are submitted
10 that wish to be made?
11 Yes, Dr. Bell.
12 DR. BELL: Thank you.
13 I am David Bell from the Centers for
14 Disease Control and Prevention in Atlanta, and my
15 position there is to coordinate CDC's antimicrobial
16 resistance activities.
17 I'd like to say that from a public health
18 point of view, CDC is delighted that the
19 pharmaceutical industry is developing and seeking to
20 market new drugs for the treatment of resistant
21 infections. We very much depend on these new drugs to
22 help us out of the predicament that we are now in with
23 drug resistant organisms.
24 However, the potential for overuse of the
25 new drugs hastening the developing of resistance and

1 shortening the new drugs' useful lifetime must also be
2 considered in the approval process.
3 In the case of a drug approved for
4 treatment of penicillin-resistant pneumococcal
5 pneumonia, there is a potential for overuse because of
6 the widespread confusion among clinicians regarding
7 the distinction between intermediate resistant and
8 fully resistant pneumococci.
9 For pneumonia, experts generally believe
10 that only fully resistant pneumococcimay not reliably
11 respond to penicillin or cephalosporins. Pneumonia
12 caused by pneumococci classified as intermediate
13 resistant is readily treatable with penicillins or
14 cephalosporins, and fluoroquinolones offer no
15 advantage.
16 The confusion is exacerbated by the fact
17 that the term "nonsusceptible" is used to describe
18 both intermediate resistant and fully resistant
19 strains, and that these break points were developed
20 for use in the treatment of meningitis, and so are
21 overly conservative when applied to the treatment of
22 pneumonia.
23 Since this is the first application for
24 approval of an antibiotic for penicillin-resistent
25 pneumococcal pneumonia, this unfortunate confusion

1 must be addressed. If a clinician receives a culture
2 result from a patient with pneumonia, indicating
3 pneumococciwithintermediate resistancetopenicillin
4 or cephalosporins, the clinician should not be under
5 the impression that he or she needs to use an
6 alternative drug.
7 For out-patient empiric treatment of
8 community-acquiredpneumonia, clinicians may choose to
9 use a fluoroquinolone if they wish to provide coverage
10 against both atypical organisms and full penicillin-
11 resistant pneumococci.
12 However, they should not be given the
13 impression that fluoroquinolones are necessary or
14 advantageous in treating pneumonia due to pneumococci
15 with penicillin MICs below two. Some experts would
16 say including two, which are still the great majority
17 of invasive pneumococci in the United States.
18 Other drugs, such as macrolides still
19 offer effective empiric treatment for most cases of
20 community-acquired pneumonia.
21 Now, I want to emphasize that CDC is not
22 at all opposing this proposed indication if it is
23 otherwise acceptable to the committee. In fact, as I
24 mentioned, we are delighted that pharmaceutical
25 companies are bringing forth drugs to treat these

1 resistant organisms.

2 However, it is important to prolong the

3 useful life of these valuable new drugs.

4 Fluoroquinolone use will over time lead to resistance

5 among respiratory and gastrointestinal flora,

6 particularly in a situation like this where drug

7 overuse may result from honest confusion among

8 clinicians regarding microbiologic nomenclature.

9 The phrasing of the indication, a comment

10 in the label, and especially promotional materials

11 should take steps to assist clinicians and patients by

12 reducing the potential for overuse due to this

13 confusion.

14 DR. RELLER: Thank you, Dr. Bell.

15 Are there any questions or comments for

16 Dr. Bell?

17 (No response.)

18 DR. RELLER: Dr. Mark Goldberger, who

19 directs the Division of Special Pathogen Immunologic

20 Drug Products at the agency, will present the FDA's

21 introduction.

22 DR. GOLDBERGER: Thank you.

23 I'd like to extend my welcome to Dr.

24 Reller, advisory committee participants, members of

25 R.W. Johnson Pharmaceutical Company, and all the other

1 participants in today's meeting.

2 As some of you or many of you may

3 remember, we had an advisory committee almost exactly

4 a year ago devoted largely to the issue of looking at

5 the development of drugs for resistant indications,

6 and in fact, information about the indication being

7 sought today and the underlying data was presented by

8 the company at that time, and in fact, there was an

9 opportunity to get some advice about what the

10 committee thought at that point in time might seem to

11 be a reasonable amount of data to gain an indication

12 such as that which the company is seeking today.

13 Some of the issues that came up then were

14 the potential value of preclinical data, PK/PD data,

15 the demonstrated effectiveness of the drug in

16 susceptible isolates of pneumococci in patients, as

17 well as some number of resistant patients, some number

18 of resistant isolates actually in patients who were

19 treated.

20 There was a little bit of discussion about

21 the numbers, and it always becomes difficult to come

22 down to an exact number, but there were comments along

23 the lines of ten to 15 cases, some bacteremic cases,

24 et cetera, and depending on how much overall data

25 there was against the pneumococcus.

1 We have been working with R.W. Johnson
2 Pharmaceutical Company. We believe the advice we've
3 provided has been consistent with that provided by the
4 committee a year ago, and we hope, therefore, that
5 there is sufficient information here to allow a
6 reasonable discussion of the issue in question.
7 I would also like to extend my thanks to
8 R.W. Johnson for the effort that they have put in to
9 collect the amount of data that we have today.
10 I think one other issue that I think ought
11 to be brought up in terms of what was discussed a year
12 ago was that there was interest by committee members
13 in understanding how the pattern of penicillin
14 resistance to pneumococcus, as well as potentially
15 quinalone resistance might change over time, and there
16 were issues about whether there needed to be ongoing
17 data collection.
18 And it may well be that that's also an
19 issue that will need to be discussed during this
20 afternoon's meeting.
21 So I won't take up anymore time now. I
22 would just like to thank everyone here who's
23 participating in the meeting, and I hope we will have
24 a useful discussion about this issue.
25 Thank you.

1 DR. RELLER: Undergirding this afternoon's
2 discussion and the reason for this meeting very much
3 hinges on the whole issue of where we are with regard
4 to resistance in this important pathogen and what the
5 trends are, and to update us on that Dr. Cynthia
6 Whitney from the CDC will do that for us.
7 Cynthia.
8 DR. WHITNEY: Good afternoon. I'd like to
9 spend a few minutes just reviewing epidemiology of
10 antimicrobial resistance in regards to Streptococcus
11 pneumoniae. I'll give you some of the latest
12 information, then spend a couple of minutes just
13 reviewing the literature about whether resistance
14 matters in terms of patient outcomes with regard to
15 pneumonia, and then spend the last couple of minutes
16 focusing on what we know about resistance to -- the
17 epidemiology of resistance to fluoroquinolones.
18 Drug resistance Strep. pneumoniae really
19 became in the United States in the 1990s. Throughout
20 the 1980s, there really was just a small amount of
21 intermediate levelresistance, but in the early 1990s,
22 we saw the emergence of high level penicillin
23 resistance, and that trend has continued to increase.
24 CDC uses a system called the active
25 bacterial core surveillance, or ABCS, to track drug

1 resistant Streptococcus pneumoniae. This is a system
2 that started back in 1994. It currently operates in
3 eight states, which are shown here.
4 It's a population based system that tracks
5 pneumococcal disease in a total population of about 17
6 million persons.
7 This is how ABCS works. ABCS is an
8 active, population based surveillance system for
9 Strep. pneumoniae. A case is defined as a situation
10 in which pneumococcus is isolated from a general site
11 in a resident of one of the surveillance areas.
12 To identify cases, surveillance personnel
13 contact all area clinical laboratories, andthentwice
14 a year they conducted audits of laboratory records to
15 insure complete reporting.
16 Isolates are collected and sent to
17 reference laboratories where they undergo
18 susceptibility testing and serotyping. In addition,
19 surveillance personnel collect case patient
20 information which includes demographic and clinical
21 data.
22 Here are the results from 1998. In 1998,
23 decreased susceptibility of cotrimoxazole or
24 trimetheprim sulfa was the single most frequently
25 identified resistance. About 24 percent of isolates

1 had decreased susceptibility to penicillin. It was
2 about half a high level resistance and half
3 intermediate in our data.
4 Between 14 and 18 percent of isolates had
5 decreased susceptibility of cefuroxime, amoxicillin,
6 erythromycin, or cefotaxime. There were only a small
7 number of isolates that were resistant the
8 levofloxacin or trovafloxacin, which were the two
9 fluoroquinolones in our panel, and we have not yet
10 identified an isolate with decreased susceptibility to
11 vancomycin.
12 Over the last four years, we have seen an
13 increase in many of the resistances. Between 1995 and
14 1998, we saw a significant upward trend for
15 penicillin, cefotaxime, erythromycin, cotrimoxazole,
16 and between 1995 and 1997 for ofloxacin.
17 In addition, we've seen a significant
18 upward trend in the proportion of isolates that are
19 not susceptible to at least three different drug
20 classes.
21 Interestingly, when you look at the
22 proportion of isolates that are pan susceptible,
23 meaning that they're susceptible to every drug we have
24 in our panel, those proportion of isolates has stayed
25 relatively stable at about 60 percent.

1 So what we're seeing is that there's a
2 fairly large population of isolates that remain
3 susceptible to all agents and are probably easily
4 treated, but there is a population of isolates that
5 have at least one resistance that are gaining
6 additional resistances. So the problem of cross-
7 resistance is increasing.
8 Let me just illustrate this issue of
9 cross-resistance another way. In this table, I've
10 taken the ABCS isolates and grouped them by whether
11 they're penicillin susceptible, penicillin
12 intermediate, or penicillin resistant, and the numbers
13 in each of these columns here are the proportion of
14 isolates that are resistant to the drugs here.
15 So, for example, in the population of
16 penicillin susceptible isolates, no isolates are
17 resistant to ceflotaxime, and very few isolates are
18 resistant to either clindamycin, tetracycline,
19 erythromycin, cotrimoxazole, levofloxacin, or
20 trovafloxacin.
21 So if you've got a penicillin susceptible
22 isolate, you can choose from among a variety of agents
23 that will probably be effective. This is not the case
24 if you've got a penicillin-resistant strain, however.
25 I'd like to focus your attention in this

1 last column. You've got penicillin-resistant isolate.
2 Over 40 percent will be resistant to cefotaxime, 12
3 percent to clindamycin, a quarter to tetracycline,
4 almost two-thirds to erythromycin. Almost all will be
5 resistant to cotrimoxazole. Levofloxacin and
6 trovafloxacin, however, will remain highly effective
7 against these isolates.
8 One of the hallmarks of the epidemiology
9 of antimicrobial resistant pneumococcus is that there
10 really is geographic variation. In these figures I've
11 got penicillin, susceptibility to penicillin and
12 erythromycin by our ABCS areas.
13 The two areas from the southeast United
14 States, Tennessee and Georgia, almost always have the
15 biggest problems with resistance, and this has been
16 reported in other studies.
17 Not only does resistance vary by
18 geographic area, but it really also varies by patient
19 population. This is a figure showing the proportion
20 of isolates that are not susceptible to penicillin
21 just within the State of Connecticut for 1997. I
22 think there are 18 individual institutions here that
23 have had at least ten isolates during that time.
24 As you can see, the overall prevalence in
25 the state was 18 percent at that time, and we've got

1 a range here from almost no resistant isolates to over
2 40 percent.
3 So your patient population really can
4 influence the prevalence of penicillin-resistant
5 pneumococcus that we see.
6 So what is the relevance of that? Well,
7 I think if you have been reading the literature
8 lately, there are a lot of different reports from a
9 lot of different surveillance systems, and you'll see
10 different numbers based on the patient populations
11 that those samples are drawn from.
12 For example, to illustrate this point,
13 I've taken isolates here from TSN, Century, and ABCS.
14 These are three large U.S. surveillance systems that
15 collect -- that have microbiologic data, and I've
16 taken just blood isolates, and from the same time
17 period, which is February to June, 1997.
18 At this point in time ABCS had 24 percent
19 decreased susceptibility to penicillin. TSN had
20 almost 30 percent, and Century had 41 percent. so you
21 can see even controlling for time and site of
22 isolation, you can get a pretty wide variety of
23 results based on the patient population that your
24 sample comes from.
25 One of the factors that we know that

1 affects the prevalence of drug resistance are
2 demographic factors. Penicillin resistance is much
3 more common in young children.
4 Here the percent of nonsusceptible
5 isolates by age and by race, and children for
6 penicillin have a higher prevalence of nonsusceptible
7 isolates than older persons and the elderly.
8 And also white persons, which are
9 represented here by the red bars, in general, tend to
10 have more resistance or are more likely to have
11 resistant isolates than black persons.
12 This is data from 1998. If I showed you
13 this data from 1995, the ratio gap would be much
14 larger than it is here.
15 One of the issues to discuss today is, you
16 know, we're really focusing on community-acquires
17 pneumonia, and I'm showing you data from sterile site
18 surveillance systems. If we were to have data from
19 surveillance systems that included non-sterile site
20 isolates, are probably going to show you a higher
21 prevalence of drug resistance.
22 In this table, I'm showing data from four
23 surveillance systems that included both blood isolates
24 and the lower respiratory tract isolates, and if you
25 compare these two columns, in all four of these

1 studies the prevalence of penicillin nonsusceptible
2 isolates was higher for lower respiratory tract
3 isolates than for blood isolates, and this is true for
4 both of these studies from the USA and also from
5 Norway, where the prevalence of penicillin resistance
6 is very low, and from Taiwan where it's very high.
7 So I'm pointing out these things just
8 because when we see some data later today, you may see
9 slightly different numbers, and these are some of the
10 reasons that you can see slightly different numbers
11 from different surveillance systems.
12 Now I'd like to shift gears and talk about
13 whether drug resistance matters in terms of patient
14 outcome. We know from case reports of patients with
15 meningitis that with pneumococcal meningitis, yes, it
16 does matter, and NCCLS has set their cutoffs for
17 intermediate resistance based on that clinical
18 information.
19 But it has been a much harder question to
20 answer for patients with pneumococcal pneumonia. The
21 first studies that look at this were by Pallares and
22 Friedland, and in both of these studies they found no
23 difference between patients that had either
24 intermediate or resistant isolates compared to
25 patients with susceptible isolates.

1 In three published studies that came after
2 that, they also found no difference, and in each of
3 these studies there was fairly small numbers in terms
4 of the percent of isolates that were resistant.
5 In two recent studies that are both in
6 press, there has been shown an increase in mortality
7 when you compared isolates that were resistant to
8 isolates that susceptible, and I'm going to just
9 present some data now from this Feikin study, which is
10 a CDC study.
11 In the Feikin study, what we did was focus
12 on deaths that occurred in hospitalized patients after
13 hospital day four, and the reason the study was done
14 this way is because of the findings from this **data**
15 from Robert Austrian that was published back in 1964.
16 With this data, you can see that in
17 untreated patients and patients that received serum
18 therapy from long ago and in patients that were
19 treated with penicillin, there really is no difference
20 in outcome before hospital day four. Many patients
21 will die of their pneumococcal disease no matter what
22 treatment they're given.
23 After hospital day four, however, it
24 appears that having an effective therapy really can
25 make a difference.

1 So Daniel Feikin really focused on deaths
2 that occurred after hospital day four. Here are his
3 final results of the logistic regression model that
4 adjusted for things like age, race, area, and the
5 presence of underlying diseases.
6 What Dr. Feikin found is that when you
7 compare isolates that are either penicillin
8 intermediate or even have MICs of two to the record
9 group, which is susceptible isolates, you really see
10 no difference in the risk of death between these
11 groups.
12 However, when you focus on the group of
13 patients that had penicillin MICs of greater than or
14 equal to four, there's a very high odds ratio of 7.1,
15 which is statistically significant, compared to the
16 reference group of penicillin susceptible isolates.
17 Here's the same analysis looking at
18 cefotaxime. Again, if you look at cefotaxime
19 intermediate isolates, there's really no difference
20 compared with the reference group of susceptible
21 isolates. It's among those that are defined as
22 cefotaxime resistant according to NCCLS where you see
23 an elevated odds ratio for late deaths.
24 So what does this mean in terms of the
25 prevalence of isolates where we may see treatment

1 failures occur?

2 This is again 1998 data from ABCS, and if
3 you look at all nonsusceptible isolates defined by
4 NCCLS, there's about 24 percent of isolates, and in
5 this group of patients we probably would see
6 meningitis treatment failures if you tried to use
7 penicillin to treat these patients.

8 However, if you look at the range in which
9 pneumonia treatment failures might occur, it's
10 somewhere between 14 percent and seven percent,
11 depending on whose study you look at. So it's really
12 a much smaller proportion of isolates that we're
13 concerned about for pneumonia treatment failures.

14 Here are the data for defotaxime. Again,
15 14 percent have decreased susceptibility defined as an
16 MIC greater than one according to the NCCLS cutoffs.
17 These are the patients that might have meningitis
18 treatment failures. Only about six percent might have
19 a pneumonia treatment failure if you tried to treat
20 pneumonia patients with cefotaxime.

21 In the last minute or two, I just want to
22 summarize some of the latest data on fluoroquinolone
23 resistance. There was a recent paper by Chen, et al.,
24 that did a nice study of fluoroquinolone resistance in
25 Canada, and I just want to summarize this for you.

1 In this paper, they looked at the
2 prevalence of fluoroquinolone resistance by age and
3 found that all of the isolates occurred in these two
4 age groups, either 15 to 64 or 65-plus years. They
5 found no fluoroquinolone resistance among children.
6 If you look at the prevalence of
7 resistance in those two age groups over time, they
8 really didn't have any isolates before 1993, and
9 between 1994 and 1998 they've had a steady increase in
10 the prevalence of resistant isolates.
11 I should note that in this study they used
12 an interesting definition of what they were calling
13 fluoroquinolone resistant. It was a definition of
14 having a ciprofloxacin MIC of at least four micrograms
15 per mL.
16 In this figure you can see that the
17 increase in use of fluoroquinolones in the population
18 seems to correlate with the increasing prevalence of
19 fluoroquinolone resistance.
20 Chen and colleagues did a logistic
21 regression analysis looking for predictors of
22 fluoroquinolone resistance. What they found is that
23 age, by increasing decade, was a predictor of
24 fluoroquinolone resistance; that there was an increase
25 in resistance over time; and that if you lived in

1 Ontario you were also more likely to have a resistant
2 isolate.
3 In addition, isolates from respiratory
4 secretions were more likely to be fluoroquinolone
5 resistant. In addition, if you had an isolate that
6 was resistant to penicillin, an MIC of greater than
7 two, you also were more likely to have a
8 fluoroquinolone resistant strain, and this is really
9 the first study that's been published that has
10 illustrated that there might be a cross-resistance
11 between fluoroquinolones and penicillin.
12 Here are some of the recent U.S. data from
13 ABCS, looking at some of these same issues. I have
14 found that in the last few years, we have seen
15 increasing resistance to the fluoroquinolone.
16 Between 1995 and 1997, we included
17 ofloxacin in our susceptibility testing panels, and we
18 saw an increase of about 50 percent in the proportion
19 of isolates that were not susceptible to this agent.
20 In 1998 and 1999, we've had levofloxacin
21 and trovafloxacin in the panel. The proportion of
22 isolates that have decreased susceptibility to these
23 two agents remains low, but if you look between the
24 two years, there is a hint that it may be increasing.
25 The 1999 data is really only about 50 percent complete

1 at this time. So I think we have to consider these
2 results preliminary, but I think it is concerning that
3 we are seeing a little bit of increase in the
4 proportion of resistant isolates.
5 In the U.S. data, we also are finding this
6 association with age. Among persons less than 18,
7 none of the isolates have decreased susceptibility to
8 levofloxacin or trovafloxacin. All of the isolates
9 occur, with decreased susceptibility, occur among
10 adults who have an indication for this drug.
11 If you look at the prevalence of decreased
12 susceptibility to these two drugs by its relationship
13 to penicillin susceptibility, there does seem to be a
14 little bit of a relationship. If you just look at the
15 levofloxacin numbers, if you have a penicillin
16 susceptible isolate, only .1 percent have reduced
17 susceptibility to levofloxacin; with penicillin
18 resistance 1.2 percent, have decreased susceptibility
19 to levofloxacin.
20 Again, the overwhelming majority of
21 isolates are susceptible to these agents, but it's a
22 little bit concerning that we may be seeing the first
23 signs of some cross-resistance, but again, numbers are
24 small. So we'll just have to wait and see.
25 And just to close, I want to present some

1 data that I think is a little bit concerning and
2 illustrates the problems that we might see with
3 overuse of these agents.
4 This involves an outbreak of multi-drug
5 resistant Streptococcus pneumonia that have been
6 occurring in New York City over the last few years.
7 The outbreak started in the winter of 1995 and 1996.
8 At that time, there were seven cases of serious
9 pneumococcal disease, either pneumonia or sepsis, in
10 a long term care facility, which I'll call Long Term
11 Care Facility A. There were two deaths, and the
12 infections really were clustered among 77 residents on
13 two wards. There were no infections among the staff
14 or residents on other wards with the outbreak strain.
15 The outbreak strain was a serotype 23F.
16 That appears to be somewhat related to the Spanish 23
17 clone. When this outbreak first started, it was
18 resistant to penicillin, cefuroxine, erythromycin,
19 quindomycin, chlorophenocol, trimetheprim sulfa, and
20 tetracycline. It was intermediate to ceftriaxoline
21 and meropenem, and was only susceptible to ofloxacin
22 with rifampin and vancomycin. So you can see this is
23 a very concerning strain, probably one of the most
24 highly resistant strains I've ever seen.
25 The New York City Health Department did a

1 carriage study and found that there was a carriage of
2 nine percent among the residents of this outbreak
3 strain.
4 The Health Department, in conjunction with
5 the long term care facility, did an intervention to
6 try and control this outbreak. They gave everybody
7 who was not immunizedpolysaccharide vaccine, and they
8 gave residents on two wards that were involved
9 ofloxacin and rifampin for a seven day course.
10 This may seem like a pretty radical
11 intervention, but this has been done in other
12 outbreaks in long term care facilities where people
13 have tried to eradicate the strain by giving
14 antibiotic therapy.
15 These did follow-up carriage studies. At
16 one week there was one percent carriage of
17 pneumococcus. At four weeks there was two percent
18 carriage, and by eight weeks, there was six percent
19 carriage.
20 So if you compare this to the original
21 nine percent, there was initially some decrease in
22 carriage, but then the carriage came back, and in
23 addition, all of the post intervention multi-drug
24 resistance outbreak strains now were rifampin
25 resistant, and at week eight there was one isolate

1 that was also now ofloxacin resistant.

2 Well, this ofloxacin resistant strain has
3 persisted. Between 1996 and September 1998, there
4 have been four sporadic cases due to this
5 fluoroquinolone resistant strain, and over the last
6 winter, there has been another cluster of disease
7 where we see five cases due to the fluoroquinolone
8 resistant strain in residents of several wards,
9 including wards that weren't originally involved.

10 Overall carriage of the outbreak strain is
11 now 5.6 percent, and no staff seem to be carrying it.
12 The carriage all seems to be among the residents.

13 Since the outbreak strain in the post
14 intervention area has a levofloxacin MIC of great than
15 or equal to 16 and a trovafloxin MIC of two; so what
16 we've seen is a situation where there was widespread
17 use of ofloxacin, and now we've developed a resistant
18 strain.

19 So just to sum up my main points, the
20 recent data suggests that multi-drug resistant Strep.
21 pneumoniae is increasing. One of the hallmarks of
22 drug resistant Strep. pneumoniae is that there's
23 marked geographic variation in the prevalence, and
24 also there's marked variation between patient
25 populations.

1 For most drugs other than
2 fluoroquinolones, isolates from children and non-
3 sterile sites are more often drug resistant.
4 Penicillin or cefotaxime are probably
5 effective for pneumonia due to isolates that are
6 intermediate to these drugs, and half of all
7 nonsusceptible isolates are in a range where treatment
8 failures may occur. In other words, about half of the
9 isolates that we see that are nonsusceptible are
10 highly, highly resistant.
11 Fluoroquinolone resistanceisunusual, but
12 may be increasing, and finally, we've seen some
13 evidence, such as the outbreak and the fact that
14 resistance only occurs among in adults that suggests
15 that fluoroquinolone use is leading to resistance in
16 some cases.
17 Are there any questions?
18 DR. MURRAY: Hi, Cindy. On the mortality
19 data for Feikin, I think you mentioned this, but I
20 faded out for a minute. So that was controlled for
21 severity of underlying disease like AIDS or being on
22 steroids or having disease that might be known to be
23 associated with higher mortality and penicillin
24 resistance, both?
25 DR. WHITNEY: Right. We were able to

1 control for underlying conditions. We weren't able to
2 control for severity of illness at presentation.
3 DR. NORDEN: Cindy, in the Feikin study
4 what was the age range? I just missed it. You
5 probably said it.
6 DR. WHITNEY: Among adults it was over 18,
7 just persons hospitalized with pneumonia, and they
8 excluded patients with nodes of co-pneumococcus
9 (phonetic).
10 DR. NORDEN: Thank you.
11 DR. RELLER: Any other discussion of Dr.
12 -- yes, Celia.
13 DR. CHRISTIE-SAMUELS: Regarding the
14 hospital data that you showed us with about 40
15 hospitals, there was one hospital that was an outlier
16 or something like 40, 50 percent. What kind of
17 hospital was that? Can you say?
18 PARTICIPANT: Can you repeat the question?
19 DR. WHITNEY: Yes, I think you're asking
20 about the data that I showed from Connecticut where
21 there's this wide range of hospitals. I'm actually
22 not familiar with that hospital per se. I can't tell
23 you for sure.
24 DR. CHRISTIE-SAMUELS: Thank you.
25 DR. RELLER: Dr. Soper.

1 DR. SOPER: Do you have a sense as to what
2 proportion of resistance leads to a modification of
3 physician behavior and the prescribing of a different
4 antimicrobial? I mean, when you see physicians that
5 are changing their prescribing habits, is it in
6 response to a five percent increase in resistance, a
7 15 percent?
8 DR. WHITNEY: That's a very good question,
9 and I don't have a number for you. I would imagine if
10 a physician is aware that resistance is problem in
11 their community, they'd change their behavior, and if
12 they don't think it is, they don't, but I don't have
13 numbers for you on that.
14 DR. SOPER: I agree with you, and I think
15 proportionately, I'm not sure that any of us have set
16 that threshold. So even though there may be a
17 relatively low proportion of resistance in your
18 community, the fact that information is out there that
19 Streptococcus pneumoniae is resistant may be changing
20 behavior across the country.
21 DR. WHITNEY: Yeah. So I think, yeah, I
22 would agree, and I think our opportunity to use -- to
23 promote judicious antibiotic use in terms of using
24 narrow spectrum and things like that is we really need
25 culture information, andwithpatients with pneumonia,

1 the diagnostics are not very sensitive. So I think
2 it's a real problem.
3 DR. RELLER: Dr. O'Fallon.
4 DR. O'FALLON: Just a question about those
5 logistic regression. Were there single variable
6 models or was it a multivariate model that you were
7 showing us? You were showing the factors that are
8 associated with resistance.
9 DR. WHITNEY: Both the Feikin model and
10 the model from the Candida paper there were
11 multivariate models.
12 DR. RELLER: Mark.
13 DR. GOLDBERGER: On the Feikin study, so
14 that was you said hospitalized patient --
15 DR. WHITNEY: Yes.
16 DR. GOLDBERGER: -- who received
17 intravenous penicillin.
18 DR. WHITNEY: We don't know the treatment
19 for most of those patients. That's right. So we
20 can't say for sure that the patients that died failed
21 -- were given penicillin and, therefore, died because
22 they failed penicillin therapy. That's right. We
23 don't know that for those patients.
24 DR. GOLDBERGER: So then it's possible
25 that penicillin susceptibility or resistance in that

1 study sort of reflects the status of the patient and
2 other factors rather than the antibiotic therapy they
3 actually got?
4 DR. WHITNEY: In some cases that may be
5 true. I think these outcome studies have been
6 extremely difficult because of that factor. I mean,
7 to look at a -- there has been some data that suggests
8 if you get a patient on the correct therapy up front
9 they're going to do better, and in this cases, since
10 it was all culture confirmed patients, it's doubtful
11 that they would have stayed on inappropriate therapy
12 for the whole course of their illness.
13 It may just be that at the time that study
14 was done the fluoroquinolone were not in wide use. So
15 it is likely that a lot of the patients with resistant
16 strains were given either beta lactems or macrolide,
17 and we know because of cross-resistance between beta
18 lactems and macrolides they may have failed either
19 therapy.
20 DR. RELLER: Any other discussion for Dr.
21 Whitney?
22 (No response.)
23 DR. RELLER: Thank you very much.
24 We'll then move to the sponsor
25 presentation. Dr. Graham Burton will provide the

1 introduction, followed by Drs. Bush and Corrado.
2 The request has been made and honored that
3 the sponsor be enabled to make their entire
4 presentation, and then we'll have ample time for
5 discussion of all of the issues generated therefrom.
6 Dr. Graham Burton.
7 DR. BURTON: Good afternoon, Mr. Chairman,
8 members of the advisory committee, colleagues at the
9 Food and Drug Administration, ladies and gentlemen.
10 My name is Dr. Graham Burton. I am Vice
11 President of Clinical Research and Regulatory Affairs
12 at the R.W. Johnson Pharmaceutical Research Institute.
13 Now, that's a little bit of a mouthful.
14 So if you hear myself **and** my colleagues refer to PRI,
15 that's the institution which we represent this
16 afternoon.
17 I'd like to thank our colleagues at the
18 FDA for inviting us along here this afternoon to
19 present you the data that underpins our supplemental
20 new drug application on the use of levofloxacin in the
21 treatment of community-acquired pneumonia associated
22 with penicillin resistant and intermediate strains of
23 Streptococcus pneumoniae.
24 We will all use the name of this organism
25 as the pneumococcus or Streptococcus pneumoniae

1 interchangeably this afternoon. So please bear with
2 us for correctness sake.
3 May I just provide a short background to
4 this application? Levofloxacin received approval by
5 the FDA for marketing in December 1996, following a
6 worldwide development program that involved us at PRI
7 in the United States, Hoechst Marion Rousseau in
8 Europe, and Daichi in Japan.
9 The original approval was for the
10 treatment of skin, urinary tract, and respiratory
11 infections, including community acquired pneumonia,
12 due to a wide variety of organisms, and these
13 organisms included the pneumococcus based upon studies
14 involving over 650 patients treatment with
15 levofloxacin in our pivotal trials.
16 The labeling at that time included the
17 spectrum of activity of the following organisms
18 isolated from the patients with community acquired
19 pneumonia and were based upon a microbiological
20 eradication rate of 95 percent and a clinical success
21 rate of 95 percent from our pivotal clinical trials.
22 Now, following approval at the end of
23 1996, we had -- the clinical program stated in '91.
24 We have approval in '96, and we've noticed from three
25 of the cases in the original NDA that were fully

1 resistant to penicillin that levofloxacin worked.

2 And so we started the clinical program for

3 community acquired pneumonia and the investigation

4 prospectively and the collection of these cases during

5 the process of the NDA examination in 1996, and we've

6 submitted the supplement earlier this year.

7 We've based a lot of what we've done in

8 collaboration with our colleagues at the FDA and also

9 bearing in mind the information that you yourselves

10 gleaned and brought into the public focus at the two

11 open committee meetings that have been held.

12 Sine marketing throughout the world has

13 taken place, we estimate that there have been 100

14 million courses, and by courses I mean treatment

15 courses of levofloxacin throughout the world, between

16 ten and 14 days each, ten million of which have been

17 used in the United States.

18 The only additional activity that we've

19 had is the addition of an extra indication just about

20 a year ago.

21 So why did we do this program? We've

22 noticed that there's been an increasing penicillin

23 resistance of the pneumococcus identified, and this is

24 increasingly so.

25 Community acquired pneumonia is a common

1 disease. I think we all recognize that, and as I
2 mentioned earlier, we did identify a small number of
3 cases where levofloxacin had eradicated the penicillin
4 resistant organism.

5 So in close cooperation with the FDA, we
6 embarked on our prospective program and have collected
7 the cases of both fully resistant organisms and
8 intermediate strains for submission.

9 Now, the organization of our presentation
10 this afternoon, first of all, we'll start with a
11 microbiological overview by Dr. Karen Bush, who is our
12 team leader for the anti-infective agents. She will
13 describe data that leads us to believe, of course,
14 that the penicillin resistance of the pneumococcus is
15 continuing to increase, and you've heard about that.

16 That clinical isolates of thepneumococcus
17 that we have gathered from around the world remain
18 sensitive to levofloxacin in more than 97 percent of
19 cases.

20 And that levofloxacin is equally active *in*
21 *vitro* against the resistant pneumococcus and wild
22 strains that we have tested to date.

23 And she will also discuss the mechanisms
24 of resistance, comparing and contrasting levofloxacin
25 with other antimicrobial agents.

1 Following Dr. Bush, Dr. Michael Corrado
2 will present the clinical aspects. Mike was involved
3 from the early days of the clinical program for the
4 development of levofloxacin. He was then a member of
5 the staff at PRI, and he has since left and formed his
6 own contract research organization, but has been
7 intimately involved with the development program and
8 is here to present you the clinical data.
9 Some of the findings from Mike show some
10 interesting features. Levofloxacin is differentially
11 taken up by many tissues in the body and especially so
12 in the lung. We believe that this may have a bearing
13 upon its efficacy in community acquired pneumonia.
14 Indeed, the clinical data does support the
15 fact that community acquiredpneumonia associated with
16 resistantpneumococcican be treated successfully with
17 levofloxacin, and that levofloxacin has a safety
18 profile that's well known and similar to beta lactem
19 and macrolides, and that data comes from our clinical
20 trials.
21 We also have three other experts with us,
22 four other experts with us -- I'm sorry -- one of
23 whom, Dr. Tony Medeiros, Professor of Medicine at
24 Brown University, is going to take **a** short time to
25 present the clinician's dilemma. What happens when